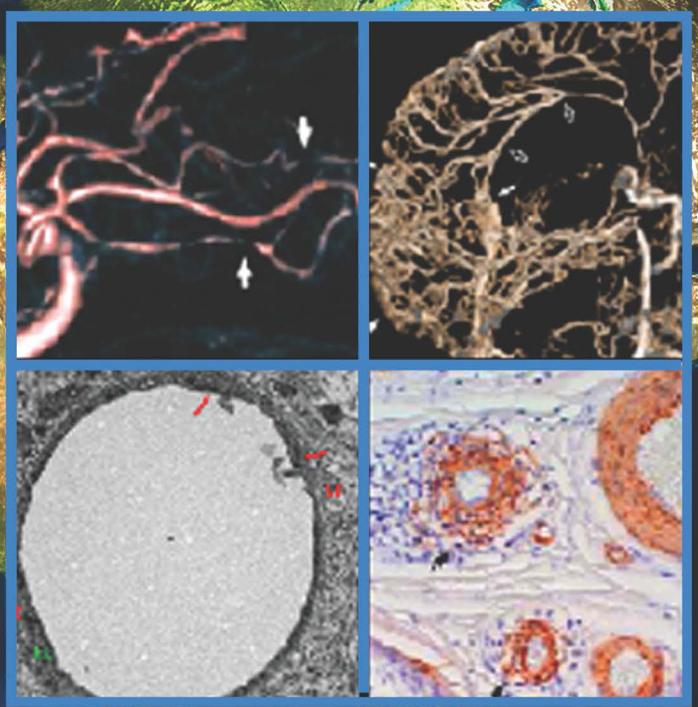
David S. Younger, MD, MPH, MS
Editor

The Vasculitides

Nervous System Vasculitis and Treatment

(Second Edition)

Volume 2



Public Health in the 21st Century

NOVA

Nova Biomedical

THE VASCULITIDES

VOLUME 2

NERVOUS SYSTEM VASCULITIS AND TREATMENT

(SECOND EDITION)

PUBLIC HEALTH IN THE 21ST CENTURY

Additional books and e-books in this series can be found
on Nova's website under the Series tab.

PUBLIC HEALTH IN THE 21ST CENTURY

THE VASCULITIDES

VOLUME 2

NERVOUS SYSTEM VASCULITIS AND TREATMENT

(SECOND EDITION)

DAVID S. YOUNGER, MD, MPH, MS
EDITOR

nova
Medicine & Health
New York

Library of Congress Cataloging-in-Publication Data

ISBN: 978-1-53615-136-7 (eBook)

Published by Nova Science Publishers, Inc. † New York

CONTENTS

FOREWORD TO THE VASCULITIDES

Charles D. Pusey and Richard A. Watts

Clinical and basic research into the systemic vasculitides have continued to gather momentum over the last four years since publication of the first edition of this book. We have attended two more International Vasculitis and ANCA Workshops, in London in 2015 and Tokyo in 2017. Both of these excellent meetings have covered the area of vasculitis more broadly and extensively than in the past. The present edition of this book contains contributions from many of those participating in these meetings.

Classification and nomenclature in vasculitis is increasingly harmonised and agreed across different specialties. There have been a number of genetic studies in ANCA-associated vasculitis (AAV) in which the genetic associations appear to be more closely related to ANCA specificity, i.e., MPO-ANCA or PR3-ANCA, than to clinical classification. The extent of overlap between the different vasculitic conditions is also becoming more apparent, in particular the co-existence of AAV and anti-GBM disease.

In terms of pathogenesis, there is increasing evidence for the contribution of complement activation in AAV. This has been nicely demonstrated in animal models, and a phase 2 trial of a C5a receptor inhibitor has recently been reported. Another area of increasing interest is the role of neutrophil extracellular traps (NETs) which appear to play a part both in tissue inflammation and in the generation of autoimmunity.

The number of clinical trials in vasculitis continues to expand. The use of rituximab for induction therapy in AAV is now well established, and different approaches to its use in maintenance therapy have been published. There are ongoing investigations of other novel agents, such as belimumab and abatacept. The results of the PEXIVAS study, which examines the use of additional plasma exchange, and of standard or reduced corticosteroid dose, are eagerly awaited.

In the area of large vessel vasculitis, there have also been rapid developments. The genetic basis of Takayasu arteritis and giant cell arteritis is becoming clearer, with evidence of different genetic risk factors underlying the two conditions. Imaging, especially the role of PET-CT in disease assessment, is becoming better established. The treatment of giant cell arteritis has taken a large step forward with the introduction of IL-6 blockade as an established therapy. However, many questions remain, especially when to use IL-6 blockade and for how long. This

treatment should permit many patients to avoid the deleterious consequences of long term high dose steroids.

We believe that the breadth and depth of the contributions in the second edition of this book surpass the high standards set in the first edition. The publication of this new edition precedes the 19th International Vasculitis and ANCA Workshop to be held in April 2019 in Philadelphia.

PREFACE

Systemic and nervous system vasculitides are a heterogeneous group of related disorders, each characterized by vascular inflammation such that it has the potential to cause serious morbidity and mortality if unrecognized and therefore untreated. Systemic vasculitis affect all populations and every nationality and walk-of-life, from childhood to older age. The first edition of *The Vasculitides* published in 2014 to meet the urgent need for a clear, concise and reliable textbook regarding the epidemiology, pathogenesis, clinical presentation, laboratory evaluation and management of these disorders, assembled participants of the 16th International Vasculitis and ANCA Workshop in Paris, France. Five years later, two subsequent meetings have taken place, in London and Tokyo. The 19th International Vasculitis & ANCA Workshop in April 2019 at the University of Pennsylvania promises to be an exceptional venue to share translational scientific discoveries, data from clinical trials, and advances in the clinical assessment, pathophysiology, genetic biomarkers, and standard-of-care and novel therapies of vasculitis.

The second edition, which is an update of the original two-volume book, remaining encyclopedic in content, adds six new chapters, incorporating the participation of investigators who did not have an opportunity to contribute the first volume, including some from the previous meeting in Japan. The new chapters are Health Related Quality of Life and Measurements, Neutrophilic Cell Pathology, Complement Factors in ANCA-Associated Vasculitis, Isolated Aortitis/IgG4 Disease, Anti-GBM Disease, and the Autoimmune Encephalitides. An additional six chapters were reassigned or incorporate new contributors. Five chapters left out of the present edition, made room for new and updated content without increasing the page length. Participants attending the 19th International Vasculitis & ANCA Workshop and preparing to both share their experience and enrich their knowledge in the clinical and scientific complexities and broad scope of organ involvement, that are the hallmarks of vasculitis, will no doubt want to receive an advance copy of this book or obtain one at the meeting.

I wish to express my appreciation to my coauthors, all experts in their individual field of interest in vasculitis, for allowing me to, once again, assemble them for the task of producing a 2nd edition of *The Vasculitides*. And many thanks to Ms. Lauren Bangug, Clinical Coordinator, for assisting in the preparation of the final manuscript.

I have had the good fortune of interacting with thought-provoking medical students, neurology trainees, public health doctoral students and professors at New York University, in the Department of Neurology, Division of Neuroepidemiology, and at City University of New

York, in the Department of Health Policy and Management. Like my coauthors, we strive for the highest ethical standards in medical and public health practice and research. My wife Holly and sons Adam and Seth encourage me to take on projects that promote core values of medicine and humanity, as my patients educate me daily in empathy and humility.

David S. Younger, MD, MPH, MS
September 30, 2018
New York, NY

I. NERVOUS SYSTEM VASCULITIS

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 1

THE CLINICAL APPROACH TO PATIENTS WITH VASCULITIS

David S. Younger**, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health, City University of New York, New York, NY, US

ABSTRACT

The systemic vasculitides are a heterogeneous group of disorders. Pathologically defined by the presence of vascular inflammatory infiltrate, primary vasculitides occur in the absence of a known cause or associated disease state, while secondary vasculitides occur in association with known underlying disorders and disease triggers. The vasculitic process is often systemic however vascular inflammation may be confined to an isolated organ system such as the kidney or even central nervous system. This chapter provides an overview of the approach to patients with systemic vasculitis including the clinical presentation, differential diagnosis, imaging and histopathologic evaluation, and short- and long-term treatment-related complications.

INTRODUCTION

The primary systemic vasculitides are a diverse group of multisystem syndromes characterized according to the size of the blood vessels involved and the organ systems affected. Inflammation in the blood vessels can lead to diminished blood flow or vessel occlusion resulting in ischemia, necrosis and subsequent tissue damage. The blood vessels themselves can be damaged in vasculitis resulting in permanent stenosis, aneurysmal change and vessel rupture. Any combination of vessels from large arteries to tiny venules and capillaries may be involved in the inflammatory process. The 2012 Revised Chapel Hill Consensus Conference

* Corresponding Author's E-mail: youngd01@nyu.edu

(CHCC) [1] provides useful nosology for the primary vasculitides based upon the caliber of the vessels, both arteries and veins, involves. Small vessel vasculitis (SVV) includes granulomatosis with polyangiitis (GPA) (Wegener type]), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome [CSS]), known collectively as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV).

Vasculitic disorders associated with immune complexes (IC) include IgA vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies. Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome. Medium vessel vasculitides (MVV), exemplified by polyarteritis nodosa (PAN) also includes Kawasaki disease (KD) in children. Large vessel vasculitides (LVV) are represented by giant cell arteritis (GCA), and Takayasu arteritis (TAK). Vascular inflammation confirmed to a single organ system such as the kidney, peripheral nerves, brain or vessel such as IgG4 related aortitis, are deemed single organ vasculitides (SOV).

In 2008, the Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) reported methodology and overall clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides [2] followed by a final validated classification [3] based upon vessel size, similar to the CHCC nomenclature [1].

This chapter provides an overview of the clinical approach and management of patients with primary systemic vasculitis including aspects of the clinical presentation, differential diagnosis, imaging, histopathologic evaluation, and short- and long-term treatment-related complications.

HISTORY AND EXAMINATION

Clinical acumen combined with a thorough history and physical exam is essential to making the diagnosis and defining the correct testing to complete the diagnosis and assess the extent of disease. Thus, while it may seem obvious, the first challenge in the diagnosis of primary systemic vasculitis is in fact considering it as a possible diagnosis. The diagnosis is often delayed as more common causes of multi-system disease like infections and malignancies are investigated. One population-based study reported a median time interval between the onset of symptoms and diagnosis of 11 months (range, 1 to 50 months) in TAK [4]. The past decade has witnessed a decrease in the time to diagnosis of AAV from a mean of 17 months to 4 months; however delays in diagnosis occur in subgroups of patients with flu-like prodromal and upper respiratory symptoms [5]. Failure to make a timely diagnosis can have devastating consequences such as blindness due to unrecognized GCA, renal failure caused by untreated AAV, and death due to a rupture of an unrecognized mesenteric aneurysm caused by PAN.

Despite significant overlap, vasculitic disorders generally manifest characteristic patterns of organ involvement. Fever, weight loss, fatigue, arthritis, skin rash, peripheral (PNS) and central nervous (CNS) manifestations are common symptoms and signs of systemic

vasculitides. In spite of expected disparities in vessel involvement and resultant end-organ damage, in one cohort of 800 patients with AAV, PAN, GCA, and TAK [6], greater than 30% of those with LVV, and more than 70% of patients with SVV and MVV experienced constitutional symptoms at the time of diagnosis. Certain clinical presentations should prompt swift evaluation for systemic vasculitis such as mononeuritis multiplex, pulmonary-renal syndrome with a rapidly progressive glomerulonephritis, alveolar hemorrhage and infarction in multiple vascular beds.

The presence of concomitant infection should be sought in suspected patients. Both hepatitis B (HBV) and C virus (HCV) infections are associated with concomitant IC-mediated vasculitis, and there are recognized relationships between HBV and PAN, and HCV contributes to the pathogenesis of mixed cryoglobulinemic vasculitis. Although effective vaccine programs in the developed world may already have dramatically reduced the rate of acute HBV infection, large cohort studies have found an association between HBV and PAN in up to a third of patients [7]. Hepatitis B surface antigen (HBsAg) and antibody (HBsAb), and core antibody (HBcAb), and HCV should thus all be included in the routine evaluation of such patients. Human immunodeficiency virus-type 1 (HIV-1) is an associated cause of vascular inflammation predominating in SVV [8]; and in the absence of systemic vasculitis, patients with HIV may demonstrate ANCA-seropositivity. HIV-infected patients become susceptible to opportunistic infection including cytomegalovirus (CMV). The latter may be associated with true vasculitis with discernible CMV inclusions in the inflammatory infiltrate, especially in those with established acquired immune deficiency syndrome (AIDS), and skin, gastrointestinal, pulmonary, and CNS involvement. Other opportunistic infections that cause vasculitis in the immunocompromised hosts include *Pneumocystis jeroveci* and *Toxoplasma gondii*. Endovascular infection by bacterial or fungal agents in the course of endocarditis and mycotic aneurysms can mimic systemic vasculitis. Koening and colleagues [9] identified a *Burkholderia*-like gram-negative bacterial strain in the temporal arteries of subjects with GCA. Two other pathogens, *Treponema pallidum*, the spirochete pathogen of tertiary syphilis, and *Mycobacterium tuberculosis* (TB), both contribute to the development of aortitis and LVV, with histologically evident-evident chronic granulomatous in endemic areas where the prevalence of TAK is highest.

A knowledge of potentially offending medications or known drug abuse may give valuable clues to the origin of vasculitis in susceptible patients. There is an ever-growing list of medications associated with hypersensitivity vasculitis, the clinical presentation of which is usually self-limited and resolves once the causative agent has been identified and removed. The prescription drugs hydralazine and propylthiouracil are both associated with ANCA-seropositivity but not true vasculitis. One important distinction in the diagnosis of drug-induced AAV is that unlike idiopathic AAV, those associated with drug-induced ANCA-seropositivity often have antibodies against more than one antigen [10]. The acute onset of headache and focal neurological deficit in a known cocaine abuser should lead to consideration of cocaine-induced vasospasm with cerebral hemorrhage. Such patients will often have midline destructive nasal sinus lesions. Cocaine-induced midline destructive lesions (CIMDL) may also resemble GPA, further complicating the distinction between CIMDL and AAV is often present ANCA-seropositivity. Cocaine-induced CIMDL can be associated with p-ANCA, c-ANCA or both. The most common autoantibody in CIMDL, occurring in 84% of patients in one study, was atypical p-ANCA directed against human neutrophil elastase (HNE) [11]. Requesting specific

ANCA serology by the immunofluorescence technique (IFT), and not just the ANCA pattern, avoids misdiagnosis between CIMDL and sino-nasal GPA.

Fever, purpuric rash, acute renal failure, and neurologic involvement may also be the clue to SVV. While prothrombotic disorders may mimic systemic vasculitis, the manifestations of anti-phospholipid syndrome (APS) can overlap with systemic vasculitis. Affected patients with catastrophic APS can present with pulmonary-renal syndrome, and unlike those with SVV, such patients require anti-coagulation. The non-criterion manifestations of APS-like skin ulcers and emboli from verrucous valvular heart disease can appear grossly similar to vasculitic lesions however skin biopsy which instead shows in situ thrombi instead of vascular inflammation distinguishes the two entities.

Ischemic limb pain and claudication may well be the presenting manifestations of MVV and LVV in older patients with diabetes, hyperlipidemia, hypertension and tobacco use that is due to atherosclerosis. Moreover, both vasculitis and atherosclerosis may reveal abnormalities on non-invasive vascular imaging and contrast angiography studies. While the suspicion of primary systemic vasculitis should generally be reserved for younger patients and older individuals lacking traditional cardiovascular risk factors, the exception occurs in cholesterol crystal embolism [12]. Such patients manifest distal embolization of atherosclerotic plaques lading to livedo skin rash, digital ischemic, visual and renal manifestations. Arteriolar cholesterol clefts are demonstrable in tissue biopsy of skin, muscle, and cutaneous nerve specimens.

A history of malignancy or the suspicion of cancer may be indispensable and life-saving. The majority of malignancy-associated vasculitides occur in conjunction with hematologic malignancies and myelodysplastic syndromes. A reported 4.5% to 8% of patients with lymphoproliferative disease developed primary systemic vasculitis with renal, cerebral, pulmonary, and cutaneous involvement [13]. There are reports of homology between the genetic sequences of serine proteinase-3, the antigenic target in GPA, and myeloblastin a protein found in certain human leukemic cells, explaining in part the association between hematologic malignancy and systemic vasculitis [14]. Hairy cell leukemia may be the proximate cause of necrotizing systemic vasculitis. Other tumors can cause constitutional symptoms mimicking vasculitis and embolic phenomena including atrial myxoma, so noted in more than 30% of patients that manifested fever, arthralgia and weight loss in association with laboratory features of acute inflammation [15]. These benign tumors express increased levels of IL-6, a pro-inflammatory cytokine implicated in the pathogenesis of LVV such as GCA. A history of thyroid endocrinopathy may lead to consideration of autoimmune thyroid disease and Hashimoto thyroiditis and encephalopathy.

Although very rare, the literature describes cases of Hashimoto encephalopathy attesting to its occurrence [16]. Affected patients present with seizures, stroke-like episodes, transient focal and global neurological deficits, and a variety of neuropsychiatric disturbance from dementia to hallucinations and psychosis. The encephalopathy evolves with concomitantly elevated anti-thyroid peroxidase antibodies, independent from hormonal thyroid function setting it apart from thyrotoxicosis and myxedema. Albeit rare, such cases may be indistinguishable from CNS vasculitis and share an autoimmune vasculitic etiopathogenesis.

The autoimmune encephalitides [17], so suggested by cognitive, neuropsychiatric complaints and seizures, are clinically and histopathologically associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens, and constituents of the limbic system neuropil. This has led to a reconsideration of a number of neuropsychiatric and

neurocognitive disorders as having shared mechanisms of origin. While there are no convincing cases of vasculitis autoimmune encephalitis, there may be difficulty in clinically distinguishing them from primary CNS vasculitis.

A detailed genetic pedigree may not be practical in all cases, but knowledge of a familial disorders or genetic syndromes affecting the vasculature resembling vasculitides may signal the need for associated targeted genetic testing in given patients. At least three congenital disorders, Ehlers-Danlos syndrome, type-4 Loeys-Dietz and Marfan syndrome [18-20], all enter in to the differential diagnosis of LVV and idiopathic aortitis, also a component of the IgG4-related disorders (IgG4-RD); and a fourth disorder termed Grange syndrome that resembles PAN.

LABORATORY EVALUATION

Accurate diagnosis depends upon familiarity with the myriad of clinical features of the various vasculitides together with results of carefully selected laboratory studies including screening metabolic, autoimmune and infectious serology, followed by appropriate vascular imaging studies, and appropriate tissue biopsies or sampling of body fluids.

Blood studies will often reflect the severity and type of immunological storm due to underlying primary vasculitis in analysis of a complete blood count (CBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), basic metabolic panel, ANCA by IFT and enzyme-linked immunosorbent antibody (ELISA) serology specific for proteinase-3 (PR3) and myeloperoxidase (MPO); T- and B-cell subset quantitation; C1q binding and Raji cell circulating immune complexes and C3, C4, and CH50 complement protein levels; quantitative immunoglobulins, subsets, and immunofixation (IFE); with rheumatoid factor (RF) titers, cryoglobulins, serologic analysis for HBV, HCV, HIV, lupus and anticardiolipin antibodies, acute and convalescent *Borrelia* and coinfectious serology; and human leukocyte antibody (HLA) alleles appropriate for different types of primary vasculitides.

Urine should be obtained for spot analysis and 24-hour collection for chemical and cellular microscopic constituents to screen for renal impairment.

The *radiologic evaluation* of patients with primary vasculitis should include color-Doppler sonography (CDS), and 3-Tesla (T) magnetic resonance imaging (MRI) combined with angiography (MRA) or CT angiography (CTA) to assess the temporal arteries and great vessels. Digitial subtraction angiography (DSA) of individual vascular organ beds can be employed to visualize the vessel walls and luminal changes. Mural changes with vessel wall thickening correlate with early inflammation while vascular luminal stenoses and aneurysm formation indicate late vasculitic complications. ^{18}Fluorodeoxyglucose positron emission tomography (PET) detects metabolically active inflammatory cells infiltrating vessel walls in affected patients especially in large vessels. However, the extent of disease and monitoring of luminal changes is best appreciated by employing a combination of PET and DSA techniques. Likewise the combination of nuclear medicine cerebral perfusion with single photon emission CT (SPECT) and PET fused with MRI provides a unique estimation of perfusion across the blood-brain barrier in relation to cerebral regional metabolism.

Cerebrospinal fluid (CSF) obtained in patients with presumed CNS involvement, should be obtained atraumatically and sampled for an extensive panel of constituents with an extra tube placed in a negative 80 degree Celsius freezer for future analysis or to replace specimens lost in transport. This includes analysis of CSF total protein and glucose levels, white blood cell and red blood cell counts, IgG and albumin levels, oligoclonal bands, cytology, bacterial gram stain, latex agglutination of meningitis-associated bacterial antigens related to *Group B strep*, *Strep pneumoniae*, *Haemophilus influenza* (Type b), *Neisseria meningitidis* (Groups A,B,C,Y & W135) and *E. coli* K1 infection; India ink preparation, cryptococcal antigen, acid-fast stains; bacterial, fungal, parasitic, and TB cultures. New York State has a viral encephalitis panel that includes Adenovirus, West Nile virus, HSV 1 and 2, CMV,VZV, EBV, and HHV6 DNA viruses, as well as Eastern Equine Encephalitis, Saint Louis Encephalitis and Enterovirus RNA viruses, all analyzed by real-time polymerase-chain reaction (PCR). Patients suspected of *Borrelia burgdorferi* infection undergo paired serologic and PCR analysis of CSF and serum to demonstrate intrathecal production of *Borrelia*-specific antibodies [21]. A commercially available panel of CNS antibodies for patients with autoimmune or paraneoplastic dementia with or without sensory and motor neuronopathy or dysautonomia includes N-methyl-D-asparatate receptor (NMDA-R), voltage-gated potassium channel (VGKC)-complex, glutamic acid decarboxylase (GAD) 65, gamma-amino butyric acid beta receptor (GABA-R), anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), anti-neuronal nuclear antibody (ANNA)-1, -2, -3; anti-glial nuclear antibody (AGNA)-1; Purkinje cell cytoplasmic antibody (PCA) types 2 and Tr; amphiphysin, N and P/Q-type calcium channels, ganglionic neuronal and muscle acetyl choline receptors (AChR), and collapsin response-mediated protein-5-(CRMP-5-IgG).

Tissue biopsy is important in defining the type, extent and character of the inflammatory process and categorizing the underlying systemic vasculitic disorder. In AAV, histologic evidence of necrotizing SVV with accompanying granulomatous inflammation noted in GPA can be used to support the diagnosis in conjunction with clinical and serologic information. Although nasal, sinus and upper airway involvement in GPA may be noted overall in 92% of patients at onset of disease [22], tissue biopsy of these regions is associated with vasculitis and necrosis in only 23% of upper airway biopsy specimens; vasculitis and granulomatous inflammation in 21%; and vasculitis together with necrosis and granulomatous inflammation in only 16%. The small amount of tissue available in biopsy specimens from areas of the head and neck make it surprisingly difficult or impossible to identify the classical pathological features of GPA in some patients. By comparison, renal biopsy in patients with GPA show varying degrees of segmental necrotizing glomerulonephritis in 80% of tissue. In the absence of renal involvement, targeted biopsy of radiographically abnormal lung parenchyma via a thoracoscopic or open lung biopsy technique showed granulomatous changes in 22% and capillaritis in 31% of those so studied [20] compared to the efficacy of transbronchial biopsy in establishing the diagnosis of pulmonary vasculitis in 10% of suspected tissues [23].

The finding of focal, segmental necrotizing vasculitis in medium-sized arteries confirms the diagnosis of PAN in suspected patients. Angiographic demonstration of microaneurysm formation is an acceptable surrogate to the histopathologic confirmation when tissue cannot be readily obtained [24]. Histologically-proven PAN is ascertained in 70% of patients by nerve, muscle or skin tissue biopsy in one large cohort [25]. Of 129 patients underwent nerve biopsy including 108 with peripheral neuropathy and 21 without peripheral neuropathy, vasculitic lesions were noted respectively in 83% and 81% of patients compared to muscle biopsy which

showed vasculitis respectively in 68% and 60%. Angiography showed renal and gastrointestinal microaneurysms or stenosis respectively in 66% and 57% of patients. While PAN frequently involves the gastrointestinal tract especially the small intestine, biopsy of visually apparent lesions on luminal exam rarely provide histopathologic confirmation of vasculitis [26]. Renal biopsy may be negative even in patients with frank organ involvement due to sampling error. Unlike AAV, where the histopathologic renal lesion is the kidney glomerulus, microaneurysm formation due to PAN increases the risk of bleeding associated with renal biopsy.

Histopathologic evidence of vascular wall infiltration by giant cells at the junction of the intima and media, leading to thrombosis, intimal hyperplasia, and fibrosis [27] is the gold standard method of GCA diagnosis. Accordingly, temporal artery biopsy is recommended for all patients with suspected GCA [28]. The sensitivity of temporal artery biopsy in GCA has been estimated to be 85% [29]. Evidence in support of unilateral as compared to bilateral temporal artery biopsy is lacking, leaving it up to the judgment of the treating physician. Temporal artery ultrasonography can be used to guide the surgeon to the arterial segment with the clearest halo sign in performance of temporal artery biopsy [30], however the discontinuous nature of inflammation in GCA leading to skip lesions may still lead to unforeseen false-negative results when the tissue specimen is of insufficient length and multiple sections are not examined. Certain clinical features, such as the presence of jaw claudication can increase the positivity predictive value of a temporal artery biopsy. Arteritis can be observed histologically even after several weeks of high dose corticosteroid therapy [31]. Notwithstanding, the heightened risk of ischemic complications culminating in irreversible visual loss in early untreated GCA has led to the recommendations for prompt administration of high-dose corticosteroid therapy while awaiting tissue biopsy results.

Skin biopsy can be performed for IF analysis of vessel walls to search for microscopic analysis for leukocytoclasia, Ig and complement deposition. Two 3 mm punch skin biopsies of along the distal calf and proximal thigh fixed in anti-protein-gene-product 9.5 (PGP 9.5) solution will discern epidermal nerve fiber depletion useful in the designation of small and large fiber neuropathy, and in the selection of patient who should undergo surgical biopsy of the sural nerve or branch of the superficial fibular sensory nerve and corresponding soleus and peroneus brevis muscle to search for vasculitic lesions and confirm the neuropathic or myopathic changes found on electrodiagnostic studies. Adults and children with CNS involvement whether clinically, by MRI, SPECT, PET imaging of the brain, cerebral angiography, or CSF examination, especially in the setting of acute mental change, new focal neurological deficit, CSF protein content >100 mg/dL or pleocytosis, may be candidates for empiric therapy for primary CNS angiitis [32] or combined leptomeningeal and brain biopsy to diagnose granulomatous or non-granulomatous necrotizing arteritis [33-34].

TREATMENT

Most experts concur with the following three principles to guide management of patients. First, vasculitis it is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction. Second, undiagnosed and untreated, the outcome of vasculitis is potentially fatal. Third, a favorable response to an empiric course of

immunosuppressive and immunomodulating therapy should not be considered a substitute for the histolopathologic confirmation of vasculitis. Physicians treating vasculitides must choose the sequence and combination of available immunosuppressant and immunomodulating therapies to induce and sustain remission and treat relapses, recognizing the possible beneficial and adverse effects. Recommended treatment options for the different categories of vasculitis are summarized in Table 1.

The standard of care for the treatment of vasculitides, notably AAV, has been evolving in response to many factors [35]:

First, the steady influx of data from multicenter, national and international collaborative, evidence-based randomized clinical trials (RCT) and observational cohorts in adult vasculitides, notably from the French Vasculitis Study Group (FVSG) database, United States-Canadian Vasculitis Clinical Research Consortium (VCRC), European Vasculitis Study Society (EUVAS), the European League Against Rheumatism (EULAR), The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System (COVAC), and the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS). Childhood vaculitides have been represented by the Pediatric Vasculitis Initiative (PedVas), a Canadian and United Kingdom collaborative study of ARChiVe Investigators Network within the PedVas Initiative and ARChiVe registry, including BrainWorks and DCVAS, of pediatric and adult cases of AAV (GPA) and PACNS (NIH identifier, NCT02006134). PedVas has been prospectively collecting clinical and biobank data of registered cases within 12 months of study entry since 2013.

Second, while many vasculitides still lack well-validated measures of disease activity or state for use in clinical trials, there have nonetheless been advances in standardized approaches to conducting clinical trials as advocated by the EULAR and its collaborators worldwide [36]. Moreover, the Vasculitis Working Group of the Outcome Measures in Rheumatology (OMERACT) initiative is actively pursuing projects to advance development of valid measures in the vasculitides [37-39], such as disease-specific self-reported patient-related outcomes (PRO) applicable to AAV to distinguish treatments of varying efficacy, included among them, Health Related Quality of Life (HRQoL) measures, that are further separable by the caliber of vessels involved [40, 41]. Children's' self-reported HRQoL measured by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL) Generic Scores Scales, repeatedly measured over time in pediatric inflammatory brain disease (IBrainD) [42], including cPACNS, shows poor HRQoL scores in >50% of patients at that associates with cognitive dysfunction as the most presenting symptom, as well as, small vessel cPACNS (SV-cPACNS) [43].

Third, the influence of gene-wide association studies (GWAS) and biobank data such as the UK Biobank to elucidate risk gene loci, single nucleotide polymorphism (SNP) and human HLA polymorphisms in disease clusters and population cohorts [44]. Such inherited and environmental factors, gene-gene interactions, epigenetic factors, and other influences upon the immunopathogenesis of vasculitides have had important theoretical importance for the performance of RCTs in vasculitides subtypes, as well as, relevance for screening studies and timing of therapy.

Fourth, historically, the introduction of effective therapy for AAV, beginning with corticosteroids in 1948, and cyclophosphamide two decades later, together with adjunctive therapies, transformed the outcome of AAV with five-year rates approaching 80% [45]. The AAVs were thus transformed into chronic relapsing disorders with progressive organ damage and disability. Hope for a better treatment was heralded by the effectiveness of a daily oral

regimen of 2 mg/kg/day of oral cyclophosphamide and prednisone in GPA that served as a template for the treatment of virtually all types of systemic vasculitis for decades. However, almost all patients had serious morbidity from irreversible features of their disease or side effects of treatment, including the cumulative exposure to corticosteroids leading to osteoporosis and bone fractures; and cytotoxic therapy-related chronic myelosuppression, infection, urothelial malignancy, and infertility [46, 47]. Three later adjustments in the use of cyclophosphamide in AAV were instructive. One was the sequential replacement of cyclophosphamide by azathioprine [48]. A second was the replacement of cyclophosphamide by methotrexate by for early systemic disease without critical organ manifestations in the NORAM study [49]. A third was pulsed intravenous cyclophosphamide with a dose reduction in patients >60 years of age and renal impairment rather than daily oral cyclophosphamide as in the CYCLOPS study [50], enabling a cumulative dose reduction of approximately one-half. Follow-up analyses [51], however showed that reduced cyclophosphamide dose was associated with a higher risk of relapse, while methotrexate was associated with less effective disease control than with cyclophosphamide induction [52]; neither with increased long-term morbidity or mortality.

Fourth, the licensing of rituximab for the treatment of AAV was the most significant recent achievement but the optimal treatment strategy after rituximab induction-remission awaits delineation. Rituximab is a chimeric monoclonal anti-CD20 antibody that selectively depletes B-cells, but not plasma cells. The Rituximab in ANCA-Associated Vasculitis (RAVE) Study [53] found that rituximab was not inferior to daily cyclophosphamide treatment for induction of remission in severe AAV and possibly superior in relapsing disease. The Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) [54] demonstrated non-superiority of rituximab to standard intravenous cyclophosphamide for severe AAV with high-sustained remission rates in both groups. Rituximab-based therapy was not associated with reductions in early adverse events. However, rates of cardiovascular disease and malignancy in AAV increased, as well as, underlying patterns of disease such as accelerated atherosclerosis [55] raising other concerns that there might be non-traditional risk factors such as endothelial activation and excessive vascular remodeling [56]. Early outcome results for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues on behalf of ARCHiVe Investigators Network and the PedVas [57] have been less encouraging than in adults. Among 105 children with AAV, mainly GPA, who received CS, CYC, MTX, or RTX for remission-induction, and PE in conjunction with CYC and/or RTX, 42% achieved remission at 12 months (Pediatric Vasculitis Activity Score [PVAS] of 0, CS dose < 0.2 mg/kg/day), 21 (48%) of whom discontinued corticosteroids by 12 months; all but 3 remaining on maintenance treatment at 12 months receiving azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide. However, up to 63% had a Pediatric Vasculitis Damage Index [PVDI) score of 1 or more by 12 months, with the presence of renal, ear, nose and throat, or pulmonary damage; and 41% of children reported hospitalizations. Thus, a significant proportion of patients were not in remission at 12 months, and more than one-half of the patient cohort experienced damage early in the disease course. The 12-month remission rate of 42% in the cohort was significantly lower than Sacri and colleagues [58], who reported 73% remission at post-induction and 90% overall remission rate (including secondary remissions after a median time of 6.7 months). Disappointing early outcomes in the PedVas treatment study for GPA [57] serve as a cautionary note in the treatment of IBrainD and cPACNS with similar immunosuppressive regimens.

Table 1. Recommendations for the Treatment of Vasculitides

Large Vessel Vasculitis *GCA, TAK*: CS, AZA, RTX, infliximab, anti-TNFα, anti-IL-6R, tocilizumab, and MM. Adjunctive therapy: ASA and AC.
Medium Vessel Vasculitis *PAN, KD*: CS and CYC; MM.
Small Vessel Vasculitis-AAV Type *GPA, EGPA, MPA*: Induction with CS + CYC; CS + RTX; or CS + MM and maintenance RTX, AZA or MM.
Small Vessel Vasculitis- IC Type *CV*: MM; INF-alpha and PegINF-alpha plus ribovarin or RTX in HCV-associated MC. *IgAV*: CS and/or MM; and supportive care.
Hypocomplementic-C1q: Antihistamines, IVIg, PE.
Variable Vessel Vasculitis *Cogan Syndrome*: CS. *BD*: CS, MM; colchicine or anti-TNFα.
Single Organ Vasculitis-Isolated Aortitis, PACNS *Isolated Aortitis:* CS, AZA, MM, MTX. *cPACNS*: Induction with CS, CS +CYC or RTX, followed by maintenance with AZA, MTX or MM *PCNSV*: Induction with CS, CS +CYC or RTX, followed by maintenance with AZA, MTX or MM
Vasculitis Associated With Systemic Collagen Vascular Disease-SLE, RAV *SLE*: CS, MM; and AC. *RAV*: CS, RTX, infliximab and AZA or MTX
Vasculitis Associated with Illicit Substance Abuse Avoid illicit substance.
Vasculitis Associated with Infection Antimicrobial agents chosen specifically to treat a given etiologic organism.

Abbreviations: AC, anticoagulation; ASA, aspirin; AZA, azathioprine; BD, Behçet disease; CS, corticosteroids, CV, cryoglobulinemic vasculitis; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HCV, hepatitis C virus; IC, Immune complex; IgAV, IgA vasculitis; INF, interferon; IL, interleukin; IVIg, intravenous immune globulin; KD, Kawasaki disease; MC, mixed cryoglobulinemia; MM, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; cPACNS, childhood primary angiitis of the central nervous system; PCNSV, primary central nervous system vasculitis; PAN, polyarteritis nodosa; PE, plasma exchange; RAV, rheumatoid arthritis vasculitis; RTX, rituximab; SLE, systemic lupus erythematosus; TAK, Takayasu arteritis; TNF, tumor necrosis factor.

Fifth, animal models of AAV [59] have enabled the transfer of murine MPO-ANCA IgG without functioning B-, or T-cells, resulting in pauci-immune, necrotizing crescentic glomerulonephritis similar to human AAV [60, 61], while other lines of evidence link infection to ANCA-related autoimmunity through molecular mimicry [62]. Using experimental material from patients with inflammatory vascular disease caused by ANCA and specificity for PR-3, autoimmunity can be initiated through an immune response against a peptide, antisense or

complementary to the autoantigen, which then induces anti-idiotypic antibodies cross-reactive with the autoantigen [63].

Sixth, there is increasing evidence for the role of both humoral-mediated and cell-mediated immunity in AAV, with involvement of complement activation in the renal damage of human ANCA-associated pauci-immune vasculitis [64]. Cell-mediated immunity is exemplified by activation of circulating T-cells and B-cells, with infiltration of plasmoblasts into affected tissues [65] are co-stimulated by the secretion of pro-inflammatory cytokines including IL-6 and TNFα. While T-cells contribute an important role in the pathogenesis of AAV [66], B-cells are still the main therapeutic target as precursors of ANCA-secreting plasma cells.

CONCLUSION

The heterogeneous nature of the systemic vasculitides expresses itself in the diversity of clinical presentations. The diagnosis rests upon first considering it as a possibility based upon the history and physical examination and supportive findings thereof on laboratory studies. Accurately diagnosed and so treated, the outcome can be favorable.

REFERENCES

[1] Jennette, J. C., Falk, R. J., Bacon, P. A., et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013; 65:1-11.

[2] Ruperto, N., Ozen, S., Pistorio, A., et al. EULAR/PINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: Overall methodology and clinical characterization. *Ann. Rheum. Dis.* 2010; 69:790-7972.

[3] Ozen, S., Pistorio, A., Iusan, S. M., et al. EULAR/PRINTO/PReS criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis. Ankara 2008. Part II: Final Classification. *Ann. Rheum. Dis.* 2010; 69:798-806.

[4] Dreyer, L., Faurschou, M. and Baslund, B. A population-based study of Takayasu's arteritis in eastern Denmark. *Clin. Exp. Rheumatol.* 2011 (Suppl. 64):S40-S42.

[5] Jayne, D. The diagnosis of vasculitis. *Best Pract. Res. Clin. Rheumatol.* 2009; 23:445-453; Poulton, C. J., Nachman, P., Hu, Y., et al. Pathways to renal biopsy and diagnosis among patients with ANCA small-vessel vasculitis. *Clin. Exp. Rheumatol.* 2013; 31 (Suppl. 75):S32-S37.

[6] Grayson, P. C., Cutherbertson, D., Carette, S., et al. New features of disease after diagnosis in 6 forms of systemic vasculitis. *J. Rheumatol.* 2013; Aug. 1 [Epub. ahead of print.

[7] Pagnoux, C., Seror, R., Henegar, C., et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between

1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010; 62:616-626.

[8] Guillevin, L. Infections in vasculitis. *Best Pract. Res. Clin. Rheumatol*. 2013; 27:19-31.

[9] Koening CL, Katz BJ, Hernandez-Rodriguez J, et al. Identification of a Burkholderia-like strain from temporal arteries of subjects with giant cell arteritis. *Arthritis Rheum.* 2012; 64:S373.

[10] Wiik, A. Drug-induced vasculitis. *Curr. Opin. Rheumatol*. 2008, 20:35-39.

[11] Weisner, O., Russell, K. A., Lee, A. S., et al. Antineutrophil cytoplasmic antibodies reacting with human neutrophil elastatse as a diagnostic marker for cocaine-induced midline destructive lesions but not auto-immune vasculitis. *Arthritis Rheum.* 2004; 50: 2954-2965.

[12] Bendixen, B., Younger, D. S., Hair, L., et al. Cholesterol emboli syndrome: a patient with peripheral neuropathy. *Neurology* 1992; 42; 428-430.

[13] Wooten, M. D., Jasin, H. E. Vasculitis and lymphoproliferative diseases. *Semin. Arthritis Rheum.* 1996; 564-574.

[14] Musette, P., Labbaye, C., Dorner, M. H., et al. Wegener's autoantigen and leukemia. *Blood* 1991; 77:1398-1399.

[15] Pinede, L., Duhaut, P., Loire, R. Clinical presentation of left atrial cardiac myxoma. A series of 112 consecutive cases. *Medicine* 2001; 80:159-172.

[16] Younger DS. Hashimoto's Thyroiditis and Encephalopathy, *World Journal of Neuroscience* 2017; 7:307-326.

[17] Younger DS. Autoimmune Encephalitides. *World Journal of Neuroscience*. 2017; 7:327-361.

[18] Beighton, P, De Paepe A, Steinmann, B, et al. Ehlers-Danlos syndrome: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (US) and Ehlers-Danlos Support Group (UK). *Am. J. Med. Genet.* 1998; 77:31-37.

[19] Kontusaari, S., Tromp, G., Kuivaniemi, H., et al. A mutation in the gene for type III procollagen (COL3A1) in a family with aortic aneurysms. *J. Clin. Invest.* 1990; 86: 1465-1473.

[20] Pyeritz, R. E., McKusick, V. A. The Marfan syndrome. *N. Engl. J. Med.* 1979; 300: 772-777.

[21] Younger D. S. Serologic testing. Chapter 6, *Human Lyme Neuroborreliosis.* Nova Biomedical: New York; 2015; 85-98.

[22] Hoffman, G. S., Kerr, G. S., Leavitt, R. Y., et al. Wegener's granulomatosis: an analysis of 158 patients. *Ann. Intern. Med.* 1992; 116:488-498.

[23] Schnabel, A., Holl-Ulrich, K., Dalhoff, K., et al. Efficacy of transbronchial biopsy in pulmonary vaculitides. *Eur. Respir. J.* 1997; 10:2738-2743.

[24] Basu, N., Watts, R., Bajema, I., et al. EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. *Ann. Rheum. Dis.* 2010; 69: 1744-1750.

[25] Pagnoux, C., Seror, R., Henegar, C., et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between

1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010; 62:616-626.

[26] Pagnoux, C., Mahr, A., Cohen, P., et al. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine* 2005; 84:115-128.

[27] Salvarani, C., Cantini, F., Boiardi, L., et al. Polymyalgia rheumatic and giant cell arteritis. *N. Engl. J. Med.* 2002; 347:261-271.

[28] Mukhtyar, C., Guillevin, L., Cid, M. C., et al. EULAR recommendations for the management of large vessel vasculitis. *Ann. Rheum. Dis.* 2009; 68:318-323.

[29] Younge, B. E., Cook, B. R., Bartley, G. B., et al. Initiation of glucocorticoid therapy: before or after temporal artery biopsy? *Mayo Clin. Proc.* 2004; 79:483-491.

[30] Blockmans, D., Bley, T., Schmidt, W. Imaging for large-vessel vasculitis. *Curr. Opin. Rheumatol.* 2009; 21:19-28.

[31] Achkar, A. A., Lie, J. T., Hunder, G. G., et al. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? *Ann. Intern. Med.* 1994; 120:987-992.

[32] Calabrese, L. H. Evidence-based clinical science and art in the diagnosis of central nervous system vasculitis. Presse Med. 2013; 42:600-602; Benseler, S. M. Central nervous system vasculitis in children. *Curr. Rheum. Rep.* 2006; 8:442-449.

[33] Younger, D. S., Calabrese, L. H., Hays, A. P. Granulomatous angiitis of the nervous system. *Neurol. Clin.* 1997; 15:821-834.

[34] Salvarani, C., Brown, R. D. Jr., Calamia, K. T., et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann. Neurol.* 2007; 62:442-451.

[35] Hoffman, G. S. Vasculitis treatment: is it time to change the standard of care for ANCA-associated vasculitis? *Presse Med.* 2013; 42:643-650.

[36] Geetha D, Jin Q, Scott J, et al. Comparisons of Guidelines and Recommendations on Managing Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Kidney Int Rep*. 2018; 3:1039-1049.

[37] Merkel P, Aydin S, Boers M et al. Current status of outcome measure development in vasculitis. *J Rheumatol* 2014; 41:593-598.

[38] Merkel PA, Aydin SZ, Boers M, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. *J Rheumatol* 2011; 38:1480-1486.

[39] Hatemi G, Merkel PA, Hamuryudan V, et al. Outcome measures used in clinical trials for Behçet syndrome: a systematic review. *J Rheumatol* 2014; 41:599-612.

[40] Robson JC, Dawson J, Doll H, et al. Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. *Ann Rheum Dis* 2018; 77:1157-1164.

[41] Robson JC, Dawson J, Cronholm PF, et al. Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure. *Patient Relat Outcome Meas*. 2018; 9:17-34.

[42] Twilt M, Benseler SM. Childhood inflammatory brain disease: pathogenesis, diagnosis and therapy. *Rheumatology (Oxford)* 2014; 53:1359-1368.

[43] Liu E, Twilt M, Tyrrell PN, et al. Health-related quality of life in children with inflammatory brain disease. *Pediatr Rheumatol Online J* 2018; 16:73.

[44] Lyons, P. A., Rayner, T. F., Trivedi, S., et al. Genetically distinct subsets within ANCA-associated vasculitis. *N. Engl. J. Med.* 2012; 367:214-223.

[45] Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med.* 1992; 116:488-498.

[46] Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis* 2008; 67:1004-1010.

[47] Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; 124:477-484.

[48] Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349:36-44.

[49] De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2005; 52:2461-2469.

[50] De Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med.* 2009; 150:670-680.

[51] Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis*. 2012; 71:955-960.

[52] Faurschou M, Westman K, Rasmussen N, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012; 64:3472-3477.

[53] Stone, J. R., Merkel, P. A., Spiera, R., et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N. Engl. J. Med.* 2010; 363:221-232].

[54] Jones, R. B., Tervaert, J. W., Hauser, T., et al., for the European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N. Engl. J. Med.* 2010; 363:211-220.

[55] De Leeuw K, Kallenberg C, Bijl M. Accelerated atherosclerosis in patients with systemic autoimmune diseases. *Ann NY Acad Sci*. 2005; 1051:362-371.

[56] Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis*. 2010; 69:1036-1043.

[57] Morishita KA, Moorthy LN, Lubieniecka JM, et al. Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2017; 69:1470-1479.

[58] Sacri AS, Chambaraud T, Ranchin B, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. *Nephrol Dial Transplant*. 2015; 30 Suppl 1:i104–112.

[59] Little MA, Al-Ani B, Ren S, et al. Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. *PloS One*. 2012; 7:e28626.

[60] Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest*. 2002; 110:955-963.

[61] Kain R, Exner M, Brandes R, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. *Nat Med.* 2008; 14:1088-1096.

[62] Popa ER, Stegeman CA, Kallenberg CG, et al. Staphylococcus aureus and Wegener's granulomatosis. *Arthritis Res*. 2002; 4:77-79.

[63] Pendergraft WF 3rd, Preston GA, Shah RR, et al. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3. *Nat Med*. 2004; 10:72-79.

[64] Xing GQ, Chen M, Liu G, et al. Complement activation is involved in renal damage in human antineutrophil cytoplasmic autoantibody associated pauci-immune vasculitis. *J Clin Immunol*. 2009; 29:282-291.

[65] Popa ER, Franssen CF, Limburg PC, et al. In vitro cytokine production and proliferation of T cells from patients with anti-proteinase 3- and antimyeloperoxidase-associated vasculitis, in response to proteinase 3 and myeloperoxidase. *Arthritis Rheum*. 2002; 46:1894-1904.

[66] Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003; 349:160-169; Lamprecht P. Off balance: T-cells in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. *Clin Exp Immunol*. 2005; 141:201-210.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 2

POLYARTERITIS NODOSA

Loïc Raffray[1] and Loïc Guillevin[2,*]
[1]Department of Internal Medicine, Hôpital Félix Guyon,
Centre Hospitalier Universitaire Réunion, Saint-Denis, Réunion Island, France
[2]Department of Internal Medicine, National Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris,
University of Paris Descartes, Paris, France

ABSTRACT

Polyarteritis nodosa is an exemplary multi-systemic medium-sized, primary systemic vasculitis of adults and children. Once the most frequent vasculitis, it has become progressively less common notably in developed countries due to eradication of hepatitis B virus infection, one of its most frequent causes. The evolution of clinical manifestations commences with the acute phase of neutrophilic and variable lymphocytic and eosinophilic inflammation of arterial vessel walls with medial necrosis, followed by aneurysm formation, and later by the healing of lesions that entrains fibrotic endarteritis and vascular occlusions. The coexistence of necrotizing vasculitis, healed lesions and normal arteries in different tissues or portions of the same tissue is a pathognomonic feature of the disease. Effective treatment of polyarteritis nodosa, which includes consideration of corticosteroids and cyclophosphamide depending upon the presence of favorable or unfavorable prognostic factors, and an antiviral agent if complicated by hepatitis B infection, have improved the 5-year survival of patients. This chapter considers aspects of the classification criteria, epidemiology, etiopathogenesis, main clinicopathologic features, treatment and outcome of PAN.

Keywords: polyarteritis nodosa, vasculitis, CNS, PNS, systemic vasculitis

* Corresponding Author's Email: loic.guillevin@aphp.fr.

INTRODUCTION

In 1852, Carl von Rokitansky, Professor of Pathology at the University of Vienna described polyarteritis nodosa (PAN) in a 23-year-old man with a 5-day history of fever and diarrhea [1]; Küssmaul and Maier [2] rediscovered the disorder in 1866. Within decades, PAN was one of the most frequent vasculitides which became progressively less common in developed countries as a consequence of the eradication and treatment of one of its most frequent causes [3], hepatitis B virus (HBV) infection. This chapter reviews the classification criteria, epidemiology, etiopathogenesis, main clinicopathologic features, treatment and outcome of PAN.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Table 1. 1990 ACR criteria for the classification of polyarteritis nodosa*

Criterion		Definition**
1.	Weight loss >4 kg	Loss of ≥4 kg of body weight since illness began, not due to dieting or other factors
2.	Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
3.	Testicular pain or tenderness	Pain or tenderness of the testicles, not due to infection, trauma or other causes
4.	Myalgia, weakness, or leg tenderness	Diffuse myalgia (excluding shoulder and hip girdles), or weakness of muscles or tenderness of leg muscles
5.	Mononeuropathy or polyneuropathy	Development of mononeuropathy, mononeuropathy multiplex, or polyneuropathy
6.	Diastolic BP > 90 mm Hg	Development of hypertension with the diastolic BP > 90 mm Hg
7.	Elevated BUN or creatinine	Elevation of BUN > 40 mg/dL (14.3 mmol/L) or creatinine >1.5 mg/dL (132 µmol/L), not due to dehydration or obstruction
8.	Hepatitis B virus	Presence of hepatitis B surface antigen or antibodies in serum
9.	Arteriographic abnormality	Arteriogram showing microaneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or non-inflammatory causes
10.	Biopsy of small- or medium-sized artery containing neutrophils	Histological changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

* Adapted from, reference [4].

** For classification purposes, a patient with vasculitis shall be said to have PAN if at least 3 of these 10 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%.

Abbreviations: ACR, American College of Rheumatology; BP, blood pressure; BUN, blood urea nitrogen; kg, kilogram; mmHg, millimeters of mercury.

In 1990, the American College of Rheumatology (ACR) (Table 1) established criteria for the classification of PAN [4], and although frequently cited, it did not distinguish between PAN and microscopic polyangiitis (MPA). These two disorders were initially considered different forms of the same disease because of similar main clinical manifestations. However, the two entities were clearly distinguished by the 2012 Revised Chapel Hill Consensus Conference

(CHCC) Nomenclature [5], defining PAN as a necrotizing arteritis of medium- or small-sized arteries without glomerulonephritis, vasculitis in arterioles, capillaries or venules; and absent anti-neutrophil cytoplasm antibodies (ANCA). While both disorders involve the kidneys such as glomerulonephritis in MPA and vascular nephropathy in PAN, the former is associated with lung capillaritis while the latter has at most subclinical lung involvement. Moreover, the two disorders may be difficult to discern when nephropathy and lung capillaritis are absent, and especially when tissue biopsy does not distinguish involved vessel types or size. The 2012 Revised CHCC Nomenclature classifies PAN in the category of medium-sized vessel vasculitis (MVV), and vasculitis associated with a probable etiology when associated with HBV infection. ANCA serology, so noted in the majority of patients with MPA and other small-sized–vessel vasculitides (SVV) including granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), is virtually never detected in PAN. Accordingly, a positive ANCA serology excludes the diagnosis in a given patient. It is important to emphasize that the Chapel Hill Consensus defined the nosology of vasculitides, but not the diagnostic criteria. Given that the 1990 ACR criteria are misleading, internationally recognized criteria are needed. Table 2 lists criteria useful in the diagnosis of PAN [6].

EPIDEMIOLOGY

PAN affects all racial and ethnic groups with an estimated annual incidence in the general population from 4.6 per 1,000,000 inhabitants in England [7], to 9.0 per 1,000,000 inhabitants in Olmsted County, Minnesota, to 77 per 1,000,000 inhabitants in a hepatitis B-hyperendemic Alaskan Eskimo population [8]. In a German study [9], the incidence of PAN was 0.3 to 0.4 per 1,000,000 inhabitants depending on the year and part of the country. A comparison of the incidence of PAN among two European areas of Lugo, Spain, and Norwich, United Kingdom (UK) found insignificant incidence differences of 6.2 and 9.7 and 1,000,000 inhabitants [10, 11]. In France, the prevalence of PAN was 34 per 1,000,000 inhabitants in Seine–Saint-Denis, a northern suburb of Paris [12].

Table 2. Diagnostic criteria for adult-onset polyarteritis nodosa*

Criteria**	OR	95% CI	R^2
Positive for PAN			
HBV infection	16.85	6.30–45.08	0.320
Myalgia	1.93	1.06–3.53	0.517
Mononeuropathy or polyneuropathy	3.36	1.93–5.86	0.619
Arteriographic abnormalities	20.40	7.30–56.99	0.640
Testicular pain or tenderness	5.27	1.98–28.26	0.661
Negative (exclusion) for PAN			
ANCA-positivity	0.11	0.05–0.23	0.668
Glomerulonephritis	0.07	0.02–0.29	0.674
Recent asthma onset	0.01	0.01–0.06	0.433

* Adapted from reference [6]. **Based on the analysis of 582 systemic vasculitis patients with all data available in the French Vasculitis Study Group's database: 194 PAN (among whom 117 had HBV-related PAN) and 388 other systemic vasculitides (GPA, n = 144; EGPA, n = 115; MPA, n = 101; cryoglobulinemia, n = 28). Abbreviations: OR, odds ratio; CI, confidence interval; R, coefficient of determination.

The incidence of PAN has dramatically declined in parallel with HBV infection [3], and is now very rare indeed. Public health measures including vaccine prophylaxis, blood-transfusion safety and other prophylactic measures against infectious exposure have resulted in the sharp drop in the annual number of PAN cases, suggesting a contributory infectious etiopathogenesis. Although HBV infection is a known cause of PAN, other infectious agents including viruses may be implicated in its onset. Although incidence of PAN has significantly decreased, paralleling HBV infection control, the incidence of PAN not related to HBV seems to increase again in France.

PATHOGENESIS

The immunopathogenic mechanisms leading to vascular injury in PAN are likely heterogeneous and remain largely unexplained. Vascular inflammation is the consequence of immune-complex (IC) mediated lesions [13–15]. When HBV infection causes PAN, evidence supports IC disease with HBV surface antigen (HBsAg) as the triggering factor [16, 17]. Almost all patients with HBV-related-PAN are associated with wild-type HBV, HBe antigenemia and high HBV replication, bolstering the concept that lesions could result from the deposition of soluble HBV antigen–antibody complexes in antigen excess, possibly involving HBeAg. Immune complexes could activate the complement cascade, the activated components of which could in turn attract and stimulate neutrophils. Circulating HBV-related antigens, distinct from HBeAg may be involved, as could direct endothelial cell injury due to viral replication [18]. Anti-endothelial cell autoantibodies (AECA), directed against antigens expressed on the endothelial cell surface, have been implicated as a pathogenic factor participating in vasculitis [19] leading to direct endothelial damage. There is yet little known of the possible vasculitic target autoantigens and whether AECA are of pathogenic significance. However, the sera of some patients with PAN and AECA recognize a 60-kDa heat-shock protein [20, 21]. Markedly increased interferon (IFN)-α and interleukin (IL)-2 levels, and moderately elevated tumor necrosis factor (TNF)-α and IL-1β levels were detected in the sera of patients with PAN [22]. Inflammatory infiltrates, mainly macrophages and T-cells, particularly of CD8+ subset, were observed in perineural and muscle vessels of patients with PAN [23]. T-cell–mediated immune mechanisms likely play a role in the development and perpetuation of PAN lesions however to date there have been no experimental animal models. A PAN-like disorder in *cynomolgus* macaques [24, 25] very similar to the human disease sporadically occurs.

ETIOLOGY AND PRECIPITATING FACTORS

Relation to HBV Infection

Trepo and colleagues [16, 26] described the close relation between PAN and HBs antigenemia. In 1987 Guillevin and colleagues [3] reported one of the first addict patients who were proven to be contaminated by intravenous drugs. Intravenous drug abuse and sexual transmission of HBV to at risk, non-vaccinated individuals are the major causes of HBV-related

PAN. The development and distribution of anti-HBV vaccines to at-risk individuals explains the dramatic decrease in the number of new cases since 1989. Over the past few years, the frequency of HBV-related PAN has progressively declined and almost disappeared. Indeed, for the last 5 years, fewer than five cases have been identified annually throughout France.

Other Etiologies

In spite of occasional anecdotal cases [27], neither hepatitis C (HCV) nor GB virus, the latter phylogenetically related to the former were considered etiologically important in the development of PAN. Although there were several reported patients with parvovirus B19-infection [28], systematic testing of PAN patients did not find their occurrence to be statistically significant compared to controls [29]. Calabrese [30], and Gisselbrecht and colleagues [31] suggested a role for human immunodeficiency virus type 1 (HIV1) in the development of vasculitis. A close relation between hairy-cell leukemia and PAN was suggested by Elkon and colleagues [32, 33], but the relation to other malignancies has not been apparent. A Cleveland Clinic Foundation retrospective study by Hutson and coworkers [34] reported 69 patients with systemic vasculitis and malignancy, twelve of whom had both diseases occurring in same twelve months period, including two with PAN.

In 2014 a new monogenic autoinflammatory disease has been characterized, with many clinical and pathological features corresponding to hallmarks of PAN [35, 36]. The newly named DADA2 (Deficiency in Adenosine DeAminase 2) corresponds to a loss-of-function mutation in the CECR1 gene (Cat Eye syndrome Chromosome region 1). Although the role of ADA2 protein as a growth and differentiation factor for monocytes is known, the underlying pathophysiological mechanisms of the disease remain unclear. Children may present with necrotizing vasculitis, mimicking PAN, with strokes and hypogammaglobulinemia. Nevertheless, adult-onset cases have been reported and clinicians should be aware of this misleading disease for which new mutations have been described recently [37, 38]. DADA2 could be considered as a differential diagnosis for patients diagnosed as PAN if they have a family history of vasculitides, early stroke, an immune deficiency, or fail to respond to conventional therapy. Indeed, conventional immunosuppression is frequently ineffective while TNF-α blockers show interesting results [37, 39, 40].

We recommend CECR1 screening for unaffected siblings of index cases, cases of familial vasculitis, and cases of PAN that is resistant to standard treatment. Indeed, ADA2 deficiency could be a differential diagnosis of PAN or one of its cause. The phenotypic expression of PAN is common to infectious or non-infectious disease and shows that PAN could be a heterogeneous disease, due to different etiologies or pathogenic mechanisms. It may be that the individualization of ADA2 deficiency is one of the steps in deciphering PAN.

PATHOLOGY

PAN lesions can occur in any artery, but involvement of the aorta, other large elastic arteries and the pulmonary vasculature have rarely been described. The acute phase of arterial wall inflammation is characterized by fibrinoid necrosis of the media and intense pleomorphic

cell infiltration, with predominant neutrophil and variable lymphocytic and eosinophilic inflammatory cells. The normal architecture of the vessel wall, including the elastic lamina, is completely destroyed and replaced by a band of amorphous eosinophilic material that resembles fibrin when appropriately stained. Arterial aneurysms and thromboses can occur at lesion sites. Arterial healing is characterized by fibrotic endarteritis that can lead to aneurysm regression or when too abundant, vascular occlusion. A characteristic histological feature of PAN is the coexistence of necrotizing vasculitis and healed lesions or normal arteries in different tissues or in portions of the same tissue sample. Indeed, the lesions are usually segmental with presence of damages of different ages.

SPECIFIC ORGAN SYSTEM MANIFESTATIONS

Clinical Features

Table 3 shows the main clinical manifestations of PAN. This disorder occurs in patients of all ages, including children and the elderly, albeit most often between the ages of 40 and 60 years, without sexual predominance. A poor general condition is common, with two-thirds of patients experiencing weight loss and fever. Non-specific symptoms which occur early in the course of disease may be present at onset or even the singular manifestation. Although PAN is most often diagnosed after systemic manifestations appear, it is important to consider the diagnosis among individuals with unexplained or prolonged poor general health.

Table 3. Main Organ or System Involvement and Clinical Manifestations of Polyarteritis Nodosa in the Literature

Reference	Patients (n)	Mean age	Organ/system involved or manifestation (%)						
			Heart	Hyperten-sion	Skin	CNS	PNS	Kidney	GI
Pagnoux et al. [41]	348	51	22	35	50	5	74	51	38
Günal et al. [42]	15 (children)	10	67	20	20	0	0	13	47
Travers et al. [43]*	17	41	89	29 (mild) 41 (severe)	65	41	59	77	65
Schrader et al. [44]*	36	–	61	72	–	–	–	76	–
Fortin et al. [45]	45	54	18	–	44	24	51	44	53
Cohen et al. [46]*	53	54	4	14	58	–	60	66	25
Leib et al. [47]*	64	47	30	25	28	25	72	63	42
Frohnert et al. [48]*	130	–	10	–	58	3	52	8	14
Guillevin et al. [49]	165	48	23	31	46	17	67	29	31
Ludici et al. [50]	21 (children)	11	10	14	81	–	38	24	19

*These older studies may have included PAN patients who would now be diagnosed as having MPA.
Abbreviations: CNS, central nervous system; GI, gastrointestinal; PNS, peripheral nervous system.

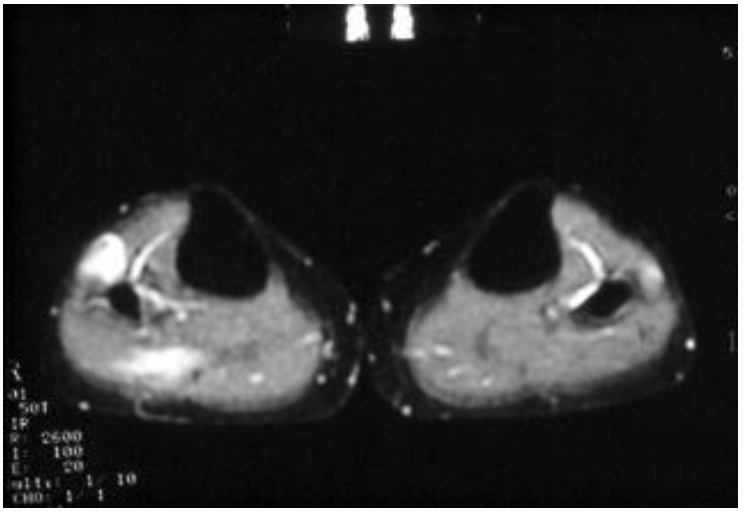


Figure 1. Peroneus muscle hyperintense signals on T_2-weighted MRI in a PAN patient with skeletal muscle involvement.

Myalgia and Arthralgia

Up to one-half of patients have variably intense, diffuse and spontaneous myalgia, with normal or slightly elevated muscle enzyme levels. Amyotrophy may be marked reflecting weight loss sometimes exceeding 20 kilograms (kg), or underlying peripheral neuropathy. Affected patients may be bedridden due to pain severity and amyotrophy. Magnetic resonance imaging (MRI) of painful muscles can show hyperintense signal intensities on T_2-weighted enhanced images after administration of gadolinium (Figure 1) due to inflammatory lesions. Skeletal muscle MRI, which correlates poorly with the presence of vasculitis, is not recommended in the selection of the site for muscle biopsy. Rather, the biopsy should be performed distally in an affected limb especially in painful areas to maximize pathogenic vasculitic lesions which may be in differing stages of evolution. Arthralgia occurs in the knees, ankles, elbows and wrists, rather in the shoulders or hips; arthritis is typically absent and joint deformities do not occur.

NERVOUS SYSTEM INVOLVEMENT

Peripheral Neuropathy

Peripheral neuropathy is the most common peripheral nervous system (PNS) manifestation, so noted in up to 75% of affected patients [41, 48], and may be the earliest symptom in up to a third. Segmental edema precedes the development of cranial nerve palsy reflecting capillary-permeability dysfunction. Hypo- and hyperesthesia, dysesthesia and frank pain, resulting from sensory nerve involvement, are prominent and earliest presenting complaints. Motor deficits typically affect the legs often preceding sensory involvement, commencing suddenly with involvement of one nerve at a time, termed mononeuritis or

mononeuropathy multiplex, in one-half to two-thirds of patients [41, 51]. The peripheral neuropathy is typically distal and asymmetric, preferentially affecting the fibular, sural, radial, ulnar, and median nerves. A symmetrical process may be observed due to the coalescence of nerve lesions. Cerebrospinal fluid (CSF) findings are typically normal and electromyography (EMG) and nerve conduction studies (NCS) are compatible with an axonopathy process evidenced by reduced compound muscle action potential (CMAP) amplitudes with normal or near normal conduction velocities. Rare patients are encountered with brachial plexus neuropathy [52] and peripheral motor conduction block [53] indicative of a demyelinating process similar to Guillain–Barré syndrome or other acquired demyelinating neuropathies, and peripheral nerve entrapment [54]. Isolated sensory neuropathy is a rare complication of PAN and may be the consequence of isolated small fiber involvement vasculitis [55]. Mononeuropathy multiplex regresses slowly and improves to a variable degree in over 12 to 18 months following effective therapy without residual lesions, however paresthesia can persist longer or indefinitely.

Isolated peripheral nerve vasculitis, categorized as a single organ vasculitis (SOV) [56] by the 2012 Revised CHCC Nomenclature [5], differs from the isolated phenotypic expression of PAN that often conveys a more benign and chronic outcome.

Central Nervous System Manifestations

Central nervous system (CNS) involvement was observed in 4.6% of patients with PAN [41]. Affected patients with encephalopathy have altered cognitive function with disorientation, psychosis, hallucinations. There can be focal or multifocal neurological disturbances leading to seizures, strokes or subarachnoid hemorrhages [57] resulting from focal cerebral arteritis leading to cerebral artery-aneurysm rupture and hematoma, alternatively due to malignant hypertension. Distal occlusion of spinal vessels engenders sphincter dysfunction [58]. MRI of the brain typically shows non-specific T_2-weighted white matter subcortical hyperintensities, while MR angiography (MRA) and conventional cerebral angiography may be normal.

Cranial Nerve Manifestations

Albeit rare, involvement of the oculomotor, trochlear, abducens, facial, and vestibulocochlear nerves are most often affected in PAN [59]. Effective treatment can lead to partial or full recovery, which is less likely in the vestibulocochlear nerve [60]. There may be vasculitis of the optic nerve, optic chiasm or occipital cortex. Cerebrospinal fluid is typically normal.

Dermatologic Manifestations

Despite involvement of medium-sized vessels, one-half of patients with systemic PAN have cutaneous lesions [41] including cutaneous and subcutaneous nodules, and palpable purpura, which can be bullous or necrotic (Figure 2). Skin nodules occur in clusters along the trajectories of superficial arteries, often disappearing spontaneously over a few days prior to

new lesions. Palpable nodules can reach a size of 20 mm. Skin ulcerations and livedo reticularis occur less frequently [47]. The latter is typically localized to the legs, the backs of the arms, and sometimes the trunk with a fish net reticular pattern of infiltrated areas. Painful distal ulcerations may be associated with ischemia of the fingers and toes, and distal gangrene. Digital ischemia should lead to consideration of cholesterol and atherosclerotic emboli. Angiography demonstrates vascular stenosis or microaneurysm formation [61].

PAN may be limited to the skin for decades before development of systemic vasculitis, without systemic involvement, abnormal biological markers of inflammation or circulating autoantibodies [62, 63]. Skin relapses are not uncommon.

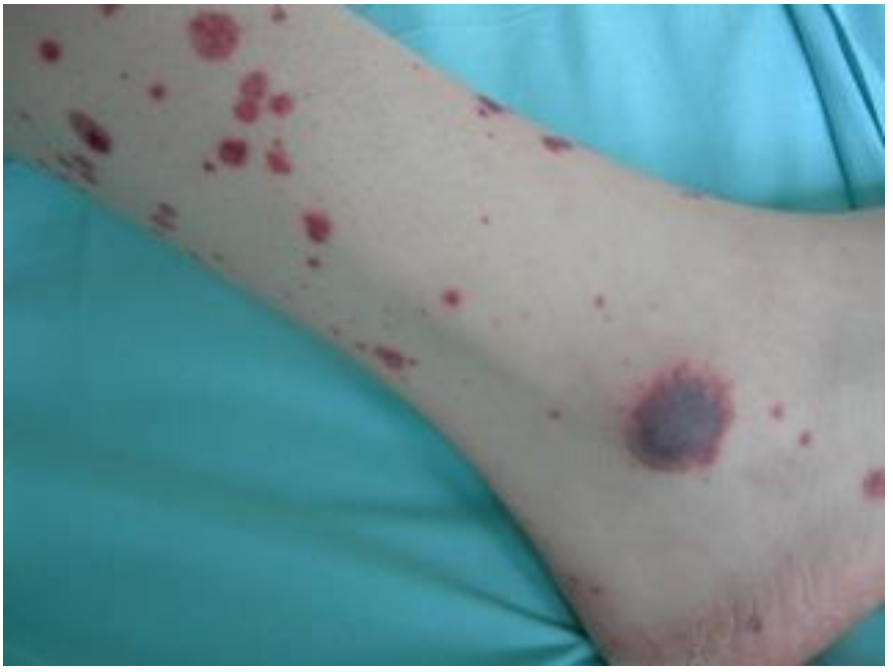


Figure 2. Necrotic purpura in the legs and ankles of a patient with PAN.

Renal Manifestations

Renal manifestations result from medium-sized–vessel involvement leading to renal infarcts and microaneurysm formation. Malignant arterial hypertension [64], which occurs in 6.9% of patients [41], reflects vascular ischemic nephropathy. Renal insufficiency is an overall poor prognostic factor [65]. Angiography shows renal parenchymal infarction (Figure 3), with characteristic multiple stenosis and microaneurysms of branches of celiac, mesenteric and renal arteries (Figure 4). Microaneurysms can spontaneously rupture notably after renal biopsy, the latter of which is strongly contraindicated when microaneurysms are present. Renal hematoma can be extensive requiring embolization [66] or nephrectomy [67]. Acute renal insufficiency can occur soon after onset or following a disease flare. Plasma exchanges may be required initially however renal function is unpredictable. Some patients develop end-stage renal failure decades after the first PAN flare.

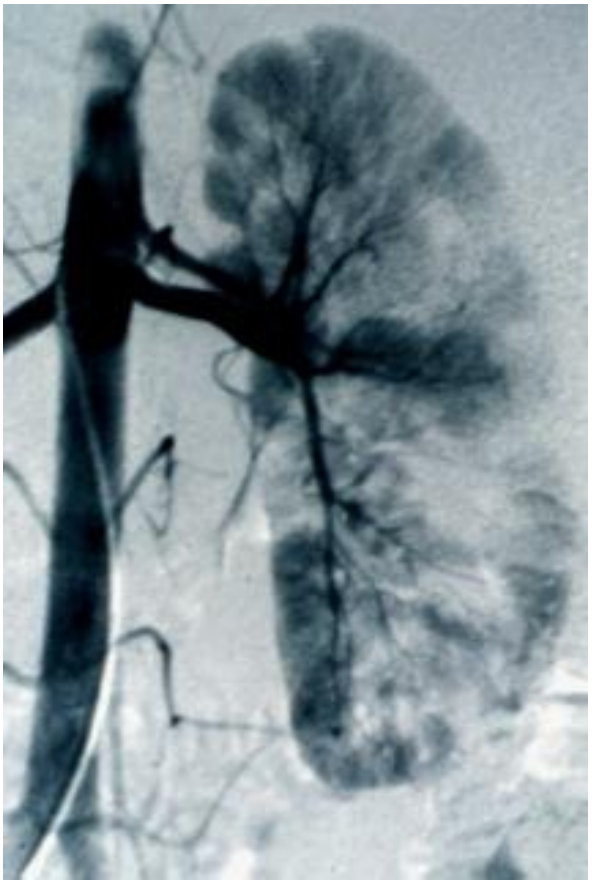


Figure 3. Renal infarcts reflecting vascular nephropathy.

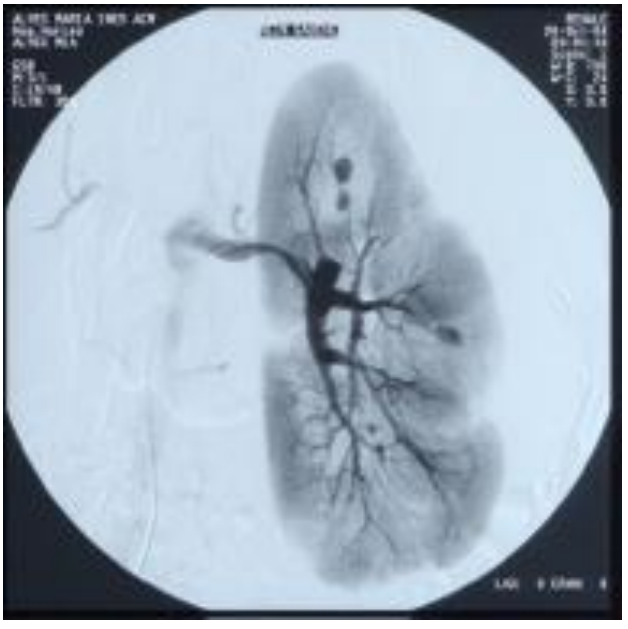


Figure 4. Multiple renal artery microaneurysms.

Cardiac Manifestations

Cardiac involvement was mentioned in the first publication of PAN [2] that described a patient with "nodular coronaritis". Clinical cardiac involvement occurs in 10% of patients with clinical expression of PAN [48], with an increase to 40% after recognition of radiologic and electrocardiographic abnormalities, and in 78% of those studied histopathologically [68]. Although one recent series [41] found cardiac involvement in 22.4% of patients with PAN, this frequency may have underestimated the true occurrence since newer laboratory investigations were not employed to gauge cardiac involvement. Congestive heart failure, the main clinical manifestation of cardiac involvement, reflects both vasculitis of the coronary arteries and its branches with myocardial arteriolar infarcts, and end-organ renovascular or hypertensive disease.

Cardiomyopathy occurs 3 to 4 months after onset of PAN onset. Despite coronary artery vasculitis, angina and myocardial infarctions are uncommon. Among 66 postmortem studied patients, 41 had features of myocardial infarction, of whom three had clinical cardiac symptoms, and three had coronary atherosclerosis [68]. Coronary angiography and CT of the coronary arteries demonstrate coronary involvement in most affected patients with clinical signs of myocardial infarction, and in some, the latter be a result of small coronary artery vessel vasculitis or vasospasm [69]. Coronary artery aneurysm, notably in children, suggests Kawasaki disease (KD), however rupture of them is uncommon but severe, because it can cause a hemopericardium.

There are no current guidelines for the evaluation of coronary artery involvement in PAN, however cardiac MRI may be promising. Heart murmurs are generally due to anemia and not endocardial involvement, the latter of which is infrequent in PAN such that its presence should lead to an alternative diagnosis. Even less common non-specific pericardial manifestations reflect secondary myocardial involvement so noted in up to 5% of patients with PAN [70]; a frequency that increased to one-third in postmortem series [68]. Supraventricular cardiac arrhythmia and conduction disorders occur in 2 to 19% of PAN patients [68, 71] due to arteritis of the sinus node and neighboring nerve fibers.

Aortic Dissection and Peripheral Vascular Manifestations

These authors have not observed a case of PAN-related aortic dissection, a rare complication that is attributed to diffuse vasculitis of the vasa vasorum which manifested in one such case as fatal tamponade [72]. Dissection of proximal aortic branches and Raynaud phenomenon when present may be complicated by vasonecrosis. Cryoglobulinemia may be found in patients with cardiac disease and HBV-related PAN.

Gastrointestinal Manifestations

Gastrointestinal manifestations are among the most severe in PAN, affecting 38% of patients [41], most often associated with HBV infection, so noted respectively in 50.4% versus 31.1% of patients. While generally reflective of systemic involvement, they may also be the initial findings of PAN [3]. Gastrointestinal complications are a major cause of death in the

first year of disease ranking third after infection and cardiac disease [73]. Abdominal pain was the most common symptom, so noted in 30 to 40% of patients with PAN and overall in 97% of those with gastrointestinal involvement. The intensity and persistence of abdominal pain despite corticosteroids treatment, suggests a vascular cause and confer a less favorable prognosis [74]. Hemorrhage and small intestine perforation are the most feared manifestations with respective reported frequencies of 20% to 50% and 2% to 40% (mean, 5%) [75]. When present, ischemic vasculitis affects the small bowel and more rarely the colon and stomach. Perforation of the esophagus is unusual; and vasculitis of the gallbladder occurs in 2% to 17% of patients [75–77].

Vasculitic appendicitis may be the first manifestation of PAN or a localized form thereof. Patients with isolated and histologically-proven vasculitic appendicitis progress to systemic PAN within five years. The prognosis of closely monitored and surgically treated necrotizing vasculitis of the gallbladder or appendix is generally favorable without immunosuppressant treatment. Acute necrotizing and chronic pancreatitis, the latter often accompanied by pseudocyst formation, were diagnosed in 3.7% of patients [41], however the prognosis is extremely dismal because of the frequent association with small intestinal ischemia and perforation. Exploratory surgery should be performed in such patients to detect underdiagnosed bowel perforation. Digestive malabsorption and exudative enteropathy rarely occurs. The liver and spleen can be involved with or without hematoma formation [78] that may be clinically silent. One patient with fibrinoid necrosis of the splenic artery and later splenic rupture was described [45]. When abdominal pain is present, computed tomography (CT) and MRI of the abdomen can be useful to detect organ infarction and pancreatitis. Gastric and colonic endoscopy can detect areas of ischemia and ulceration that precede perforation. Of note, despite increasing resolution performance of CT and MRI imaging, angiography remains the gold standard to detect microaneurysms.

Angiography, which images areas of organ infarction, hematoma and microaneurysm formation measuring 5 mm in diameter, identifies suggestive areas of arterial stenosis in up to 90% of patients with PAN. Angiography also depicts vascular lesions in renal, celiac, and mesenteric vessels respectively in 54%, 24%, and 14% of patients, although even more often in hepatic and splenic arteries [41, 79] without prognostic significance. While not rapidly fatal, intraperitoneal ruptures of such aneurysms are treatable with selective arterial embolization. Gastrointestinal tissue biopsy, i.e., during GI tract endoscopy or liver fine needle biopsy, rarely detects vasculitis and may be life-threatening with a risk of aneurysm rupture. However, histologic examination of whole organ after surgery is of outmost importance as it regularly confirms diagnosis.

Severe GI manifestations, like bowel perforations and ischemia, peritonitis and intestinal occlusion, confer a poor prognosis [65]. Effective treatment combines prompt surgical intervention and medical therapy with corticosteroid and immunosuppressive treatment.

Testicular Manifestations

Unilateral orchitis and testicular tenderness due to testicular artery ischemia were common findings in PAN, so noted in 17% of patients, although rarely the first manifestation of disease [41, 80]. Indeed, orchitis was included in the 1990 ACR classification criteria of PAN [4]; and although it typically improves with a prompt course of corticosteroids, however in some

instances it can be irreversible. We noted orchitis in association with HBV-related PAN however an etiologic relation between viral infection and testicular manifestations was not discerned [3]. Fertility is usually preserved.

Ureteral and Urogenital Manifestations

Ureteral manifestations are rare and ureteral stenoses are specific of small-sized-vessel vasculitis SVV. Urodynamic and electrophysiological studies may demonstrate detrusor hypoactivity in patients with voiding difficulty when the cause is vasculitis of vasa nervorum supplying the bladder. It is unusual to discern a vasculitic spinal cord etiology for bladder disturbances.

Pulmonary Manifestations

Unlike MPA, GPA and EGPA, pulmonary involvement in PAN is either asymptomatic or subclinical, even when histopathologic involvement is found at postmortem examination. Size of involved vessels in PAN explains the absence of lung manifestations as only bronchial arteries are medium-sized vessels and parenchymal vessels are exclusively small-sized arterioles, capillaries and venules.

Bone Manifestations

Periosteal involvement resulting from pan develops mainly in the legs (Figure 5) with associated pain and localized edema, tissue biopsy of which may reveal underlying necrotizing vasculitis [81, 82].

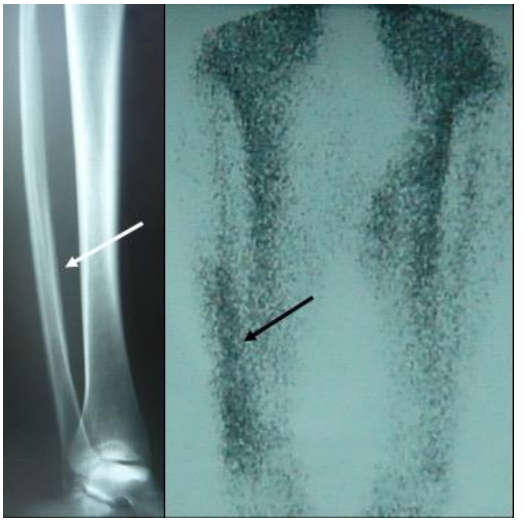


Figure 5. Fibula periostitis during PAN illustrated on X-rays radiograph and nuclear imaging, adapted from [82].

Ophthalmologic Manifestations

Ocular manifestations of necrotizing vasculitis were noted in 42/393 (10.7%) of patients with PAN [83] the most common features of which included blurred vision in 31%, sudden visual loss in 19%, retinal vasculitis in 16.7%, and uveitis in 11.9% of patients. Conversely to AAV, scleritis, episcleritis and other manifestations are rarely observed.

HBV-Related Manifestations

An onset before age 40 years, concomitant malignant hypertension, renal infarction, orchi-epididymitis, gastrointestinal manifestations, and surgical emergencies were all more frequent in HBV-associated infection. Sergent and coworkers [84] noted that two of the three deaths among nine patients were attributed to colon vasculitis. Ischemia was responsible for gastrointestinal and renal manifestations that were due to microaneurysm formation and infarction noted on visceral angiography. Effectively treated, microaneurysms regress on serial angiography [85] that may result from microaneurysmal thrombosis with evolution to fibrosis. Hepatic cytolysis is usually moderate and cholestasis is minor or absent. Liver biopsy pathology exhibits signs of chronic hepatitis even when PAN becomes manifest a few months after HBV infection. HBV-related PAN is acute and initially severe but the outcome is excellent for most patients when adequate treatment is associated with seroconversion. The sequela of vascular nephropathy is similarly favorable in those patients able to obtain substantial recovery with little residual functional renal impairment.

Childhood PAN

PAN is the most common systemic necrotizing vasculitis in children after KD and IgA vasculitis (Henoch–Schönlein purpura or HSP) [86]. Neither the ACR criteria [4] nor the 2012 Revised CHCC Nomenclature [5] were validated for children. The European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) proposed specific classification criteria for juvenile vasculitides [87].

The EULAR/PReS criteria [87] were based mainly on a literature review and a consensus-based process. The primary objective of the 2008 Ankara Consensus Conference was to validate the EULAR criteria for pediatric vasculitides. The final EULAR/PRINTO/PReS childhood PAN (cPAN) classification criteria achieved a sensitivity of 89.6% and a specificity of 99.6% and are indicated in Table 4 [88]. Since their setting, several case-series used these criteria [50, 89]. In the work from the French Vasculitis Study Group's database, among 21 cPAN patients 86% met the criteria [50].

The mean age at diagnosis of childhood PAN is age 9 ± 4 years, with an equal ratio of boys and girls. Clinical manifestations fall within the same spectrum as for adults, except for more frequent cutaneous involvement in children. Indeed, 80% of affected children manifest skin involvement, with a limited cutaneous form accounting for one-third of cases. Prognosis is more favorable for children than adults with an overall mortality rate of 1% to 16%.

Table 4. EULAR/PRINTO/PReS Proposed Classification Criteria for Childhood Polyarteritis Nodosa*

A systemic inflammatory illness characterized by the presence of
-At least 1 mandatory criterion:
1. Biopsy showing small- and medium-sized artery necrotizing vasculitis
2. Angiographic abnormalities on medium or small-sized arteries: aneurysms, stenoses or occlusions †
-Plus 1 among the 5 clinical criteria:
1. Skin involvement: livedo reticularis, skin nodules, superficial or deep skin infarctions
2. Myalgia or muscle tenderness
3. Systemic hypertension, greater than 95th percentile for the age
4. Peripheral neuropathy: mononeuropathy or polyneuropathy
5. Renal involvement: abnormal urine analysis (proteinuria >0.3 g/24h or hematuria) and/or impaired renal function with GFR < 50% of normal

* Adapted from reference [88] †Should include angiography if MR angiography is negative. Abbreviations: EULAR/PRINTO/PReS, European League against Rheumatism/Pediatric Rheumatology Inter National Trials Organization/Pediatric Rheumatology European Society; GFR, glomerular filtration rate.

Relapses are more frequent and occur only many years following diagnosis, sometimes preceded by ear, nose and throat infections. Penicillin can contribute to a cure by effectively lowering the relapse rate when *Streptococci* are involved as the cause or target factor [90]; however, the optimal antibiotic regimen is unknown. Relapses have been described up to 20 years after the first episode.

LABORATORY EVALUATION

Inflammation markers are found in the majority of patients. A one-hour erythrocyte sedimentation rate (ESR) >60 mm is noted in three-quarters of patients; and an elevated C-reactive protein, α-2 globulin levels and white blood-cell counts in one-half to three-quarters of patients. Eosinophilia >1,500/mm^3 and normochromic anemia can occur. HBsAg and ANCA serology should be routinely tested.

As previously described, the DADA2 syndrome can mimic PAN, therefore genetic testing should be performed for the following: childhood-PAN-like presentation with familial history of vasculitis or early stroke for the patient, unresponsiveness to standard therapy protocols.

IMAGING

Bron and coworkers [91] showed the diagnostic value of angiography in visualizing saccular or fusiform microaneurysms measuring 1 to 5 mm in diameter, and stenosis in medium-sized vessels. Although not pathognomonic for PAN, they are predominantly seen in the kidneys, mesentery and liver. Angiography is a useful tool when other diagnostic examinations are negative, especially when abdominal pain and nephropathy are present. As cited for HBV-related PAN, the microaneurysms may disappear after several months with the resolution of the causative agent [85].

Of note, despite increasing resolution performance of CT and MRI imaging, angiography remains the gold standard to detect microaneurysms as these technics currently fail to detect

such aneurysms in all cases [92]. Nonetheless, it is likely that in the future invasive angiography is abandoned thanks to imaging progress.

Unlike large-vessel vasculitides, PET/CT scan usage as a diagnosis tool appears limited in PAN, mainly due to the smaller size of affected vessel. Nonetheless its positivity has seldom been reported as localized [93] or diffuse [94] 18-FDG uptake. Therefore PET/CT is not routinely recommended for PAN diagnosis or follow-up.

PROGNOSIS AND OUTCOMES

Table 5. Causes of Death in Polyarteritis Nodosa*

	Gayraud et al. [95]	Cruz et al. [102]	Cacoub et al. [104]	Leib et al. [47]	Cohen et al. [46]	Guillevin et al. [3]	Pagnoux et al. [41]
Number of patients	278	26	165	64	53	115	348
Type of vasculitis (n)	HBV-related PAN (63), PAN (93), MPA (58) and CSS (64)	Patients admitted to ICU, PAN (5), MPA (4), CSS (7) and others (10)	PAN	PAN	PAN	HBV-related PAN	PAN
Deaths, n (%)	85 (31)	2/5 PAN (20)	61 (37)†	32 (50)	22 (42)	41 (36)	86 (24.7)
Progressive vasculitis	22 (26)	0	21 (43)†	20 (63)	–	11 (27)	29 (33.7)
Bowel infarction	10	–	8	–	6 (27)	7	
Cardiac failure	5	–	4	–	–	1	
Multi-visceral involvement	3	–	2	–	–		
Renal failure	3	–	5	–	6 (27)		
Stroke	1	–	2	–	–		6 (7)
Infectious treatment side effects	11 (13)	2 (100)	13 (27)	2 (6)	–	4 (10)	
Bacterial pneumonia	5	1	11	–	–	–	
Septicemia	6	1	6/11	–	–	3/4	10 (11.6)
Sudden deaths	9 (11)	0	3 (6)	–	–	1 (2)	12 (14)
Heart disease	8 (9)	0	6(12)†	5 (16)	8 (36)‡	5 (12)‡	
Cancer	13 (15)	0	5 (10)	1 (3)	1 (5)	3 (7)	5 (5.8)
Pulmonary embolism	3 (3.5)	0	2 (4)	–	–		
Chronic respiratory disease	3 (3.5)	0	–	–	–		
End-stage renal disease	–	–	–	3 (9)	–		
Fulminant viral hepatitis	2 (2)	0	–	–	–	1 (2)	
Miscellaneous	14 (17)	0	2 (4)	1 (3)	1 (5)	16 (39)	24 (27.9)

* Including HBV-associated PAN. †Some patients may have died for example from heart disease due to vasculitis alone, treatments or other associated conditions, not always specified; hence, the total of listed causes exceeds 100%. ‡Includes cerebrovascular and cardiovascular complications. Abbreviations: ICU, intensive care unit; n, number.

Untreated, 12% of patients with PAN survived [48]. However, with effective therapy the overall survival rate exceeded 80% [95] for PAN alone, and 70% in those with associated HBV infection [3]. A systematic retrospective study of 348 patients with PAN registered in the French Vasculitis Study Group (FVSG) database [41] satisfying ACR [4] and CHCC

Nomenclature [5], and followed for 68.3 months showed relapses in 76 (21.8%) and deaths in 86 (24.7%). Mortality and relapse rate were significantly different between PAN groups with and without HBV infection. HBV infection appears associated to higher mortality but lower relapses rates. Indeed, 44 patients died (19.6%) with PAN alone versus 42 (34.1%) with associated HBV infection ($P = 0.003$). Regarding relapses, 63 (28%) relapsed with PAN alone versus 13 (10.6%) with associated HBV infection ($P < 0.001$) and the 5-year relapse-free survival rate for PAN was 59.4% (95% confidence interval [CI] 52.6–67.0) versus 67.0% (95% CI 58.5–76.8) with HBV-associated infection.

Age is another important prognosis factor. As previously detailed for cPAN, early-onset of the disease is associated with lower mortality, although higher relapse rates. This has been further confirmed in pediatric case-series [89, 96] and with direct comparison between adult- and childhood-onset PAN [97]. Of note, age is part of the prognostic FFS score detailed further.

Fulminating vasculitis, which may manifest gastrointestinal involvement, renal failure, pulmonary hemorrhage and rarely, cerebral involvement, may be unresponsive to treatment resulting in excessive mortality and morbidity in the first few months following diagnosis.

Relapse

In contrast to GPA and MPA, remission once obtained, disease tends to recur less frequently during first years in PAN. The outcome is even better during HBV-related PAN: in one large cohort [95] 8% of the HBV infection-associated PAN and 19% of the HBV-free PAN demonstrated a first relapse at 37 months and 29 months from disease onset respectively. In another cohort study, only 10% with HBV-related PAN relapsed [3]. Relapses associated with HBV infection occur in those with persistent active virus replication after treatment. A stepwise multivariate analysis [41] calculated hazard ratios (HR) and CI for independent predictors of relapse that included, HBV-related PAN (2.27 [95% CI 1.11–4.63) and cutaneous manifestations at diagnosis (HR 1.85 [95% CI 1.08–3.23]), especially when only nodules were considered (HR 2.21 [95% CI 1.30–3.78]) Although the severity of relapses was unpredictable, rash and arthralgia conferred a more favorable prognosis for a less severe disease status compared to the initial clinical presentation. Long-term follow-up studies until 8 to 10 years from disease onset indicated relapses rate of approximately 50% [98, 99].

Mortality

The major causes of mortality in PAN are shown in Table 5. Mortality can be divided into two types: those attributed to the vasculitic process involving major organ and others due to severe treatment-related side effects. While a few patients may die during the first few months of the disease due to unresponsiveness to treatment [73], the majority occur with longer durations of multi-organ involvement associated with fever and rapid weight loss, especially those with gastrointestinal involvement. Mortality related to treatment side effects generally occur in the years following treatment for controlled or uncontrolled vasculitis with infections representing the primary cause of death due to intense initial therapy with corticosteroids and cytotoxic agents. Viral infections, notably *Pneumocystis jirovecii*, occur later in the course associated with profound drug-induced immunosuppression [100, 101]. A small number of

patients suffer die within the first weeks or months following the diagnosis of PAN despite adequate treatment. Bourgarit and colleagues [73] showed that 38/309 (12%) patients died during the first year predominantly due to vasculitis (58%), while other deaths were related to treatment side effects or factors independent of vasculitis. The primary cause of early mortality in PAN is severe gastrointestinal involvement with associated perforation and hemorrhage, so noted by the FFS [65]; however, HBV infection was not a factor of severity. Among patients hospitalized in intensive care units (ICU), the main prognostic factor for early mortality was predicted by the Acute Physiology and Chronic Health Evaluation (APACHE) [102] which was not specifically devised for vasculitis. Neither the vasculitis-specific Birmingham Vasculitis Activity Score (BVAS) [103] nor the FFS scoring system [65], predicted ICU mortality [102].

TREATMENT

The FFS [105] is a useful guide to treatment, the associated features of which predicted increased mortality: proteinuria >1 g/day, renal insufficiency (serum creatinine >140 µmol/L or 1.6 mg/dL), specific cardiomyopathy, gastrointestinal and CNS involvement. Although treatment should not be overly influenced by FFS criteria [105], they may be considered in deciding the therapeutic strategy. Accordingly, patients lacking the poorest prognostic symptoms (FFS = 0) may be treated with corticosteroids alone to reduce the number and severity of treatment related side effects. This strategy is effective with a few minor relapses necessitating transient dose intensification and addition of an immunosuppressant agent. The 1996 FFS for systemic necrotizing vasculitides was revisited [65]. The following factors were significantly associated with increased 5-year mortality: age >65 years, cardiac symptoms, GI involvement, and renal insufficiency (stabilized peak urinary creatinine ≥150 µmol/L or 1.7 mg/dL) with each accorded +1 point; while ear, nose and throat manifestations were scored –1 point, as they were associated with better outcomes. The 5-year mortality rates for FFS of zero, one, and ≥2, were respectively 9%, 21% and 40%. The same strategy previously described for the 1996 FFS [105] has been applied to patients with PAN. Since then it has been shown that even if patients with FFS = 0 at diagnosis had good overall survival rate, relapses could occur up to 50%, particularly when m mononeuropathy multiplex is present at diagnosis [106]. Moreover, these patients were frequently treated with immune-suppressant therapy as a consequence of GC resistance.

BVAS is another tool frequently used during SNVs to assess severity and prognosis. Comparisons between FFS and BVAS showed conflicting results regarding which one would be the best scoring system for PAN [73, 95, 107]. However, the two scores frequently parallel and FFS is very simple and readily usable in daily clinical practice.

Supportive care represents an important part of the therapeutic regimen for patients with potentially fatal disease. Pain control, prevention of pressure sores and physical therapy may be needed, especially for symptomatic mononeuritis multiplex. Angiotensin-converting-enzyme inhibitors are effective antihypertensive agents in those with renal vasculitis due to the beneficial effect on renal function. Persistent abdominal pain should lead to consideration of exploratory laparotomy to identify treatable bowel perforation; such patients may require medication via intravenous route to circumvent impairment of orally administered drugs. Rapid and severe weight loss due to severe gastrointestinal involvement can be counterbalanced with

parenteral nutrition. Although weight loss is not a proven poor prognostic factor [65] common sense dictates the importance of optimizing all factors, notwithstanding optimal weight, that might mitigate increased susceptibility to infection rate with cytotoxic agents. Atherosclerosis is a potentially treatable comorbid factor that can worsen prognosis. The Vasculitis Damage Index (VDI) [108] is a useful measure of the cumulative impact of scars and sequela caused by the disease and its therapy. Since maximal immunosuppression is given at disease onset, antibiotic prophylaxis of opportunistic infections is often necessary but decided on an individual basis.

Immunosuppressant Medication

The introduction of corticosteroids, which led to an improvement in the untreated 5-year survival rate of 10% of the preceding two decades to 55% by mid-to-late 1970s [47, 48], further increased to 82% by the addition of cyclophosphamide and azathioprine [47, 109].

Corticosteroids

Corticosteroids are administered for only a few days in those with HBV infection, but is given as a prolonged course lasting up to one year in the presence of life-threatening organ involvement or the extension phase of mononeuritis multiplex, commencing with pulse methylprednisolone dose of 7.5 to 15 mg/kg IV over 60 min, repeated at 24-h intervals for 1–3 days. The side effects of an empiric dose of pulse-methylprednisolone dose <1000 mg are usually mild and transient in the short term. However, severe side effects which are fortunately rare include sudden death, cardiac arrhythmia, myocardial infarction, gastrointestinal bleeding, and seizures. This is followed by prednisone in doses of 1 mg/kg/day or the equivalent dose of methylprednisolone for two to three weeks after which tapering can begin. The FVSG trial [110] which tapered the corticosteroid dose by one-half to 20 to 30 mg per day by three months, aimed for a dose of 10 mg by six months, and 5 mg by one year. This gradual reduction had the advantage of limiting side effects. The results of a prospective trial devoted to treatment of vasculitides in the elderly ≥65 (CORTAGE) noted that the dose of corticosteroids could be even lower and still retain disease-free survival benefits [111].

Cyclophosphamide

Cyclophosphamide can be administered in combination with corticosteroids at a dose of up to 2 mg/kg/day oral route for three to six months. However, it is associated with major side effects including, hemorrhagic cystitis, bladder fibrosis, bone-marrow suppression, ovarian failure, bladder cancer, and hematological malignancy [112]. In addition, life-threatening infection can supervene when given in conjunction with high dose corticosteroids [73, 95]. Protocols employing intermittent treatment with higher dose of cyclophosphamide to limit the associated morbidity of daily doses were developed for the treatment of PAN [113]. Intravenous pulse cyclophosphamide is preferable to oral cyclophosphamide in the treatment

of systemic necrotizing vasculitis. The FVSG protocol employs a dose of 0.6 g/m^2 given every two weeks for three pulses, followed by a schedule of every three weeks for a total of six treatments. The analysis of 2 cyclophosphamide regimen strategies, 6 vs 12 months treatment, during PAN and GPA was performed after a 10-year follow-up period of the CHUSPAN trial [99]. None of the strategies was superior, indicating 6 months may be a sufficient duration for cyclophosphamide. After initial cyclophosphamide regimen, a maintenance therapy with azathioprine or methotrexate, as recommended in the treatment of AAV [114, 115], is an acceptable yet invalidated approach in PAN. For patients over 65 years, the CORTAGE study indicated that low-dose of cyclophosphamide, i.e., maximum of 6 pulses of 500 mg each, was similar to classical FSVG protocol in terms of remission, but with a lower rate of severe adverse events [111].

For pediatric PAN, treatment is currently based on adult recommendations as no controlled trial has been performed specifically in this population. The MYPAN study in childhood PAN aims at comparing cyclophosphamide and mycophenolate mofetil as experts in the field judge this drug could be a good alternative [116].

It is the authors' opinion that cyclophosphamide should be given judiciously based upon the anatomical location and severity of PAN involvement, rather than to all PAN patients. Oral low-dose cyclophosphamide was successfully employed to control disease activity and relapses within the first six months of treatment in patients with systemic vasculitis who failed to respond to pulse intravenous high-dose regimen [117]. Patients with PAN and associated poor-prognostic factors should be treated with combination corticosteroids and cyclophosphamide for six months, followed by a corticosteroid agent and less toxic immunosuppressant such as azathioprine or methotrexate. Patients without such poor prognostic factors can be treated safely with corticosteroids alone and adjuvant immunosuppression introduced only in cases of treatment failure for disease control [118]. This is confirmed by the CHUSPAN2 randomized controlled trial that compared standard corticosteroid therapy to adjunction of azathioprine in SNVs and PAN without poor prognosis factors. After 12-months treatment period, the main end-points at 24 months were not significantly different between two groups for relapses rate, mortality, adverse events [119].

Other Cytotoxic Agents

Azathioprine, methotrexate and other cytotoxic agents are all reserved for patients with contraindications to the initial or continued use of cyclophosphamide, and as maintenance therapy for up to eighteen months.

Plasma Exchange

There is little support for the use of plasma exchange in PAN in the absence of HBV infection [120], including those with poor-prognosis factors [121]. Plasma exchange is a second-line treatment of PAN refractory to conventional therapy. Its use in patients with AAV is to limit renal disease sequela.

Rituximab

At present, and contrarily to AAV, there is no suitable pathogenic mechanism, published finding, or ongoing study of the use of rituximab in the treatment of PAN. The authors have used rituximab in rare patients with PAN following failure of other treatments.

HBV-Related PAN

Patients treated with conventional regimens of corticosteroids and cyclophosphamide allows HBV to replicate, facilitating the development of chronic hepatitis and liver cirrhosis. Therefore, a preferred initial treatment commences with plasma exchange combined with vidarabine or interferon-α2b, and corticosteroids. This controls the most common life-threatening manifestations of PAN during the first few weeks of disease. Afterward, corticosteroid agent is safely discontinued enhancing the immunological clearance of HBV-infected hepatocytes favoring anti-HBeAb seroconversion. This strategy [122, 123] which is preferred over conventional regimens, was confirmed among 41 patients, 23 (56.1%) of whom no longer exhibited serological evidence of replication, and an overall cure rate of 80.5% [124]. The antiviral agent lamivudine [3], which increases the seroconversion rate from 56.1% to 60%, did not confer additional improvement in the survival rate at 18 months. Those treated with conventional corticosteroids with or without cyclophosphamide and no antiviral drugs demonstrated a mortality rate of 27.5% at 18 months compared to 17.5% when combined antiviral therapy was offered ($P = 0.46$). The benefits of adjunctive antiviral therapy appear after prolonged follow-up, since these drugs lower the risk of cirrhosis or liver failure. In 2017, treatment protocol guidelines for classical HBV infection (without PAN) highlight the need for long-term administration of nucleoside analogues limiting viral resistance such as tenofovir or entecavir [125]. This strategy has not yet been proven useful in HBV-associated-PAN.

Localized PAN

Localized forms of PAN without poor-prognostic factors can be treated initially without immunosuppression, awaiting refractory or relapsing disease. Isolated appendix or gallbladder involvement is associated with a favorable prognosis after surgical removal [126]. Cutaneous PAN, particularly in childhood forms, can be successfully treated with colchicine or dapsone in combination with topical corticosteroids. Colchicine and dapsone are both effective against PAN restricted to skeletal muscles.

CONCLUSION

Polyarteritis nodosa is an exemplary multi-systemic medium-sized, primary systemic vasculitis of adults and children. Once the most frequent vasculitis, it has become progressively less common notably in developed countries due to eradication of hepatitis B virus infection. Effective treatment of polyarteritis nodosa which includes consideration of corticosteroids and

cyclophosphamide depending upon the presence of favorable or unfavorable prognostic factors, and an antiviral regimen when complicated by hepatitis B infection, has improved the 5-year survival of patients.

REFERENCES

[1] Tesar V, Kazderová M, Hlavácková L. Rokitansky and his first description of polyarteritis nodosa. *J Nephrol* 2004; 17:172–174.

[2] Küssmaul A, Maier R. Ueber eine bischer nicht beschreibene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii une rapid fortschreitender allgemeiner Muskellhamung einhergeht. [A peculiar arterial disease (periarteritis nodosa), not described in the case of Bianca, which is associated with Brightii's disease and rapidly progressing general muscular celling.] *Dtsch Arch Klin Med*. 1866:484–518.

[3] Guillevin L, Mahr A, Callard P, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore)* 2005; 84:313–322.

[4] Lightfoot RW, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33:1088–1093.

[5] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1–11.

[6] Henegar C, Pagnoux C, Puéchal X, et al. A paradigm of diagnostic criteria for polyarteritis nodosa: analysis of a series of 949 patients with vasculitides. *Arthritis Rheum* 2008; 58:1528–1538.

[7] Scott DG, Bacon PA, Elliott PJ, Tribe CR, Wallington TB. Systemic vasculitis in a district general hospital 1972-1980: clinical and laboratory features, classification and prognosis of 80 cases. *Q J Med* 1982; 51:292–311.

[8] McMahon BJ, Heyward WL, Templin DW, Clement D, Lanier AP. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. *Hepatology* 1989; 9:97–101.

[9] Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register. *Rheumatology (Oxford)* 2002; 41:540–549.

[10] Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. *Ann Rheum Dis* 2001; 60:170–172.

[11] Watts RA, Lane SE, Scott DG, et al. Epidemiology of vasculitis in Europe. *Ann Rheum Dis* 2001; 60:1156–1157.

[12] Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a

French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum* 2004; 51:92–99.

[13] Trepo CG, Zucherman AJ, Bird RC, Prince AM. The role of circulating hepatitis B antigen/antibody immune complexes in the pathogenesis of vascular and hepatic manifestations in polyarteritis nodosa. *J Clin Pathol* 1974; 27:863–868.

[14] Guillevin L, Ronco P, Verroust P. Circulating immune complexes in systemic necrotizing vasculitis of the polyarteritis nodosa group. Comparison of HBV-related polyarteritis nodosa and Churg Strauss Angiitis. *J Autoimmun* 1990; 3:789–792.

[15] Fye KH, Becker MJ, Theofilopoulos AN, Moutsopoulos H, Feldman JL, Talal N. Immune complexes in hepatitis B antigen-associated periarteritis nodosa. Detection by antibody-dependent cell-mediated cytotoxicity and the Raji cell assay. *Am J Med* 1977; 62:783–791.

[16] Trepo C, Thivolet J. Hepatitis associated antigen and periarteritis nodosa (PAN). *Vox Sang* 1970; 19:410–411.

[17] Prince AM, Trepo C. Role of immune complexes involving SH antigen in pathogenesis of chronic active hepatitis and polyarteritis nodosa. *Lancet* 1971; 1:1309–1312.

[18] Mason A, Theal J, Bain V, Adams E, Perrillo R. Hepatitis B virus replication in damaged endothelial tissues of patients with extrahepatic disease. *Am J Gastroenterol* 2005; 100:972–976.

[19] Cid MC. New developments in the pathogenesis of systemic vasculitis. *Curr Opin Rheumatol* 1996; 8:1–11.

[20] Le Tonquèze M, Dueymes M, Giovangrandi Y, et al. The relationship of anti-endothelial cell antibodies to anti-phospholipid antibodies in patients with giant cell arteritis and/or polymyalgia rheumatica. *Autoimmunity* 1995; 20:59–66.

[21] Jamin C, Dugué C, Alard J-E, et al. Induction of endothelial cell apoptosis by the binding of anti-endothelial cell antibodies to Hsp60 in vasculitis-associated systemic autoimmune diseases. *Arthritis Rheum* 2005; 52:4028–4038.

[22] Grau GE, Roux-Lombard P, Gysler C, et al. Serum cytokine changes in systemic vasculitis. *Immunology* 1989; 68:196–198.

[23] Panegyres PK, Blumbergs PC, Leong AS, Bourne AJ. Vasculitis of peripheral nerve and skeletal muscle: clinicopathological correlation and immunopathic mechanisms. *J Neurol Sci* 1990; 100:193–202.

[24] Porter BF, Frost P, Hubbard GB. Polyarteritis nodosa in a cynomolgus macaque (Macaca fascicularis). *Vet Pathol* 2003; 40:570–573.

[25] Colmegna I, Maldonado-Cocco JA. Polyarteritis nodosa revisited. *Curr Rheumatol Rep* 2005; 7:288–296.

[26] Trepo C, Thivolet J. [Australia antigen, virus hepatitis and periarteritis nodosa]. *Presse Med* 1970; 78:1575.

[27] Servant A, Bogard M, Delaugerre C, Cohen P, Dény P, Guillevin L. GB virus C in systemic medium- and small-vessel necrotizing vasculitides. *Br J Rheumatol* 1998; 37:1292–1294.

[28] Corman LC, Dolson DJ. Polyarteritis nodosa and parvovirus B19 infection. *Lancet* 1992; 339:491.

[29] Leruez-Ville M, Laugé A, Morinet F, Guillevin L, Dény P. Polyarteritis nodosa and parvovirus B19. *Lancet* 1994; 344:263–264.

[30] Calabrese LH. Vasculitis and infection with the human immunodeficiency virus. *Rheum Dis Clin North Am* 1991; 17:131–147.

[31] Gisselbrecht M, Cohen P, Lortholary O, et al. Human immunodeficiency virus-related vasculitis. Clinical presentation of and therapeutic approach to eight cases. *Ann Med Interne (Paris)* 1998; 149:398–405.

[32] Elkon KB, Hughes GR, Catovsky D, et al. Hairy-cell leukaemia with polyarteritis nodosa. *Lancet* 1979; 2:280–282.

[33] Hasler P, Kistler H, Gerber H. Vasculitides in hairy cell leukemia. *Semin Arthritis Rheum* 1995; 25:134–142.

[34] Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: a report of 12 cases. *Arthritis Care Res* 2000; 13:417–423.

[35] Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med* 2014; 370:911–920.

[36] Navon Elkan P, Pierce SB, Segel R, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N Engl J Med* 2014; 370:921–931.

[37] Caorsi R, Penco F, Grossi A, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann Rheum Dis* 2017.

[38] Nanthapisal S, Murphy C, Omoyinmi E, et al. Deficiency of Adenosine Deaminase Type 2: A Description of Phenotype and Genotype in Fifteen Cases. *Arthritis & Rheumatology (Hoboken, NJ)* 2016; 68:2314–2322.

[39] Gonzalez Santiago TM, Zavialov A, Saarela J, et al. Dermatologic Features of ADA2 Deficiency in Cutaneous Polyarteritis Nodosa. *JAMA Dermatol* 2015; 151:1230–1234.

[40] Sahin S, Adrovic A, Barut K, et al. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. *Rheumatol Int* 2017.

[41] Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 2010; 62:616–626.

[42] Günal N, Kara N, Cakar N, Koçak H, Kahramanyol O, Cetinkaya E. Cardiac involvement in childhood polyarteritis nodosa. *Int J Cardiol* 1997; 60:257–262.

[43] Travers RL. Polyarteritis nodosa and related disorders. *Br J Hosp Med* 1979; 22:38, 40, 42–46.

[44] Schrader ML, Hochman JS, Bulkley BH. The heart in polyarteritis nodosa: a clinicopathologic study. *Am Heart J* 1985; 109:1353–1359.

[45] Fortin PR, Larson MG, Watters AK, Yeadon CA, Choquette D, Esdaile JM. Prognostic factors in systemic necrotizing vasculitis of the polyarteritis nodosa group--a review of 45 cases. *J Rheumatol* 1995; 22:78–84.

[46] Cohen RD, Conn DL, Ilstrup DM. Clinical features, prognosis, and response to treatment in polyarteritis. *Mayo Clin Proc* 1980; 55:146–155.

[47] Leib ES, Restivo C, Paulus HE. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med* 1979; 67:941–947.

[48] Frohnert PP, Sheps SG. Long-term follow-up study of periarteritis nodosa. *Am J Med* 1967; 43:8–14.

[49] Guillevin L, Le Thi Huong D u, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. *Br J Rheumatol* 1988; 27:258–264.

[50] Iudici M, Puéchal X, Pagnoux C, et al. Brief Report: Childhood-Onset Systemic Necrotizing Vasculitides: Long-Term Data From the French Vasculitis Study Group Registry. *Arthritis & Rheumatology (Hoboken, NJ)* 2015; 67:1959–1965.

[51] Said G, Lacroix C. Primary and secondary vasculitic neuropathy. *J Neurol* 2005; 252:633–641.

[52] Jamieson PW, Giuliani MJ, Martinez AJ. Necrotizing angiopathy presenting with multifocal conduction blocks. *Neurology* 1991; 41:442–444.

[53] Ropert A, Metral S. Conduction block in neuropathies with necrotizing vasculitis. *Muscle Nerve* 1990; 13:102–105.

[54] Allan SG, Towla HM, Smith CC, Downie AW, Clark JC. Painful brachial plexopathy: an unusual presentation of polyarteritis nodosa. *Postgrad Med J* 1982; 58:311–313.

[55] Collins MP, Arnold WD, Kissel JT. The neuropathies of vasculitis. *Neurol Clin* 2013; 31:557–595.

[56] Abgrall S, Mouthon L, Cohen P, et al. Localized neurological necrotizing vasculitides. Three cases with isolated mononeuritis multiplex. *J Rheumatol* 2001; 28:631–633.

[57] Moore PM, Calabrese LH. Neurologic manifestations of systemic vasculitides. *Semin Neurol* 1994; 14:300–306.

[58] Amarenco P, Amarenco G, Guillevin L, et al. [Vesical neuropathy in systemic vasculitis: 3 cases]. *Ann Med Interne (Paris)* 1988; 139:183–185.

[59] Ford RG, Siekert Rg. central nervous system manifestations of periarteritis nodosa. *Neurology* 1965; 15:114–122.

[60] Vathenen AS, Skinner DW, Shale DJ. Treatment response with bilateral mixed deafness and facial palsy in polyarteritis nodosa. *Am J Med* 1988; 84:1081–1082.

[61] Héron E, Fiessinger J-N, Guillevin L. Polyarteritis nodosa presenting as acute leg ischemia. *J Rheumatol* 2003; 30:1344–1346.

[62] Winkelmann RK, Schroeter AL, Kierland RR, Ryan TM. Clinical studies of livedoid vasculitis: (segmental hyalinizing vasculitis). *Mayo Clin Proc* 1974; 49:746–750.

[63] Diaz-Perez JL, Winkelmann RK. Cutaneous periarteritis nodosa. *Arch Dermatol* 1974; 110:407–414.

[64] Cohen L, Guillevin L, Meyrier A, Bironne P, Blétry O, Godeau P. [Malignant arterial hypertension in periarteritis nodosa. Incidence, clinicobiologic parameters and prognosis based on a series of 165 cases]. *Arch Mal Coeur Vaiss* 1986; 79:773–778.

[65] Guillevin L, Pagnoux C, Seror R, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)* 2011; 90:19–27.

[66] Hachulla E, Bourdon F, Taieb S, et al. Embolization of two bleeding aneurysms with platinum coils in a patient with polyarteritis nodosa. *J Rheumatol* 1993; 20:158–161.

[67] San A, Aydin NE, Akçay G, Selçuk Y, Okyar G. Spontaneous bilateral rupture of kidneys in a patient with polyarteritis nodosa. A case report. *Scand J Urol Nephrol* 1990; 24:319–321.

[68] Holsinger DR, Osmundson PJ, Edwards JE. The heart in periarteritis nodosa. *Circulation* 1962; 25:610–618.

[69] Rajani RM, Dalvi BV, D'Silva SA, Lokhandwala YY, Kale PA. Acute myocardial infarction with normal coronary arteries in a case of polyarteritis nodosa: possible role of coronary artery spasm. *Postgrad Med J* 1991; 67:78–80.

[70] Hu PJ, Shih IM, Hutchins GM, Hellmann DB. Polyarteritis nodosa of the pericardium: antemortem diagnosis in a pericardiectomy specimen. *J Rheumatol* 1997; 24:2042–2044.

[71] Blétry O, Godeau P, Charpentier G, Guillevin L, Herreman G. [Cardiac manifestations of periarteritis nodosa. Incidence of non-hypertensive cardiomyopathy]. *Arch Mal Coeur Vaiss* 1980; 73:1027–1036.

[72] Iino T, Eguchi K, Sakai M, Nagataki S, Ishijima M, Toriyama K. Polyarteritis nodosa with aortic dissection: necrotizing vasculitis of the vasa vasorum. *J Rheumatol* 1992; 19:1632–1636.

[73] Bourgarit A, Le Toumelin P, Pagnoux C, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine (Baltimore)* 2005; 84:323–330.

[74] Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore)* 2005; 84:115–128.

[75] Parangi S, Oz MC, Blume RS, et al. Hepatobiliary complications of polyarteritis nodosa. *Arch Surg* 1991; 126:909–912.

[76] Blidi M, Quang Tri N, Cassan P, Guillevin L. [Acute cholecystitis in periarteritis nodosa. 8 cases]. *Ann Med Interne (Paris)* 1996; 147:304–312.

[77] Ito M, Sano K, Inaba H, Hotchi M. Localized necrotizing arteritis. A report of two cases involving the gallbladder and pancreas. *Arch Pathol Lab Med* 1991; 115:780–783.

[78] Nakazawa K, Itoh N, Duan HJ, Komiyama Y, Shigematsu H. Polyarteritis nodosa with atrophy of the left hepatic lobe. *Acta Pathol Jpn* 1992; 42:662–666.

[79] Miller DL. Angiography in polyarteritis nodosa. *AJR Am J Roentgenol* 2000; 175:1747–1748.

[80] Warfield AT, Lee SJ, Phillips SM, Pall AA. Isolated testicular vasculitis mimicking a testicular neoplasm. *J Clin Pathol* 1994; 47:1121–1123.

[81] MacDonald WBG, Blake MP. Periostitis and localized myositis in polyarteritis nodosa. *Clin Nucl Med* 2004; 29:703–705.

[82] Périchon S, Pagnoux C, Seror R, et al. Periostéite au cours des vascularites systemiques nécrosantes : a propos de 4 observations d'une atteinte méconnue et pourtant évocatrice. [Periostitis in necrotizing systemic vasculitis: 4 observations of an unknown and yet evocative lesion.] *Presse Med* 2010; 39:e165-173.

[83] Rothschild PR, Pagnoux C, Seror R, Brézin AP, Delair E, Guillevin L. Ophthalmologic manifestations of systemic necrotizing vasculitides at diagnosis: a retrospective study of 1286 patients and review of the literature. *Semin Arthritis Rheum* 2013; 42:507–514.

[84] Sergent JS, Lockshin MD, Christian CL, Gocke DJ. Vasculitis with hepatitis B antigenemia: long-term observation in nine patients. *Medicine (Baltimore)* 1976; 55:1–18.

[85] Darras-Joly C, Lortholary O, Cohen P, Brauner M, Guillevin L. Regressing microaneurysms in 5 cases of hepatitis B virus related polyarteritis nodosa. *J Rheumatol* 1995; 22:876–880.

[86] Ozen S, Anton J, Arisoy N, et al. Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 2004; 145:517–522.

[87] Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; 65:936–941.

[88] Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69:798–806.

[89] Eleftheriou D, Dillon MJ, Tullus K, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. *Arthritis Rheum* 2013; 65:2476–2485.

[90] Till SH, Amos RS. Long-term follow-up of juvenile-onset cutaneous polyarteritis nodosa associated with streptococcal infection. *Br J Rheumatol* 1997; 36:909–911.

[91] Bron KM, Strott CA, Shapiro AP. The diagnostic value of angiographic observations in polyarteritis nodosa. A case of multiple aneurysms in the visceral organs. *Arch Intern Med* 1965; 116:450–454.

[92] Singhal M, Gupta P, Sharma A, Lal A, Rathi M, Khandelwal N. Role of multidetector abdominal CT in the evaluation of abnormalities in polyarteritis nodosa. *Clin Radiol* 2016; 71:222–227.

[93] Schollhammer R, Schwartz P, Jullie M-L, et al. 18F-FDG PET/CT Imaging of Popliteal Vasculitis Associated With Polyarteritis Nodosa. *Clin Nucl Med* 2017; 42:e385–e387.

[94] Shimizu M, Inoue N, Mizuta M, Ikawa Y, Yachie A. Leopard skin appearance of cutaneous polyarteritis nodosa on 18Ffluorodeoxyglucose positron emission tomography. *Rheumatology (Oxford)* 2016; 55:1090.

[95] Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; 44:666–675.

[96] Falcini F, La Torre F, Vittadello F, et al. Clinical overview and outcome in a cohort of children with polyarteritis nodosa. *Clin Exp Rheumatol* 2014; 32:S134-137.

[97] Erden A, Batu ED, Sönmez HE, et al. Comparing polyarteritis nodosa in children and adults: a single center study. *Int J Rheum Dis* 2017.

[98] Samson M, Puéchal X, Devilliers H, et al. Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors. *Autoimmun Rev* 2014; 13:197–205.

[99] Samson M, Puéchal X, Mouthon L, et al. Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial. *Clin Exp Rheumatol* 2017; 35 Suppl 103:176–184.

[100] Jarrousse B, Guillevin L, Bindi P, et al. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. *Clin Exp Rheumatol* 1993; 11:615–621.

[101] Godeau B, Mainardi JL, Roudot-Thoraval F, et al. Factors associated with Pneumocystis carinii pneumonia in Wegener's granulomatosis. *Ann Rheum Dis* 1995; 54:991–994.

[102] Cruz BA, Ramanoelina J, Mahr A, et al. Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit. *Rheumatology (Oxford)* 2003; 42:1183–1188.

[103] Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994; 87:671–678.

[104] Cacoub P, Le Thi Huong null, Guillevin L, Godeau P. [Causes of death in systemic vasculitis of polyarteritis nodosa. Analysis of a series of 165 patients]. *Ann Med Interne (Paris)* 1988; 139:381–390.

[105] Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996; 75:17–28.

[106] Samson M, Puéchal X, Devilliers H, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. *Autoimmun Rev* 2014; 13:945–953.

[107] Oh Y-J, Ahn SS, Park ES, et al. Birmingham vasculitis activity score at diagnosis is a significant predictor of relapse of polyarteritis nodosa. *Rheumatol Int* 2017; 37:685–694.

[108] Exley AR, Carruthers DM, Luqmani RA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. *QJM* 1997; 90:391–399.

[109] Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979; 301:235–238.

[110] Guillevin L. [How to treat systemic necrotizing vasculitides?]. *Presse Med* 2012; 41:1024–1030.

[111] Pagnoux C, Quéméneur T, Ninet J, et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis & Rheumatology (Hoboken, NJ)* 2015; 67:1117–1127.

[112] Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L, French Vasculitis Study Group. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. *Arthritis Rheum* 2011; 63:1435–1445.

[113] Gayraud M, Guillevin L, Cohen P, et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. *Br J Rheumatol* 1997; 36:1290–1297.

[114] Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349:36–44.

[115] Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359:2790–2803.

[116] Hampson LV, Whitehead J, Eleftheriou D, et al. Elicitation of expert prior opinion: application to the MYPAN trial in childhood polyarteritis nodosa. *PLoS ONE* 2015; 10:e0120981.

[117] Généreau T, Lortholary O, Leclerq P, et al. Treatment of systemic vasculitis with cyclophosphamide and steroids: daily oral low-dose cyclophosphamide administration after failure of a pulse intravenous high-dose regimen in four patients. *Br J Rheumatol* 1994; 33:959–962.

[118] Ribi C, Cohen P, Pagnoux C, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. *Arthritis Rheum* 2010; 62:1186–1197.

[119] Puéchal X, Pagnoux C, Baron G, et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis with Polyangiitis, Microscopic Polyangiitis or Polyarteritis Nodosa without Poor Prognosis Factors A Randomized-Controlled Trial. *Arthritis & Rheumatology (Hoboken, NJ)* 2017.

[120] Guillevin L, Fain O, Lhote F, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. *Arthritis Rheum* 1992; 35:208–215.

[121] Guillevin L, Lhote F, Cohen P, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum* 1995; 38:1638–1645.

[122] Guillevin L, Lhote F, Sauvaget F, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. *Ann Rheum Dis* 1994; 53:334–337.

[123] Guillevin L, Lhote F, Leon A, Fauvelle F, Vivitski L, Trepo C. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. *J Rheumatol* 1993; 20:289–298.

[124] Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. *Medicine (Baltimore)* 1995; 74:238–253.

[125] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67:370–398.

[126] Hernández-Rodríguez J, Tan CD, Rodríguez ER, Hoffman GS. Single-organ gallbladder vasculitis: characterization and distinction from systemic vasculitis involving the gallbladder. An analysis of 61 patients. *Medicine (Baltimore)* 2014; 93:405–413.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 3

GIANT CELL ARTERITIS

David S. Younger*, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health
City University of New York, New York, NY, US

ABSTRACT

Giant cell arteritis (GCA) or large-vessel GCA (LV-GCA) is a chronic, idiopathic, granulomatous vasculitis of medium and large arteries comprising overlapping phenotypes of cranial arteritis and extra-cranial GCA. Vascular complications associated are generally due delay in diagnosis and initiation of effective treatment. Advancements in magnetic resonance imaging (MRI) and MR angiography (MRA), computed tomography angiography (CTA), ^{18}fluoro-deoxyglucose/positron emission tomography (FDG/PET) and color duplex ultrasonography, have led to improved diagnosis of GCA. Corticosteroids are the mainstay of therapy in GCA. However, their use is associated with predictable and occasionally serious side effects. Biological agents including tocilizumab are effective and safe corticosteroid-sparing agents in treating GCA.

Keywords: giant cell arteritis, vasculitis, temporal artery biopsy, temporal artery ultrasound

INTRODUCTION

In the 10th century, Ali ibn Isâ described a man with heat and inflammation of the temporalis muscle and loss of sight [1]. In 1890, Hutchinson [2] described painful inflamed temporal arteries that prevented a man from wearing his hat. Giant cell arteritis (GCA) also known as large vessel (LV)-GCA, which was characterized as a distinct entity by Horton in 1932 [3], is now recognized as the most common primary systemic vasculitis of the Western world in those aged over 50. The 2012 Revised Chapel Hill Consensus Conference (CHCC)

* Corresponding Author's Email: youngd01@nyu.edu

Nomenclature [4] categorizes GCA as a large vessel vasculitis (LVV) prompting use of the equivalent term, large vessel (LV)-GCA. The spectrum of morphological changes have been described [5, 6]. This chapter reviews the epidemiologic, clinicopathologic features, diagnosis and treatment of giant cell arteritis.

OVERVIEW

The clinical symptoms in GCA are usually due to inflammation of the medium sized extra-cranial branches of the carotid artery, particularly the superficial temporal division [7]. About one-half the time, GCA is accompanied by aching and stiffness of the shoulder and hip girdles typical of polymyalgia rheumatica (PMR). Unfortunately neither the classical clinical presentation nor the combinations of clinical symptoms and signs predictive of a definite diagnosis of GCA occur commonly [8]. Visual loss in one or both eyes can be averted by early diagnosis and prompt treatment [9]. Temporal artery biopsy (TAB) is the gold standard of diagnosis, perhaps guided by non-invasive temporal artery ultrasound (TAUS). Glucocorticoids or corticosteroids (CS) remain the best treatment for GCA with similar long-term survival rates as age-matched population controls [10]. There are no randomized clinical trial (RCT) data in GCA to decide the correct CS dose regimen. Recent international guidelines [11, 12] provide assistance in diagnosis and treatment although the evidence base is weak and the guidance is at best advisory. The introduction of GCA care pathways may improve patient outcome [13, 14].

EPIDEMIOLOGY

The lifetime risk of developing GCA is estimated at 1% for women and 0.5% for men [15]. The disease rarely occurs in individuals under the age of 50 years and peaks in the eighth decade of life. It more commonly affects Scandinavians and North Americans of Scandinavian decent than Southern Europeans [16], and occurs rarely in Black and Asian populations [17-20]. Such racial patterns together with familial aggregation [21] point to a genetic predisposition to the disease. There is an association with the *HLA-DRB1*04* allele [7, 22].

The geographical variation and seasonal fluctuation of GCA in turn suggests a contribution from environmental and infectious factors [23] although definite links to particular microorganisms or vaccinations [24-26] have not been established. Moreover, there is no evidence that GCA occurs with increased prevalence in association with malignancy or as a paraneoplastic syndrome [27]. GCA is likely a polygenic disease wherein multiple environmental and genetic factors influence susceptibility and severity [28].

PATHOLOGY

The classical histological changes of GCA include arterial wall inflammation, internal elastic lamina fragmentation and intimal thickening (Figure 1). Although GCA derives its name from the presence of multinucleated giant cells, the latter are seen in only about one-half of

positive TAB, albeit in association with a granulomatous inflammatory infiltrate composed of CD4+ T-cells and macrophages located at the intima-media junction near fragments of the internal elastic lamina. Other TAB specimens manifest lympho-mononuclear-predominant panarteritis with occasional neutrophils and eosinophils without giant cells [29].

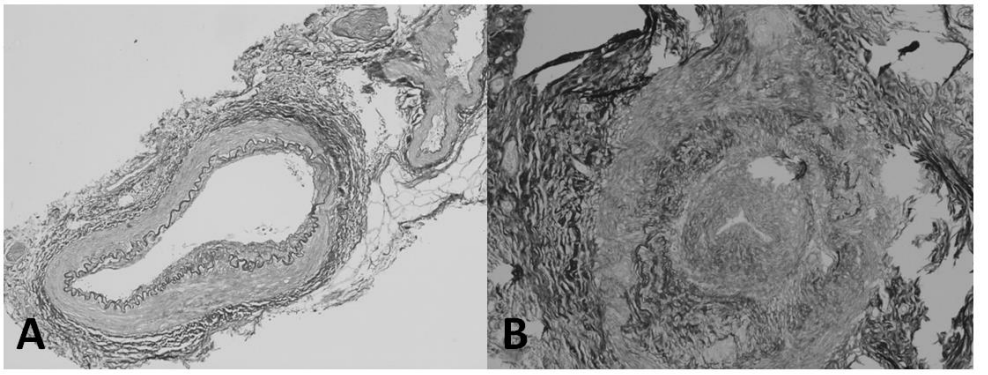


Figure 1. Temporal artery biopsies. (A) Normal (B) Typical GSA showing inflammation of the arterial wall, fragmentation of the internal elastic lamina, internal thickening and luminal occlusion.

In a small minority of TAB, inflammation may only be seen in peri-adventitial vessels external to the adventitia or the vasa vasorum in a network of small blood vessels that supply larger ones [30]. There is considerable variation in histopathology between patients as well as within a given TAB tissue sample [29]. Arteritic involvement of a given artery may be focal and segmental leading to skip lesions [7]. There may be healed arteritis suggested by intimal thickening, fragmented elastic lamina and scarred media, although these may in part be age related changes [31]. Arterial wall thickening can lead to partial or complete occlusion of the lumen and ischemic complications such as anterior ischemic optic neuropathy (AION) [23]. One subset of patients has small-vessel vasculitis surrounding non-inflamed temporal artery segments in TAB tissue specimens [30, 32], but there is no indication that such patients should be considered any differently than typical GCA. Arteritis of the temporal artery is not entirely specific for GCA, and can be encountered with polyarteritis nodosa (PAN), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), malignancy, and atypical PMR [33-37].

IMMUNOPATHOGENESIS

Inappropriate activation, maturation and retention of antigen presenting adventitial dendritic cells are early steps in the pathogenesis of GCA [24, 38]. These cells sample the surrounding environment for viral and bacterial pathogens through the action of toll-like receptors (TLR) wherein particular TLR profiles appear to be vessel specific [39] which may explain why some blood vessels are more prone to be targeted by GCA than others. Mouse models [40] show that activated vessel wall-embedded dendritic cells release chemokines that recruit CD4+ T-cells and macrophages. Moreover the pattern of arterial inflammation corresponds to TLR specificity such that TLR4 stimulation induces panarteritis and TLR5 stimulates perivasculitis [41].

At least six observations support a T-cell mediated etiopathogenesis of GCA according to Borchers and colleagues [23]. First, the inflammatory cell infiltrate in GCA is comprised mainly of T-cells and macrophages with few or no B-cells and polymorphonuclear cells notably neutrophils are often absent. Second, the formation of granulomas depends upon T-cells, particularly the CD4+ subset. Third, infiltrating T-cells in GCA lesions demonstrate main histocompatibility class II and IL-2 receptor expression with selective T-cell clonal expansion in TAB tissue specimens. Fourth, GCA is associated with specific human leukocyte antigen (HLA) alleles. Fifth, there is attenuation of vascular inflammation after depletion of T-cells in experimental models of GCA. Lastly, two types of T-cells that play important roles in GCA, Th1 and Th17, express high levels of interferon (IFN)-γ mRNA compared in TAB specimens compared to control samples without arteritis [23]. The balance between Th1 and Th17 may contribute to the clinical presentation of GCA since T-cell derived IFNγ correlates with visual symptoms and jaw claudication in a manner that those with high levels demonstrate more intense intimal hyperplasia in tissue samples [42]. In addition, T-cell derived IFNγ expression may contribute to CS resistance leading to a more chronic course, as well as the heightened expression of giant cells, ischemic complications, and neo-angiogenesis [23] and constitutional symptoms of GCA [38, 43]. The pro-inflammatory cytokine interleukin (IL)-6 appears to be a good target molecule to induce remission in GCA as serum levels mirror disease activity and IL-6 is up-regulated in the inflamed vessels of patients with GCA [44]. Macrophages are thought to be the effector cells in GCA as they are the major source of many cytokines and other drivers of the inflammatory process such as IL-1β, IL-6, TNF, TGFβ, IL-32, matrix metallo-proteins and platelet derived growth factors that are over expressed in TAB, however their precise role remains to be elucidated [23]. IL-6 concentrations correlate with a strong inflammatory response in GCA but appear to be inversely related to GCA related ischemic events. IL-6 is also a potent inducer of angiogenesis leading to the hypothesis that collateral vessel formation in the presence of high levels of IL-6 may be protective [45].

CLINICAL FEATURES

The onset of GCA tends to be insidious over weeks to months, and abrupt in up to 20% of patients [28], with a spectrum of initial disease manifestations attributable to the localized effects of vascular and systemic inflammation [46, 47] including new-onset headache, scalp tenderness, jaw claudication, fever, fatigue, malaise, anorexia, weight loss polymyalgia, and visual loss [48]. The artificial separation of cranial and extracranial features either localized to the head or owing respectively to large vessel involvement is misleading as postmortem studies show that the intracranial arteries are largely spared in GCA [49].

Headache

Although headache is a prominent feature, it is not universal [46, 50-52]. Classically it tends to be a constant ache of sudden onset in the temporal region and is usually severe enough to disturb sleep [51, 53]. It can vary greatly in intensity and location, be constant or intermittent, and assume virtually any form mimicking tension-type headache, thunderclap, migraine and even cluster headaches [1]. It may become progressively worse, or wax and wane, temporarily

subsiding in the absence of treatment [54]. A key feature is that it typically differs from any other previously experienced headache, and for this reason, the patient may deny headache, instead calling the symptom head pain [55]. The headache may be associated with scalp tenderness especially on hair brushing and combing or wearing glasses [47]. When severe, even the slightest pressure on resting the head on a pillow may be intolerable. Pain is usually localized to one or both temporal regions, the forehead or occiput. However, the pain may be generalized, spare the scalp altogether or affect the eye, ear; face, jaw or neck [55]. Tenderness, prominence and decreased temporal artery pulsation (Figure 2) increase the likelihood of GCA [46], although one-third of TAB-proven GCA patients have normal temporal arteries on clinical examination.

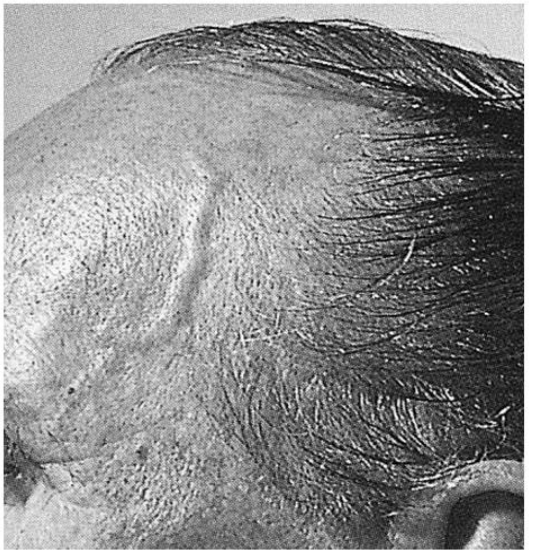


Figure 2. Prominence of the temporal artery in GCA.

Jaw Claudication

Although the most specific feature of GCA, jaw claudication, or pain and fatigue in the masseter muscles on protracted or vigorous chewing that eases with rest, is present only in about one-half of patients, it can also have an abrupt trismus-like symptom [54] and remain intermittent for weeks or months [55]. Jaw claudication should not be confused with temporo-mandibular joint (TMJ), tooth or gum disease. Tongue claudication is less common.

Constitutional Findings

With the widespread availability of CS in the empiric treatment of GCA, constitutional symptoms such as fever, fatigue, malaise, anorexia and weight loss are less often encountered at the formal diagnosis of affected patients [55]. Fever which occurs in about one-half of

patients is usually low grade. A small number of TAB-proven patients with GCA present with only symptoms of systemic inflammation without localizing vascular symptoms [29, 51, 56].

Ophthalmologic Involvement

An estimated 15% of patients with GCA experience ophthalmologic complications [57], notably ischemic optic neuropathy (AION) due to arteritic involvement of the short posterior ciliary arteries supplying the optic nerve head [58, 59], with the remainder comprised mainly of retinal blindness due to central retinal artery involvement [58, 59]. Visual loss is painless, partial or complete, and unilateral or bilateral; and once established it is usually irreversible [38]. It may be preceded by fleeting visual blurring with exercise, amaurosis fugax or diplopia, but commonly occurs without warning and may be the presenting symptom [46, 60]. Ophthalmoplegia is usually due to a partial or complete oculomotor or abducens nerve palsy, and is a recognized complication of ischemia affecting the extra-ocular muscles, cranial nerves or brainstem [14].

Other ischemic complications of GCA include transient ischemic attack (TIA) and stroke which may occur due to thrombosis, microembolism or a combination of intimal hyperplasia and distal thrombosis [55]. Although the vertebral arteries are inflamed in the large majority of patients at postmortem examination [49], clinically significant vertebrobasilar insufficiency is uncommon [55]; scalp and tongue necrosis are rare [61].

Polymyalgia Rheumatica

Although up to one-half of patients with GCA develop inflammatory shoulder and hip girdle pain and stiffness [62], only about 5% of patients with frank PMR ever develop GCA [7].

Large Vessel Involvement

Aortic inflammation can be observed in surgical biopsies or at postmortem examination in GCA [5, 63] however the true frequency is difficult to ascertain. Computed tomography angiography (CTA) [6] and helical aortic computed tomodensitometry [64] discern aortic involvement in 45 to 65% of patients with GCA, with the thoracic aorta most often affected. The relationship between aortitis and subsequent aortic aneurysm remains unclear [65]. In the first year of the disease, aortitis confers a small significant risk of dissection or rupture even in the absence of aortic aneurysm with resultant high mortality. Long term dilatation or aneurysm formation can occur with an increased risk of rupture [66, 67]. Retrospective studies note aortic aneurysm and dissection in 3% to 18% of patients with GCA [66-70]. In a cross-sectional study employing CT, 12/54 (22.2%) patients with GCA developed aortic aneurysms after 4 to 10.5 years [63] with relative risks (RR) ranging from 3 to 17.3 [66, 71]. Distal stenotic lesions of the subclavian, axillary and brachial arteries occur in 3% to 15% of patients [51, 67, 72, 73]. Lower extremity arteries are infrequently affected [67], however the identification of claudication and vascular bruits is important to ascertain before initiation of empiric CS because such findings,

which add weight to the formal diagnosis of GCA, may resolve with effective treatment [70, 74]. The management of peripheral arterial involvement rarely requires surgical intervention [55, 70, 75].

DIAGNOSIS

Classification Criteria

The American College of Rheumatology (ACR) 1990 criteria for the classification of GCA [76] required the presence of three or more of the following including, age >50 years, new onset localized headache, temporal artery tenderness or decreased pulsation, erythrocyte sedimentation rate (ESR) >50 mm/hr, and abnormal TAB, yielding a sensitivity of 93.5% and specificity of 91.2% to discern GCA from other vasculitides.

Table 1. Positive Predictive Value of Clinical Features of GCA*

Clinical Features Associated With a positive TAB	PPV Positive Predictive Value	Percentage of Patients
New headache	46%	49%
Scalp tenderness	61%	18%
Jaw claudication	78%	17%
Double vision	65%	10%
Jaw claudication + Scalp tenderness + New headache	90%	6%
Jaw claudication + Double vision or decreased vision	100%	0.7%

*Adapted from [8]. Abbreviations: GCA, giant cell arteritis; PPV, positive predictive value; TAB, temporal artery biopsy.

In the absence of consensus with regard to diagnostic criteria for GCA, the ACR criteria [76], jaw claudication, diplopia, temporal artery beading, prominence and tenderness increased the likelihood of positive TAB [46]. Jaw claudication in association with diplopia or decreased vision, or scalp tenderness and new headache were likewise predictive of GCA (Table 1). The insensitivity of the ACR Classification criteria is exemplified by the potential enigma of an 85-year-old man with headache, jaw claudication, loss of vision, temporal artery pain, and a clinically abnormal temporal artery who might only have a pre-TAB probability of GCA of 68% [77] emphasizing the difficulty in ascertaining a conclusive histopathologic diagnosis even when the clinical features are highly suggestive.

Laboratory Studies

Blood Studies

Acute phase markers of inflammation are often significantly elevated, and a normocytic normochromic anemia and thrombocytosis may be present [78], as may elevation of liver transaminase levels [79], while the serum albumin level may be depressed. The presence of rheumatoid factor, antinuclear (ANA) and other autoantibodies are not present in greater frequency than in the general population; however ascertainment of serum ANCA may help to differentiate GCA from other forms of vasculitis. Although the ESR has historically been the acute phase measure of choice in the diagnosis of GCA, up to a quarter of patients may have a normal value [47, 80-82] and elevation of the C-reactive protein (CRP) is a better predictor of obtaining a diagnostic TAB [9, 81, 83, 84]; the combination of an elevated CRP and positive TAB render the highest sensitivity and specificity for the diagnosis of GCA. Only 1 in 119 (.8%) patients to 7 in 177 (4%) patients [81, 84] with GCA presented with both normal ESR and CRP levels, however such findings may be subject to selection and referral bias. We routinely measure the CRP and plasma viscosity in all patients with suspected GCA since the latter has the advantage of paralleling the ESR, uninfluenced by age, gender, hematocrit or time to analysis.

Temporal Artery Biopsy

Temporal artery biopsy has been the gold standard test representing definitive pathological diagnosis [7, 13, 14, 38, 46, 55]. Performed correctly, TAB carries a low procedural risk of significant complications [77], and a positive result removes later doubts about diagnosis, particularly if treatment causes complications [85, 86] or if the patient fails to respond promptly to therapy [87], whereas a negative biopsy is important in averting long term risk of empiric CS [88]. Up to one-third of clinicians surveyed did not recommend TAB for the diagnosis of GCA [89] possibly because it did not alter the perceived necessity of empiric therapy when the result was inconclusive or negative [90-92]. The true sensitivity of unilateral TAB was 87% employing Bayesian analysis [93] with a variation in sensitivity of 24% to 94% in clinical cohorts [87]. The likelihood of a false-negative TAB may be influenced by the length of the specimen, the duration of prior CS therapy, pathological sectioning techniques and the presence of predominantly non-cranial disease. Retrospective reviews suggest a post-fixation biopsy length of 1 to 2 centimeters (cm) is adequate [94-97], but a length of greater than 2 cm was also recommended [97- 100]. A length of artery nearer to 3 cm probably allows for post fixation shrinkage [99]. Whether bilateral biopsies should be performed depends on the rate of discordance, which in a pooled analysis of four studies looking at 439 synchronous bilateral biopsies was 5.9% [93], although the range in individual studies was 1.4% to 12.7% (101). If the selected artery is negative for arteritis, some investigators [29, 88] advocate biopsy of the temporal artery on the contralateral side while others [12] consider the additional burden on the patient not justified for the small increase in diagnostic yield particularly if an adequate length of unilateral specimen can be ascertained and reviewed by an experienced pathologist in TAB analysis [55, 99]. The side selected for TAB should be the one, if present, with lateralizing symptoms or signs [102].

Temporal Artery Ultrasound

Temporal artery ultrasound studies (TAUS), which are cost-effective, non-invasive and lack significant complications, take about five minutes to perform, and render an image of the inflamed temporal artery characterized by edematous wall swelling. The latter conforms to a dark hypoechoic circumferential halo sign that represents continuous or segmental wall thickening (Figure 3).

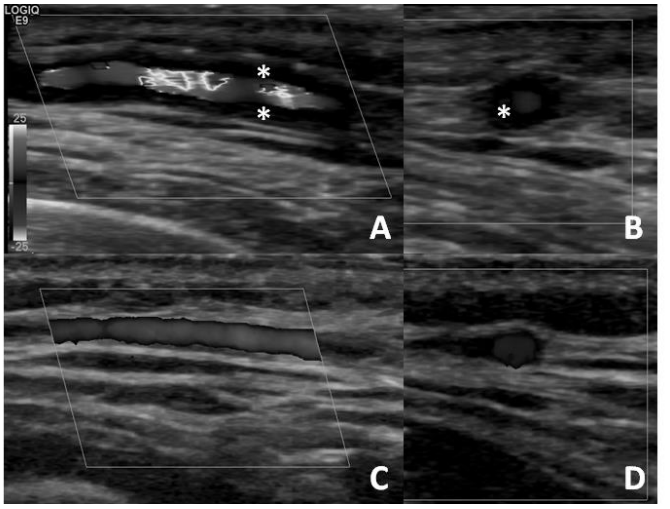
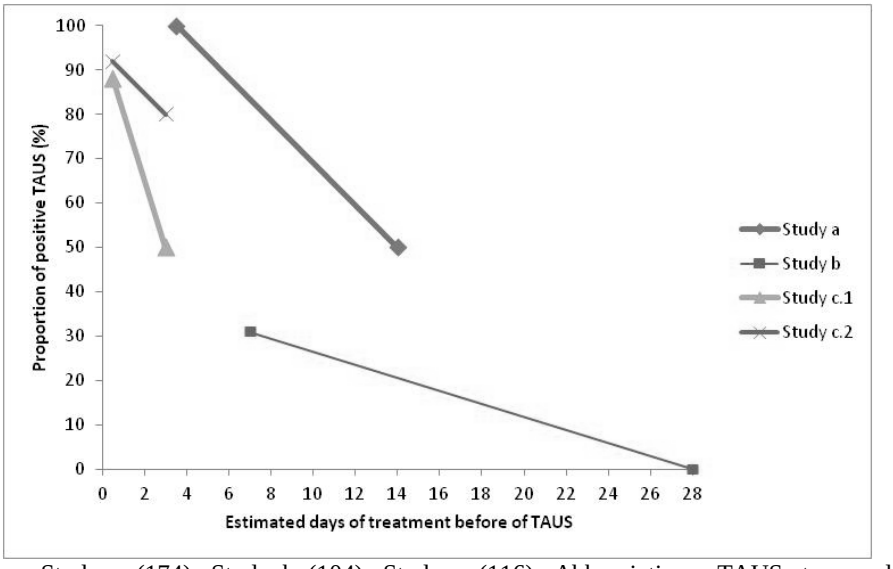


Figure 3. Temporal artery ultrasound (TAUS). The hypoechoic "halo" sigh (asterisks) on (A) longitudinal and (B) transverse section. (C) and (D) normal artery.



References: Study a (174); Study b (104); Study c (116). Abbreviations: TAUS, temporal artery ultrasound.

Figure 4. Proportion of positive temporal artery ultrasounds as a function of days on treatment with corticosteroids. An estimate of the mean length of treatment at two time points was made from each study listed below and plotted on the chart. The thickness of the lines represents the number of subjects reported in the study. Study c allowed two such estimates.

Stenosis and occlusion common in elderly patients due to atherosclerosis, neither of which are specific or sensitive for GCA, may also be noted [103, 104]. Three meta-analyses [105-107], which demonstrated the usefulness of the halo sign in the diagnosis of GCA with a sensitivity of 68% and specificity of 91% for a unilateral halo sign, showed 100% specificity for the bilateral halo sign. However, the findings may be influenced by CS use; moreover there is a presumed limited window of opportunity wherein which to correctly ascertain the diagnosis [65]. One-half of positive TAUS findings may be missed within seven days of treatment initiation (Figure 4), implying that in order to avert the low sensitivity of TAUS in those with suspected GCA, the study should be performed as soon as possible, preferably before or on the first day of treatment. Some [108] argue that it is never too late to perform TAUS because even if the sensitivity is diminished, the specificity remains. Therefore there is a rationale for its use as it has the potential to avert the need for TAB when a halo sign is noted. Furthermore, it can increase the diagnostic yield of TAB by directing the incision site to the most affected area of artery [104, 109].

Other Imaging Studies

Whereas non-invasive vascular imaging may be useful when there is atypical extracranial large vessel involvement or limb claudication and persistent acute phase reactants or fever of unknown origin [110], conventional angiography has little if any role unless a surgical intervention is contemplated [111]. Ultrasound of the thoracic aorta is generally inadequate but it may provide useful information in proximal upper limb arteries to increases the diagnostic yield of GCA [112]. Both magnetic resonance imaging (MRI), MR angiography (MRA), and contrast-enhanced computerized tomographic angiography (CTA) provide useful images of mural and luminal changes suggestive of large vessel vasculitis in GCA [6, 64, 113, 114] that include circumferential wall swelling, smoothly tapered luminal narrowing of aortic branches and aortic aneurysm formation [111]. Moreover, MRI and MRA which do not lead to radiation exposure are favored over CTA by some specialists [38, 101].

Bright mural enhancement of the temporal artery on contrast-enhanced high-resolution MRI had comparable sensitivity and specificity to TAUS in the diagnosis of GCA in one retrospective single-center analysis [115], the latter of which decreased in sensitivity over the first few days of CS treatment (85% after 0-1 days, 64% after 2-4 days, 56% after >4 days) [116].

Whole body ^{18}Fluorodeoxyglucose (FDG)-positron emission tomography (PET) increased the overall diagnostic accuracy of large vessel involvement in GCA from 54% to 70% [117]. One meta-analysis [118] found that the absence of FDG uptake conferred a negative predictive value of 88% of GCA, whereas thoracic vascular uptake was highly suggestive of GCA. However there have not been properly designed trials to assess the sensitivity and specificity of ^{18}F-FDG PET in GCA, nor does it reliably distinguish between atherosclerosis and vasculitis [119]. The radiographic features of large-vessel involvement so noted in CTA and PET imaging decrease rapidly after the initiation of CS treatment; features of large-vessel vasculitis including concentric wall thickening were significantly more frequent in treatment naïve patients compared to patients treated with corticosteroids for 1-3 days (77% versus 29%, $p = 0.005$) [6]. The diagnostic accuracy of PET in detecting large-vessel involvement was significantly higher in patients not receiving immunosuppressive therapy (93.3% vs 64.5%) [117].

Rapid Diagnostic Pathway

The author advocates a clinical review of patients within 24 hours of suspected GCA, including access to specialty assessment for the performance of necessary blood tests, followed by TAUS, and TAB within seven days [13, 14, 55]. The threshold is kept low for the performance of TAUS or TAB in all patients suspected of GCA awaiting the findings before commencement of CS in the absence of visual disturbances and jaw claudication [8]. The risk of blindness in other patients with typical GCA while awaiting results of laboratory studies is carefully weighed against the risk of potentially serious medication side effects associated with empiric CS treatment. The cost effectiveness of such pathways in secondary care has yet to be calculated, but visual loss particularly in the elderly, has major consequences for quality of life [14]. While those with monocular vision loss would trade one in three of their remaining years for unimpaired vision, this rose to two in three in those with binocular vision [120].

PROGNOSIS

Clinical studies have not validated the relation of existent classification criteria for GCA [76] to clinical and laboratory measures to prognosticate relapse likelihood and outcome. Common features of clinical relapse include recurrent headache, scalp pain and PMR-like symptoms associated with a raised acute phase response reactants [121-124]. Clinical symptoms and changes in the acute phase response can occur independently [125]. Acute phase responses can take several weeks to return to normal after initiating treatment while symptoms improve over several days [126, 127]. It can be argued that maintaining the lowest level of acute phase response achieved for each individual patient is an important goal of therapy [128] but pursuing a normal acute phase response might lead to overtreatment and unacceptably high rates of CS-related adverse events. Up to 20% of patients with a significant asymptomatic rise in ESR failed to relapse clinically [122] although clinicians may be overly concerned that improved control of the acute phase response may be protective against late atherosclerosis [129]. It seems reasonable to consider a return to higher dose treatment to improve prognosis in patients experiencing a returning headache, PMR-like symptoms, jaw claudication and visual symptoms. Since the advent of CS for GCA, the long term outcome and survival rates have been similar to age matched population [27, 130] including those with large vessel complications [131], although prior to CS estimated mortality was 12.5% [132]. The presence of clinical or subclinical aortitis could infer a poorer prognosis [6, 68] but this requires further corroboration. It is uncertain to what degree aortic involvement so noted on imaging studies resolves with standard GCA therapy, or whether it predicts a more chronic and relapsing GCA course requiring continued or more aggressive treatment [64, 68, 133]. Standard chest radiography, echocardiogram, CT, MRI and PET imaging have all been used to screen for emerging thoracic aortic dilatation [12, 38, 63, 67, 131, 134]. However there are no prospective studies comparing the sensitivity of these studies separately or together in discerning thoracic aortic aneurysm formation. Mackie and Pease [55] advocate tight control of blood pressure without regular imaging.

TREATMENT AND OUTCOME

Most experts including the British Society of Rheumatology (BSR) and European League Against Rheumatism (EULAR) recommend early initiation of high-dose CS therapy before TAB, although the evidence for this approach is weak with a level of evidence equal to 3 and strength of recommendation equal to C [11, 12]. The case can be made for early intervention with empiric treatment in patients with visual loss since untreated, the other eye is at heightened similar risk in up to one-third of cases for the ensuing three weeks [121], moreover partial visual improvement in vision is more likely if treatment commences within the first day of visual loss [135]. A similar approach may be advocated in those with features of impending visual loss such as amaurosis fugax, diplopia and jaw claudication. However, if the likelihood of GCA is low to moderate, withholding treatment and awaiting TAB that later returns negative would avoid unnecessary treatment. Figure 5, which show the proportion of positive TAB biopsies in relation to the number of weeks taking corticosteroids among several reported cohorts [8, 87, 136-138], suggests a 5% to 10% loss of TAB positivity for each week of treatment. While those with initially high likelihood of GCA pretreatment will have persistently high rates of TAB positivity weeks later, the latter would not likely influence therapeutic decisions unless such patients suffer later relapse or manifest treatment related side effects that questioned need for continued therapy. A bilateral TAB length of > 3cm so noted in one-half of specimens, predicted the subsequent need for corticosteroid therapy in 94% of patients [139], whereas a negative TAB measuring >2 cm performed before six days of starting prednisolone led to cessation of therapy without later visual loss [140].

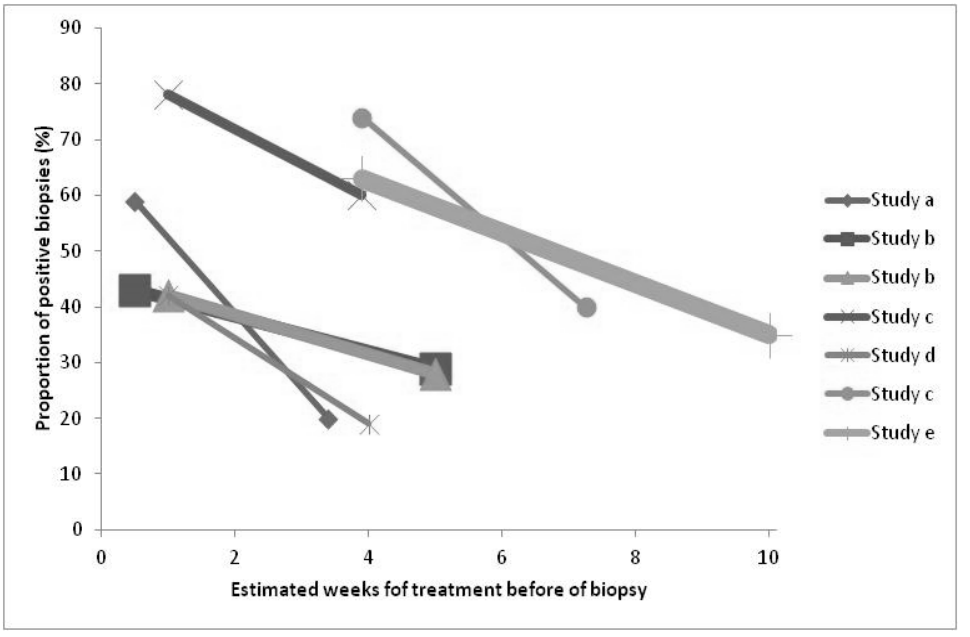


Figure 5. Proportion of positive TAB biopsy specimens as a function of weeks on treatment with glucocorticoids. An estimate of the mean length of treatment at two time points was made from each study report listed below and plotted on the chart wherein the thickness of the lines represented the number of subjects reported in the study. References: Study a: (136); Study b: (137); Study c: (87); Study d: (138); Study e: (8). Abbreviation: TAB, temporal artery biopsy.

Although there are no RCT of the use of CS in GCA [11, 12], most experts agree with daily morning treatment of prednisone at doses of 40 mg to 60 mg until symptoms and laboratory abnormalities resolve [7, 11, 12, 122]. Alternate daily CS were not as effective as a daily regimen, alone or in association with adjuvant methotrexate for GCA [122, 141]. In fact, the symptomatic response that follows CS treatment is so striking and rapid in GCA, that it is a diagnostic criterion of the disease [122]. Patients with PMR experience improvement in symptoms related to systemic inflammation over two to three days while symptoms related to impaired blood flow such as jaw claudication and visual disturbance generally take longer to respond and resolve [142]. Although sustained visual loss may be permanent and unresponsive to therapy [143], the risk of further progression is low [144]. Although prednisone in the dose range of 10 mg to 40 mg per day was effective in several cohorts [90, 145, 146], the results were not considered conclusive due to small sample sizes and apparent selection bias [86, 147]. Pulsed intravenous methylprednisolone was advocated in patients with GCA and visual disturbances [11, 12], however one observational study [128] and another RCT [148] failed to demonstrate improved efficacy in preventing visual loss compared to high-dose oral therapy. Moreover, intravenous pulsed methylprednisolone, which demonstrated no significant long term CS-sparing effects in the treatment of simple forms of GCA, was reserved for complicated forms of GCA.

The concern for CS resistance in patients with GCA has its origin in the ophthalmology community where visual loss in GCA is more prevalent [128]. One small RCT [149] that administered three consecutive days of one gram of intravenous pulsed methylprednisolone induction, followed by oral CS found higher rates of remission, less relapses, and more rapid tapering compared to patients treated with oral high-dose CS.

The apparent corticosteroid-sparing benefit of pulsed intravenous methylprednisolone [149] may not have been clinically significant since the criteria for disease relapses included instances of raised acute phase responses without clinical flares; moreover there were no differences in CS-related side effects [129]. The CS dose can be gradually tapered in the first month after the resolution of reversible clinical symptoms and the levels of acute phase reactants falls by 50% [11, 12]. Although other tapering regimens have been employed [122, 142], the available evidence [90, 142, 146, 150, 151] suggests that treatment should be continued for at least two years, with most patients weaned off of medication by four to five years. A minority of them may need continued low-dose CS [85, 121]. Among several GCA treatment trials conducted between 1988 and 2003 [90, 121-123, 142, 145, 146], the median duration of treatment of GCA ranged from 24 to 191 weeks, with an equivalent cumulative dose of prednisone that ranged from 5,275 mg to 9,194 mg. Such broad differences in the duration and dosage of administered CS would be expected to translate into a spectrum of relapse rates so noted in 27% to 84.2% of patients, with increased rates among those receiving the highest initial CS doses with more rapid tapering.

A meta-analysis of the use of adjuvant treatment with methotrexate [152] calculated the time-to-event outcomes in three randomized, placebo-controlled trials of patients with newly diagnosed GCA treated with initial high-dose CS and randomly assigned to 7.5 mg to 15 mg per week of oral methotrexate therapy or placebo [122, 123, 153]. There was a reduction in the cumulative equivalent dose of prednisone by 842 mg in 48 weeks ($P < 0.001$), but prednisone only treatment was reduced rapidly, and the rate of relapse in this group was 80% and it did not reflect current treatment practice. Current guidelines [12] of a recommended CS tapering regimen were loosely based on clinical experience at the Mayo Clinic [142] with the consensus

of a group of international clinicians. Some clinicians prefer slower dose reduction regimens with a lower anticipated rate of relapse [13], while others [126, 128, 154] favor individualized dose reduction schedules based on regular clinical review The main drive to keep the CS dose to a minimum is the fear of adverse CS effects, particularly cardiovascular and bone fractures. Several cohort studies [90, 142, 146, 155, 156] suggested the clear association between the cumulative dose of steroids and the rate of CS complications other than cardiovascular and bone fracture, whereas others [67, 68, 71] were variably confounded by patients with differing severe disease requiring more aggressive treatment. The meta-analysis by Mahr and colleagues [152] noted adverse events in two-thirds of patients treated with CS alone, with methotrexate or placebo that included infection, abnormal liver function tests, fractures, diabetes, malignancy, thrombocytopenia, and leukopenia in descending order of frequency.

There is evidence from single case reports and small patient series of a clinical benefit in GCA employing the pyrimidine inhibitor leflunomide [157], and the immunosuppressants mycophenolate mofetil [158] and cyclophosphamide [159], however their efficacy has not yet been confirmed in RCT. Cyclosporin showed no additional CS-sparing effect in GCA [160].

Therapy with the anti-tumor necrosis factors (TNF) infliximab and etanercept [161-163] was of no benefit and potentially harmful in newly diagnosed GCA. Tocilizumab, an IL-6 receptor alpha inhibitor, induced remission and reduce glucocorticoid requirements in patients with refractory GCA [44, 164-167]. A multicenter RCT underway at the time of the writing of this chapter in 2015 has been concluded [168].Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper, was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained CS-free remission in patients with GCA. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P<0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper.

The impact of aspirin use on ischemic cranial complications was demonstrated in GCA as a basis for management of GCA [169, 170], however an impact was not shown in retrospective cohorts [171-173].

CONCLUSION

GCA is a common, serious and treatable vasculitis that affects older adults. Rapid access and management care pathways ensure the early referral of untreated suspected patients for readily available TAB especially warranted in those with low to moderate probability of

disease, and appropriate primary and secondary care to prevent excess morbidity and mortality associated with empiric and often unwarranted high-dose CS therapy. Published guidelines for GCA diagnosis and management need to be rigorously examined to assess the impact of CRP, TAUS signs, large vessel imaging, and TAB in any given patient, especially those who warrant empiric high dose CS due to impending visual loss. Moreover, guidelines need to reflect a unified definition of clinical relapse. Studies assessing the link between clinical symptoms, inflammatory markers, imaging techniques and mimicking conditions will be very valuable. Finally, long-term vascular complications are increasingly recognized in GCA, and this is blurring the margin between atherosclerosis and vasculitis, which may improve our understanding of both these conditions [65]. Biological agents including tocilizumab are emerging as effective and safe CS-sparing therapy in treating GCA

REFERENCES

[1] Ward TN, Levin N. Headache in giant cell arteritis and other arteritides. *Neurol. Sci.,* 2005; 26:S134–S137.

[2] Hutchinson J. Diseases of the arteries: on a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene. *Arch. Surg.,* 1890; 1:323–329.

[3] Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of temporal vessels. *Mayo Clin. Proc.,* 1932; 7:700–701.

[4] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013; 65:1–11.

[5] Ostberg G. Morphological changes in the large arteries in polymyalgia arteritica. *Acta. Med. Scand. Suppl.,* 1972; 533:135–159.

[6] Prieto-González S, Arguis P, García-Martínez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann. Rheum. Dis.,* 2012; 71:1170–1176.

[7] Salvarani C, Pipitone N, Versari A, et al. Clinical features of polymyalgia rheumatica and giant cell arteritis. *Nat. Rev. Rheumatol.,* 2012; 8:509-521.

[8] Younge BR, Cook BE, Bartley GB, et al. Initiation of glucocorticoid therapy: before or after temporal artery biopsy? *Mayo Clin. Proc.,* 2004; 79:483-91.

[9] Hayreh SS, Podhajsky PA, Raman R, et al. Giant cell arteritis: Validity and reliability of various diagnostic criteria. *Am. J. Ophthalmol.,* 1997; 123: 285-296.

[10] Phillip, R. Mortality in systemic vasculitis: a systematic review. *Clinical and Experimental Rheumatology* 2008; 26(Suppl):S94 -S104.

[11] Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann. Rheum. Dis.,* 2009; 68:318-323.

[12] Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology,* 2010; 49:1594-1597.

[13] Quick V, Kirwan JK. Our approach to the diagnosis and treatment of polymyalgia rheumatica and giant cell (temporal) arteritis. *J. R. Coll Physicians Edinb.* 2012; 42:341-9.

[14] Patil P, Karia N, Jain S et al. Giant cell arteritis: a review. *Eye and Brain* 2013:5 23–33.

[15] Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum.* 2011; 63:633-639.

[16] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of Giant Cell Arteritis and Polymyalgia Rheumatica. *Arthritis Care & Research*, 2009; 61:1454-1461.

[17] Smith CA, Fidler WJ, Pinals RS. The epidemiology of giant cell arteritis: report of a ten-year study in Shelby County, Tennessee. *Arthritis Rheum.* 1983; 26:1214-1219.

[18] Wigley RD, Zhang NZ, Zeng QY, et al. Rheumatic diseases in China: ILAR-China study comparing the prevalence of rheumatic symptoms in northern and southern rural populations. *J. Rheumatol.*, 1994; 21:1484e90.

[19] Kobayashi S, Yano T, Matsumoto Y, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. *Arthritis Rheum.* 2003; 49:594–598.

[20] Pereira LS, Yoon MK, Hwang TN, et al. Giant cell arteritis in Asians: a comparative study. *Br. J. Ophthalmol.,* 2011; 95:214–216.

[21] Liozon E, Ouattara B, Rhaiem K et al. Familial aggregation in giant cell arteritis polymyalgia rheumatica: a comprehensive literature review including 4 new families. *Clinical and Experimental Rheumatology*, 2009; 27:S89-S94.

[22] Weyand CM, Hicok KC, Hunder GG, et al. The HLA-DRB1 locus as a genetic component in giant cell arteritis: mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. *J. Clin Invest.*, 1992, 90:2355-2361.

[23] Borchers AT, Gershwin ME. Giant cell arteritis: A review of classification, pathophysiology, geo-epidemiology and treatment. *Autoimmunity Reviews*, 2012; 11:A544-A554.

[24] Ly K, Regent A, Tamby M, et al. Pathogenesis of giant cell arteritis: More than just an inflammatory condition? *Autoimmunity Reviews* 2010; 9:635-645.

[25] Rodriguez-Pla A, Stone JH. Vasculitis and systemic infections. *Curr. Opin. Rheumatol*, 2006; 18:39-47.

[26] Helweg-Larsen J, Tarp B, Obel N, et al. No evidence of parvovirus B19, Chlamydia pneumoniae or human herpes virus infection in temporal artery biopsies in patients with giant cell arteritis. *Rheumatology*, 2002; 41:445-449.

[27] Pipitone N, Bioardi L, Bajocchi G, et al. Long term outcome of giant cell arteritis. *Clinical and Experimental Rheumatology*, 2006; 24S65-S70.

[28] Salvarani C, Cantini F, Boiardi L, et al. Polymyalgia Rheumatica and Giant Cell Arteritis. *N. Engl. J. Med.*, 2002; 347:261-271.

[29] Lie JT. Illustrated criteria for histopathologic classification of selected vasculitis syndromes. *Arthritis Rheum.* 1990; 33:1074-1087.

[30] Restuccia G, Cavazza A, Boiardi L, et al. Small-vessel vasculitis surrounding an uninflamed temporal artery and isolated vasa vasorum vasculitis of the temporal artery: two subsets of giant cell arteritis. *Arthritis Rheum.* 2012; 64:549–556.

[31] Cox M, Gilks B. Healed or quiescent temporal arteritis versus senescent changes in temporal artery biopsy specimens. *Pathology*, 2001; 33:163–166.

[32] Makkuni D, Bharadwaj A, Wolfe K, et al. Is intimal hyperplasia a marker of neuro-ophthalmic complications of giant cell arteritis? *Rheumatology* 2008; 47:488–490.

[33] Lie JT. When is arteritis of the temporal arteries not temporal arteritis. *Journal of Rheumatology*, 1994; 21:186-189.

[34] Nishino H, DeRemee RA, Rubino FA, et al. Wegener's granulomatosis associated with vasculitis of the temporal artery: report of five cases. *Mayo Clin. Proc.,* 1993; 68:115-121.

[35] Sieber SC, Cuello B, Gelfman NA, et al. Pulmonary capillaritis and glomerulonephritis in an antineutrophil cytoplasmic antibody-positive patient with prior granulomatous aortitis. *Arch. Pathol. Lab. Med.,* 1990; 114:1223-1226.

[36] Proctor PR, Lotz BP. Sarcoidosis and giant cell arteritis [letter]. *Clin. Exp. Dermatol.,* 1992; 17:143-144.

[37] Lesser RS, Aledort D, Lie JT. Non giant cell arteritis of the temporal artery presenting as the polymyalgia rheumatica-temporal arteritis syndrome. *J. Rheumatol.,* 1995; 22:2177-2182.

[38] Weyand CM, Goronzy JJ. Polymyalgia Rheumatica and Giant Cell Arteritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. *Rheumatology 5th Ed*. Maryland Heights: Mosby; 2010:1535-1545.

[39] Pryshchep O, Ma-Krupa W, Younge BR, et al: Vessel-specific Toll-like receptor profiles in human medium and large arteries. *Circulation,* 2008; 118:1276-1284.

[40] Han JW, Shimada K, Ma-Krupa W, et al. Vessel Wall-Embedded Dendritic Cells Induce T-Cell Autoreactivity and Initiate Vascular Inflammation. *Circ. Res*., 2008; 102:546-553.

[41] Deng J, Ma-Krupa W, Gewirtz AT, et al: Toll-like receptors 4 and 5 induce distinct types of vasculitis. *Circ. Res.,* 2009; 104:488-495.

[42] Weyand CM, Tetzlaff N, Bjornsson J, et al: Disease patterns and tissue cytokine profiles in giant cell arteritis. *Arthritis Rheum.* 1997; 40:19-26.

[43] Deng J, Younge B, Brian R, et al. Th17 and Th1-cell responses in giant cell arteritis. *Circulation,* 2010; 121:906-915.

[44] Unizony S, Stone JH, James R. New treatment strategies in large-vessel vasculitis. *Current Opinion in Rheumatology*, 2013; 25:3-9.

[45] Hernandez-Rodriguez J et al. Elevated production of interleukin-6 is associated with a lower incidence of disease-related ischemic events in patients with giant-cell arteritis: angiogenic activity of interleukin-6 as a potential protective mechanism. *Circulation,* 2003; 107:2428–2434.

[46] Smetana GW, Shmerling RH. Does the patient have temporal arteritis? *JAMA,* 2002; 287:92-101.

[47] Weyand CM and Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. *Ann. Intern. Med.,* 2003; 139:505-515.

[48] Hunder GG. Clinical features of GCA/PMR. *Clin. Exp. Rheumatol., 2*000; 18(Suppl 20); S6-S8.

[49] Wilkinson IM, Russell RW. Arteries of the head and neck in giant cell arteritis. A pathological study to show the pattern of arterial involvement. *Arch. Neurol.,* 1972; 27:378–391.

[50] Huston KA, Hunder GG, Lie JT, et al. Temporal arteritis: a 25-year epidemiologic, clinical, and pathologic study. *Ann. Intern. Med.,* 1978; 88:162-167.

[51] Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, et al. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine* 2005; 84:269-276.

[52] Ezeonyeji AN, Borg FA, Dasgupta B. Delays in recognition and management of giant cell arteritis: results from a retrospective audit. *Clin. Rheumatol.*, 2011; 30:259–262.
[53] Cooke WT, Cloake PCP, Govan ADT, et al. Temporal arteritis: A generalized vascular disease. *Q. J. Med.*, 1946; 15:47-75.
[54] Hunder GG. Diagnosis of giant cell (temporal) arteritis. In: *UpToDate*, Basow DS, ed., UpToDate:Waltham, MA, 2013, accessed 6/7/13.
[55] Mackie SL, Pease CT. Diagnosis and management of giant cell arteritis and polymyalgia rheumatica: challenges, controversies and practical tips. *Postgraduate Medical Journal*, 2013; 89:284-292.
[56] Calamia KT, Hunder GG. Giant cell arteritis (Temporal arteritis) presenting as fever of undetermined origin. *Arthritis Rheum.*, 1981; 24:1414-1418.
[57] Hayreh SS. Ophthalmic features of giant cell arteritis. *Baillières Clin. Rheumatol.*, 1991; 5:431-459.
[58] González-Gay MA, García-Porrúa C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine*, 2000; 79:283–292.
[59] Salvarani C, Cimino L, Macchioni P et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. *Arthritis Rheum.*, 2005; 5:293–297.
[60] Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. *Am. J. Ophthalmol.*, 1998; 125:521–526.
[61] Valesky EM, Wahle M, Vranes S, et al. Bitemporal scalp necrosis, a very rare manifestation of giant cell arteritis. *Zeitschrift Fur. Rheumatologie*, 2012; 71:806-809.
[62] Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*, 2008; 372: 234-245.
[63] Garcia-Martinez A, Hernandez-Rodriguez J, Arguis P, et al. Development of Aortic Aneurysm/Dilatation During the Follow up of Patients With Giant Cell Arteritis: A Cross-Sectional Screening of Fifty- Four Prospectively Followed Patients. *Arthritis Care Res.*, 2008; 59:422–430.
[64] Agard C, Barrier J, Dupas B et al. Aortic Involvement in Recent-Onset Giant Cell (Temporal) Arteritis: A Case–Control Prospective Study Using Helical Aortic Computed Tomodensitometric Scan. *Arthritis Care Res.*, 2008; 59:670-676.
[65] Luqmani R. Large vessel vasculitides: update for the cardiologist. *Curr. Opin. Cardiol.*, 2012; 27:578-584.
[66] Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: a population-based study. *Ann. Intern. Med.*, 1995; 122:502-507.
[67] Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum.*, 2003; 48:3522–531.
[68] Espitia O, Néel A, Leux C, et al. Giant Cell Arteritis with or without Aortitis at Diagnosis. A Retrospective study of 22 patients with longterm followup. *J. Rheumatol.*, 2012; 39:2157–2162.
[69] Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, et al. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: A population-based study. *Medicine*, 2004; 83:335-341.

[70] Klein RG, Hunder GG, Stanson AW, et al. Large artery involvement in giant cell (temporal) arteritis. *Ann. Intern. Med*., 1975; 83:806-812.

[71] Ray JG, Mamdani MM, Geerts WH. Giant cell arteritis and cardiovascular disease in older adults. *Heart*, 2005; 91:324–328.

[72] Brack A, Martinez-Taboada V, Stanson A et al. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum.* 1999; 42:311-317.

[73] Assie C, Janvresse A, Plissonnier D, et al. Long-term follow-up of upper and lower extremity vasculitis related to giant cell arteritis: a series of 36 patients. *Medicine* 2011; 90:40-51.

[74] Schmidt WA, Moll A, Seifert A, et al. Prognosis of large-vessel giant cell arteritis. *Rheumatology*, 2008; 47:1406-1408.

[75] Ninet JP, Bachet P, Dumontet CM, et al. Subclavian and axillary involvement in temporal arteritis and polymyalgia rheumatica. *Am. J. Med.*, 1990; 88:13-20.

[76] Hunder GG, Bloch DA, Michel BA et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.*, 1990; 33:1122-1128.

[77] Niederkohr RD, Levin LA. Management of the patient with suspected temporal arteritis a decision-analytic approach. *Ophthalmology*, 2005; 112:744 –756.

[78] Costello F, Zimmerman MB, Podhajsky PA et al. Role of thrombocytosis in diagnosis of giant cell arteritis and differentiation of arteritic from non-arteritic anterior ischemic optic neuropathy. *Eur. J. Ophthalmol.*, 2004; 14:245–257.

[79] Kyle V, Wraight EP, Hazleman BL. Liver scan abnormalities in polymyalgia rheumatica/giant cell arteritis. *Clin. Rheumatol.*, 1991; 10:294–297.

[80] Laria A, Zoli A, Bocci M, et al. Systematic review of the literature and a case report informing biopsy-proven giant cell arteritis (GCA) with normal C-reactive protein. *Clin. Rheumatol.*, 2012; 31:1389-1393.

[81] Parikh M, Miller NR, Lee AD, et al. Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology*, 2006; 113:1842–1845.

[82] Salvarani C, Hunder GG. Giant Cell Arteritis with Low Erythrocyte Sedimentation Rate: Frequency of Occurrence in a Population-Based Study. *Arthritis Care Res.*, 2001; 45:140–145.

[83] Walvick MD, Walvick MP. Giant cell arteritis: laboratory predictors of a positive temporal artery biopsy. *Ophthalmology*, 2011; 118:1201-1204.

[84] Kermani TA, Schmidt J, Cynthia S, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Semin. Arthritis Rheum.*, 2012; 41:866-871.

[85] Pountain G, Hazleman B. Polymyalgia Rheumatica and Giant Cell Arteritis. *BMJ*, 1995; 310:1057-1059.

[86] Pipitone N, Salvarani C. Improving therapeutic options for patients with giant cell arteritis. *Curr Opin. Rheumatol.*, 2008; 20:17-22.

[87] Narváez J, Bernad B, Roig-Vilaseca D, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. *Semin Arthritis Rheum.*, 2007; 37:13-19.

[88] Danesh-Meyer HV. Temporal artery biopsy: skip it at your patient's peril. *Am. J. Ophthalmol.*, 2012; 154:617-619.

[89] Drehmer TJ, Khanna D, Markert RJ, et al. Diagnostic and management trends of giant cell arteritis: A physician survey. *J. Rheumatol.*, 2005; 32:1283-1289.
[90] Delecoeullerie D, Joly P, Cohen de Lara A. et al. Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients). *Ann. Rheum. Dis.*, 1988; 9:733-739.
[91] Varma D, O'Neill D. Quantification of the role of temporal artery biopsy in diagnosing clinically suspected giant cell arteritis. *Eye*, 2004; 18:384-388.
[92] Thomassen I, den Brok AN, Konings CJ, et al. Steroid use is associated with clinically irrelevant biopsies in patients with suspected giant cell arteritis. *The American Surgeon*, 2012; 78):1362-1368.
[93] Niederkohr RD, Levin LA. A Bayesian analysis of the true sensitivity of a temporal artery biopsy. *Invest. Ophthalmol. Vis. Sci.*, 2007; 48:675–680.
[94] Sudlow C. Diagnosing and managing polymyalgia rheumatica and temporal arteritis. Sensitivity of temporal artery biopsy varies with biopsy length and sectioning strategy. *BMJ*, 1997; 315:549.
[95] Taylor-Gjevre R, Vo M, Shukla D, et al. Temporal artery biopsy for giant cell arteritis. *J. Rheum.*, 2005; 32:1279-1282.
[96] Ypsilantis E, Courtney ED, Chopra N, et al. Importance of specimen length during temporal artery biopsy. *Br. J. Surg.*, 2011; 98:1556-1560.
[97] Goslin BJ, Chung MH. Temporal artery biopsy as a means of diagnosing giant cell arteritis: is there over-utilization? *Am. Surg.*, 2011; 77:1158-1160.
[98] Lie T et al. Illustrated criteria for histopathologic classification of selected vasculitis syndromes. *Arthritis Rheum.*, 1990; 33:1074-1087.
[99] Murchison AP, Bilyk JR, Eagle RC, et al. Shrinkage revisited: how long is long enough? *Ophthalmic Plastic and Reconstructive Surgery*, 2012; 28:261-263.
[100] Shaw P. Temporal artery biopsy technique. In: *UpToDate*, Basow DS, ed., UpToDate:Waltham, MA, 2013.
[101] Kermani TA, Warrington KJ. Recent advances in diagnostic strategies for giant cell arteritis. *Cur. Neurol. Neurosci. Rep.*, 2012; 12:138-144.
[102] Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, et al. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. *Semin. Arthritis Rheum.*, 2001; 30:249-256.
[103] Karahaliou M. Colour duplex sonography of temporal arteries before decision for biopsy: a prospective study of 55 patients with suspected GCA. *Arthritis Res. Ther.*, 2006; 8:R116.
[104] Habib HM, Essa AA, Hassan AA. Color duplex ultrasonography of temporal arteries: role in diagnosis and follow-up of suspected cases of temporal arteritis. *Clin. Rheumatol.*, 2012; 31:231-237.
[105] Karassa FB, Matsagas MI, Schmidt WA, et al. Meta-analysis: test performance of ultrasonography for giant-cell arteritis, *Ann. Intern. Med.*, 2005; 142:359-369.
[106] Ball EL, Walsh SR,; Tang TY, et al. Role of ultrasonography in the diagnosis of temporal arteritis. *Br. J. Surg.*, 2010; 97: 1765-1771.
[107] Arida A, Kyprianou M, Kanakis M, et al. The diagnostic value of ultrasonography derived edema of the temporal artery wall in GCA: a second meta-analysis, *BMC Musc. Dis.*, 2010; 11:44.

[108] Tyndall A. Is the halo always holy? Glucocorticoid impact on detecting cranial large-vessel arteritis. The importance of temporal artery biopsy. *Rheumatology,* 2012; 51:1927-1928.

[109] Alberts M. Temporal Arteritis: Improving Patient Evaluation with a New Protocol. *The Permanente Journal,* 2013; 17:56-62.

[110] Clifford A, Burrell S, Hanly JG. Positron Emission Tomography/Computed Tomography for the Diagnosis and Assessment of Giant Cell Arteritis: When to Consider It and Why. *J. Rheumatol.,* 2012; 39:1909-1911.

[111] Schmidt WA, Imaging in vasculitis. *Best Pract. Res. Clin. Rheumatol.,* 2013; 27:107–118.

[112] Schmidt WA, Seifert A, Gromnica-Ihle E, et al. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. *Rheumatology* 2008; 47:96-101.

[113] Narvaez J, Narvaez JA, Nolla JM, et al. Giant cell arteritis and polymyalgia rheumatica: usefulness of vascular magnetic resonance imaging studies in the diagnosis of aortitis. *Rheumatology,* 2005; 44:479–483.

[114] Koenigkam-Santos M, Sharma P, Kalb B, et al. Magnetic Resonance Angiography in Extracranial Giant Cell Arteritis. *J. Clin. Rheumatol.,* 2011; 17:306-310.

[115] Bley TA, Reinhard M, Hauenstein C, et al. Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis. *Arthritis Rheum.,* 2008; 58:2574-2578.

[116] Hauenstein C, Reinhard M, Geiger J, et al. Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. *Rheumatology,* 2012; 51:1999-2003.

[117] Fuchs M, Briel M, Daikeler T, et al. The impact of ^{18}F-FDG PET on the management of patients with suspected large vessel vasculitis. *Eur. J. Nucl. Med. Mol. Imaging,* 2012; 39:344-353.

[118] Besson FL, Parienti JJ, Bienvenu B, et al. Diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. *Eur. J. Nucl. Med. Mol. Imaging,* 2011; 38:1764-1772.

[119] Rudd JH, Myers KS, Bansilal S, et al. Atherosclerosis inflammation imaging with ^{18}F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *Journal of Nuclear Medicine,* 2008; 49:871-878.

[120] Frost A, Eachus J, Sparrow J et al. Vision-related quality of life impairment in an elderly UK population: associations with age, sex, social class and material deprivation. *Eye,* 2001; 15:739-744.

[121] Graham E, Holland A, Avery A, et al. Prognosis in Giant Cell Arteritis. *BMJ,* 1981; 282:269-271.

[122] Hoffman GS, Cid MC, Hellmann DB, et al. Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Adjuvant Methotrexate Treatment for Giant Cell Arteritis. *Arthritis Rheum,* 2002; 46:1309-1318.

[123] Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone-A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.,* 2001; 134106-114.

[124] Martinez-Lado L, Calviño-Díaz C, Piñeiro A, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. *Medicine,* 2011; 90:186-193.

[125] Weyand CM, Fulbright JW, Hunder GG, et al: Treatment of giant cell arteritis: interleukin-6 as a biological marker of disease activity. *Arthritis Rheum.,* 2000; 43:1041-1048.

[126] Masson C. Therapautic approach to giant cell arteritis. *Joint. Bone Spine,* 2011; 79:219-227.

[127] Kyle V, Cawston TE, Hazleman BL. Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up. *Ann. Rheum. Dis.,* 1989; 48:667-671.

[128] Hayreh SS, Zimmerman B. Management of giant cell arteritis: our 27-year clinical study: new light on old controversies. *Ophthalmologica,* 2003; 217:239-259.

[129] Spiera RF, Spiera H. Therapy for Giant Cell Arteritis: Can We Do Better? *Arthritis Rheum.,* 2006; 54:3071-3074.

[130] Agard C, Espitia O, Neel A. Prognosis of giant cell arteritis. *Presse Medicale,* 2012; 41:966-974.

[131] Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Mortality of Large-Artery Complication (Aortic Aneurysm, Aortic Dissection, and/or Large-Artery Stenosis) in Patients with Giant Cell Arteritis. A Population-Based Study Over 50 Years. *Arthritis Rheum.,* 2003; 48:3532-3537.

[132] Crosby RC, Wadsworth RC. Temporal arteritis – review of the literature and report of 5 additional cases. *Arch .Med. Interna,* 1948:81:431-464.

[133] Marie I, Proux A, Duhaut P, et al. Long-term follow-up of aortic involvement in giant cell arteritis: a series of 48 patients. *Medicine,* 2009; 88:182-192.

[134] Bongartz T, Matteson EL. Large-vessel involvement in giant cell arteritis. *Curr. Opin. Rheumatol.,* 2006; 18:10-17.

[135] González-Gay A, Blanco R, Rodríguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: Predictors and response to treatment. *Arthritis Rheum*., 1998; 41: 1497–1504.

[136] Allison MC, Gallagher PJ. Temporal artery biopsy and corticosteroid treatment. *Annals of the Rheumatic Diseases,* 1984; 43:416-417.

[137] Achkar AA, Lie JT, Hunder GG, et al. How does previous glucocorticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? *Ann. Intern. Med.,* 1994; 120:987-992.

[138] Bury D, Joseph J, Dawson T. Does preoperative steroid treatment affect the histology in giant cell (cranial) arteritis? *J. Clin. Pathol.,* 2012; 65:1138-1140.

[139] Hall S, Persellin S, Lie JT, et al. The therapeutic impact of temporal artery biopsy. *Lancet,* 1983; 2:1217.

[140] Murchison AP, Gilbert ME, Jurij R, et al. Validity of the American College of Rheumatology Criteria for the Diagnosis of Giant Cell Arteritis, *Am. J. Ophthalmol.,* 2012;154:722-729.

[141] Hunder GG, Sheps SG, Allen GL, et al. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann. Intern. Med.,* 1975; 82:613-618.

[142] Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum.,* 2003; 49:703-708.

[143] Danesh-Meyer H, Savino PJ, et al. Poor prognosis of visual outcome after visual loss from giant cell arteritis. *Ophthalmology,* 2005; 112:1098-1103.

[144] Aiello PD, Trautman JC, McPhee TJ, et al. Visual prognosis in giant cell arteritis. *Ophthalmology,* 1993; 100:550-555.

[145] Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. I. Steroid regimes in the first two months. *Annals Rheum. Dis.,* 1989; 48:658-661.

[146] Lundberg I, Hedfors E. Restricted dose and duration of corticosteroid treatment in patients with polymyalgia rheumatica and temporal arteritis. *J. Rheumatol.,* 1990: 17:1340-1345.

[147] Ferris J, Lamb R. Polymyalgia rheumatica and giant cell arteritis. *BMJ* 1995; 311:455.

[148] Chevalet P, Barrier JH, Pottier P, et al. A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year followup study of 164 patients. *J. Rheumatol.,* 2000; 27:1484-1491.

[149] Mazlumzadeh M, Hunder GG, Easley KA, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids : a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum.,* 2006; 54:3310-3318.

[150] Kyle V 1990. Stopping steroids in polymyalgia rheumatica and giant cell arteritis. Treatment usually lasts for two to five years. *BMJ,* 1990; 300:344.

[151] Narvaez J, Nolla-Sole JM, Clavaguera MT, et al. Longterm therapy in polymyalgia rheumatica: Effect of coexistent temporal arteritis. *J. Rheumatol.,* 1999; 26:1945-1952.

[152] Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis. An individual patient data meta-analysis. *Arthritis Rheum,* 2007; 56:2789-97.

[153] Spiera RF, Mitnick HJ, Kupersmith M, et al. A prospective, double-blind, randomized, placebo-controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin. Exp. Rheumatol.*, 2001; 19:495-501.

[154] Nordborg E, Nordborg C. Giant cell arteritis: strategies in diagnosis and treatment. *Curr. Opin. Rheumatol.*, 2004; 16:25-30.

[155] Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dosing and steroid associated side effects. *Ann. Rheum. Dis.*, 1989; 48:662-666.

[156] Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J. Rheumatol.,* 1994; 21:1283–1286.

[157] Adizie T, Christidis D, Dharmapaliah C, et al. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. *Int. J. Clin. Pract.,* 2012; 66:906-909.

[158] Sciascia S, Piras D, Baldovino S, et al. Mycophenolate mofetil as steroid-sparing treatment for elderly patients with giant cell arteritis: report of three cases. *Aging Clin. Exp. R*es., 2012; 24:273-7.

[159] Quartuccio L, Maset M, De Maglio G, et al. Role of oral cyclophosphamide in the treatment of giant cell arteritis. *Rheumatology,* 2012; 51:1677-1686.

[160] Schaufelberger C, Mollby H, Uddhammar A, et al. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. *Scand. J. Rheumatol.,* 2006; 55:327-329.

[161] Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis. *Ann. Intern. Med.*, 2007; 146:621-30.

[162] Salvarani C, Macchioni PL, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann. Intern. Med.*, 2007; 146:631-639.

[163] Martinez-Taboada V, Rodriguez-Valverde V, Carreno L, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects *Ann. Rheum. Dis.*, 2008; 67: 625-630.

[164] Vinit J, Bielefeld P, Muller G, Besancenot J. Efficacy of tocilizumab in refractory giant cell arteritis. *Joint Bone Spine*, 2012; 79:317-318.

[165] Sciascia S, Rossi D, Roccatello D. Interleukin 6 blockade as steroid-sparing treatment for 2 patients with giant cell arteritis. *J. Rheumatol.*, 2011; 38:2080-2081.

[166] Seitz M, Reichenbach S, Bonel HM, et al. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med. Wkly*, 2011; 141:w13156.

[167] Beyer C, Axmann R, Sahinbegovic E, et al. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann. Rheum. Dis.*, 2011; 70:1874-1875.

[168] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; 377:317-328.

[169] Nesher G, Berkun Y, Mates M, et al. Risk factors for cranial ischemic complications in giant cell arteritis. *Medicine*, 2004; 83:114–122.

[170] Lee MS, Smith SD, Galor A, et al. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum.*, 2006; 54:3306-3309.

[171] Narvaez J, Bernard B, Gomez-Vaquero C, et al. Impact of antiplatelet therapy in the development of severe ischaemic complications and in the outcome of patients with giant cell arteritis. *Clin. Exp. Rheumatol.*, 2008; 26 (Suppl 49):S57-S62.

[172] Berger CT, Wolbers M, Meyer P, et al. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. *Rheumatology*, 2009; 48:258-261.

[173] Mackie S, Dasgupta B, Hordon L et al. Ischaemic manifestations in giant cell arteritis are associated with area level socio-economic deprivation, but not cardiovascular risk factors. *Rheumatology*, 2011; 50:2014-2022.

[174] Schmidt WA, Kraft HE, Vorpahl K, et al. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N. Engl. J. Med.*, 1997; 337:1336-1342.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 4

OPHTHALMOLOGIC AND NEURO-OPHTHALMOLOGIC ASPECTS OF VASCULITIDES

David S. Younger*, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health
City University of New York, New York, NY, US

ABSTRACT

There have been significant advances in the understanding of the vasculitides in the past several years leading to more precise classification and nosology. Ophthalmologic manifestations may be the presenting feature of and a clue to the diagnosis of vasculitis, or develop in the course of the illness due to a common disease mechanism. Precise diagnosis and prompt treatment prevents short and long-terms ophthalmologic sequela.

Keywords: neuro-ophthalmology, ophthalmology, vasculitis, CNS

INTRODUCTION

Vasculitis is a term used to characterize a spectrum of diseases associated with vascular inflammation. Ophthalmologic manifestations may be the presenting features of primary and secondary systemic vasculitis and a clue to early diagnosis to prevent ischemic vascular sequela. Unrecognized and therefore untreated, the ophthalmologic and neuro-ophthalmologic features can be catastrophic with irreversible loss of function particularly when visual involvement coincides with vasculitic brain infarction, hemorrhage, and aneurysm formation or ischemic involvement of the optic nerve or surrounding orbital structures. This chapter considers the ophthalmologic aspects of primary systemic vasculitis and primary central

*Corresponding Author's Email: youngd01@nyu.edu

nervous system vasculitis (PCNSV) in children and adults. Galetta [1] has reviewed the neuro-ophthalmologic aspects of vasculitides.

CLASSIFICATION OF VASCULITIS

Two Chapel Hill Consensus Conferences (CHCC), one in 1994, and the other revised in 2012 [2, 3], provided consensus on nosology and definitions for the commonest forms of vasculitis in adults based upon the caliber of vessels involved. The Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) proposed specific classification criteria for the commonest childhood vasculitis syndrome [4] based upon vessel size similar to the CHCC nomenclature [3]. The EULAR, PRES, and the Pediatric Rheumatology International Trials Organization (PRINTO) defined the clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides in a validated classification of pediatric vasculitis [5]. There is a continuum of vasculitic disorders with some occurring exclusively in childhood or in older adults, and others across the age spectrum although with differing epidemiology, clinical and laboratory manifestations, and response to treatment. Large vessel vasculitis (LVV) includes giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) includes polyarteritis nodosa (PAN) and Kawasaki disease (KD) with typical involvement of main visceral arteries and veins and initial branches. Small vessel vasculitis (SVV) comprises disorders with vasculitis of intraparenchymal arteries, arterioles, capillaries, veins and venules, and disease pathogenesis related to anti-neutrophil cytoplasmic antibody (ANCA) production, or the formation of immune complexes (IC). The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (Wegener granulomatosis type), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome type), and microscopic polyangiitis (MPA) (microscopic polyarteritis), while vasculitic disorders associated with IC include hypocomplementemia urticarial vasculitis (C1q), cryglobulinemic vasculitis (CV), and IgA vasculitis (IgAV) (formerly Henoch-Schönlein purpura [HSP]). Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome (CS). The category of single-organ vasculitis (SOV), that involves arteries or veins of any size in a single organ without features to indicate that it is a limited expression of a systemic vasculitis, is typified by central nervous system (CNS) vasculitis.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

This granulomatous LVV involves cranial branches of the arteries arising from the arch of the aorta. It occurs exclusively in individuals older than age 50 years, with an annual incidence of 15-25 persons per 100,000, with higher rates in Caucasian individuals compared to African Americans, and among women compared to men in a ratio of 2 to 3:1 [6-9]. The ACR 1990

criteria for the classification of GCA [10], designed for use in investigative studies to help distinguish GCA from other types of vasculitides, are not useful for making the diagnosis in individual patients [11]. Five criteria were selected by the ACR [10] from which three or more in a given patient was associated with a sensitivity of 93.5% and a specificity of 91.2%, from among the following: age equal to or greater than 50 years at disease onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated erythrocyte sedimentation rate (ESR) to 50 mm/hour or more, and vascular tissue biopsy sample showing necrotizing arteritis with predominance of mononuclear cells infiltration or granulomatous multinucleated giant cell inflammation. The histopathology of biopsy-positive GCA is typified by vessel wall infiltration by mononuclear cells, CD4+ T-cells, activated macrophages and multinucleated giant cells, that latter of which form granulomas close to the internal elastic lamina of involved vessels in up to one-half of specimens [12].

Visual loss due to anterior ischemic optic neuropathy (AION), which results from occlusion of short posterior ciliary arteries that supply the optic nerve head, is the commonest ocular symptom in GCA with a frequency that varies from 10% to 60%. Other causes of visual loss include vasculitic involvement of the choroid, posterior optic nerve and retina [13]. Visual loss may be partial, complete, or permanent, and is preceded by amaurosis fugax in 44% of patients [9]. A prospective study of 170 patients with biopsy-confirmed GCA [14] noted ocular involvement in 85 (50%) patients, including visual loss present in 83 (97.7%), amaurosis fugax in 26 (30.6%), eye pain in seven (8.2%), and diplopia in 5 (5.9%). Ocular ischemic lesions consisted of arteritic AION in 69 (81.2%), central retinal artery and cilioretinal occlusions each in 12 (14.1%), the latter after satisfactory fundus fluorescein angiography (FFA); as well as, posterior ischemic optic neuropathy in 6 (7.1%), and ocular ischemia in 1(1.2%) patient. Those with ocular involvement were significantly older than the patients without ocular involvement, and surprisingly less likely to have prominent constitutional and systemic symptomatology. Among 42 other patients from Olmsted County Minnesota studied by Huston and coworkers [15], visual symptoms preceded the clinical and histopathologic diagnosis of GCA in 15 (40%) patient, of which blurred vision was most common so noted in 6 (19%) of patients, followed by diplopia in 5 (12%), transient vision loss in 5 (12%), permanent partial loss in 4 (10%), and permanent complete loss in 3 (10%) patients. A followup Olmsted County cohort twenty-five years later totaling 168 patients with GCA by Nuenninghoff and colleagues (16) found visual disturbances overall at presentation in 16 (9.5%) patients, and at the time of diagnosis in 37 (22%) patients, of whom 14 (8.3%) patients had transient vision loss, 18 (10.7%) had permanent vision loss, and 14 (8.3%) had diplopia.

Of 18 patients with varying visual loss and occult GCA [17], amaurosis fugax was noted in 6 (33.3%), diplopia in 2 (11.1%), and eye pain in 1 (5.6%) patient. Ocular ischemic lesions included AION in 17 (94.4%) patients, and central retinal artery occlusion and cilioretinal artery occlusions each in 2 (11.1%) after FFA. The authors [17] concluded a high index of suspicion for GCA for patients older than 50 who develop amaurosis fugax, visual loss, or AION in the absence of constitutional and systemic symptoms (Figure 1).

Ocular involvement was more common in patients with GCA without large vessel vasculitic involvement according to Prieto-González and colleagues [18] who studied 40 patients with newly diagnosed biopsy-proven GCA by computed tomographic (CT) imaging to define LVV involvement of the aorta and its tributaries. Ocular involvement was noted more often in those with LVV aortic involvement than without (15% versus 54%). Conversely, ischemic events were more common in those without than with evidence of LVV aortic

involvement by CT-imaging (54% vs. 22%). The authors postulated a spectrum of GCA disease with cranial arteritis manifested by ocular symptoms, headache, and jaw claudication at one end and predominant LVV at the other.

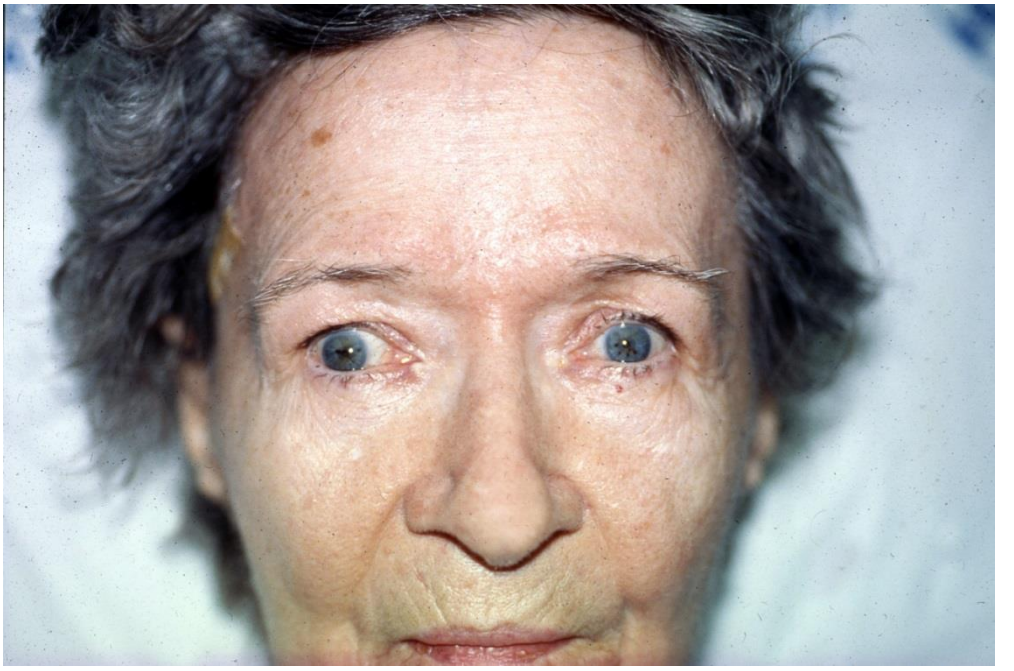


Figure 1. Patient with giant cell arteritis and brainstem stroke demonstrating left gaze paresis.

The incidence and severity of visual loss and ocular involvement appears to depend upon the promptness of diagnosis and treatment. Although AION is the commonest cause of visual loss in GCA, only 5.7% of patients with AION will have GCA making it critical to distinguish arteritic from non-arteritic AION in suspected patients [19]; FFA are a critical tool in this distinction. The appearance of posterior ciliary artery occlusion is diagnostic of arteritic AION, while non-arteritic AION is almost always due to a fall in perfusion pressure in the peripapillary choroid and not from primary ciliary artery occlusion (20). One other finding that supports the diagnosis of arteritic AION in up to one-half of affected patients presenting with visual symptoms is chalky-white optic disc swelling [21]. A small disc and cup may be associated with both arteritis and non-arteritic AION, while a normal or large cup is highly suggestive of an underlying arteritic process [22]. Color Doppler imaging of the central retinal and short posterior ciliary arteries is helpful in distinguishing GCA from non-arteritic AION. Ho and colleagues [23] compared color Doppler flow imaging in patients with GCA to matched control subjects revealing reduced central retinal and short posterior arterial mean flow velocities and increased vascular resistance.

The mainstay of treatment for GCA is corticosteroids however the exact dosing regimen and mode of administration depends upon the presence of visual involvement at the time of diagnosis. Patients with unilateral complete loss, evidence of fellow eye involvement, and amaurosis fugax are treated with 1 gram of intravenous corticosteroids every 6 to 8 hours followed by the oral prednisone. Salvarani and colleagues [24] employed 40 mg to 60 mg oral prednisone for GCA, and intravenous methylprednisolone 1g per day for 3 day for those with

recent or impending visual loss. The addition of low dose aspirin to corticosteroid therapy was beneficial in preventing cranial ischemic complications including acute visual loss and cerebrovascular complications of GCA than steroids alone. Patients treated with aspirin and corticosteroids are five-fold less likely to experience cranial ischemic complications than those who received corticosteroids alone [25]. Aiello and colleagues [26] noted visual improvement in 15% of eyes after commencing therapy for GCA and estimated a probability of further visual loss developing of 1% in the absence of a defined visual deficit, compared to 13% when an established deficit was ascertained. Danesh-Meyer and colleagues [27] evaluated the incidence and extent of visual recovery of 34 patients with biopsy-proven GCA treated with high dose systemic corticosteroids noting that 27% of eyes suffered loss of visual acuity by two or more lines within one week of starting corticosteroid treatment, while 15% of eyes so treated showed an improved visual acuity of 2 or more lines. Of the 15% of eyes that showed an improvement in visual acuity, none showed further improvement in visual fields or color vision, leading the authors [27] to conclude that the improvement in visual acuity may reflect learning to view eccentrically. Liu and colleagues [28] investigated 45 patients with biopsy-proven GCA, 25 of whom were treated with intravenous methylprednisolone, and 20 treated with oral prednisolone. Visual loss remained unchanged in 49% so treated, worsened in 17%, and improved in 34%, defined as visual acuity improvement of two or more lines and final acuity greater than 20/80. Fellow eye involvement more often occurred in patients receiving oral corticosteroid therapy compared to those receiving intravenous therapy. Similarly, visual acuity was more likely to improve after a course of intravenous treatment than oral therapy (39% versus 28%).

Takayasu Arteritis

This systemic necrotizing LVV is characterized by thrombosis of the vessels arising from the aortic arch. TAK predominantly occurs in young Japanese females, typically arising before the age of 40, in a 9:1 female to male ratio [29-31]. The incidence of TAK is estimated to be between 0.4 to 2.2 per million people, [32, 33] with higher rates in South East Asia, Africa and South America [34, 35].

The ACR [36] selected six criteria for the classification of TAK, from which three or more in a given patient were associated with a sensitivity of 90.5% and a specificity of 97.8%, from among the following: age less than or equal to 40 years, claudication of an extremity, decreased brachial artery pulse, greater than 10 mmHg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. Although the histopathology of TAK is not included as part of the ACR criteria [36], it may aid in the diagnosis, and it is characterized by an acute periarteritis with extensive cellular infiltration, necrosis of the media, and intra-arterial thrombosis [37]. Ocular features not formally part of the criteria of TAK occur in 35% to 68% of patients [38-40], typically due to ischemia and hypoperfusion resulting from occlusive arteritis of the aortic arch branches, while those arising in the setting of hypertension result from vasculitic renal artery involvement.

The commonest ischemic ocular manifestation of TAK is retinopathy, first described by Takayasu [41] who noted peculiar fundus changes consisting of dilated vessels around the optic

disc due to arteriovenous (AV) anastomoses in female patients without a palpable radial pulse. Less common ocular ischemic manifestations include anterior ischemic optic neuropathy (AION), central retinal artery occlusion, and ocular ischemic syndrome [29, 42]. The retinal changes in TAK vary in symptomatology and severity depending on the location of carotid artery involvement, the rate and duration of ocular vascular hypoperfusion, and the presence of collateral blood supply to the eye [38].

Uyama and Asayama [30] studied 80 patients with TAK noting that 38 (48%) of patients had involvement of the aortic arch and stenosis or occlusion of its proximal branches denoting type I TAK; 25 (31%) patients had type II TAK characterized by involvement of the whole aorta and its branches, and 16 (20%) had type III TAK characterized by involvement of the descending thoracic and abdominal aorta and its branches. Altogether, 38 (100%) of patients with type I TAK had retinopathy. Uyama and Asayama (30) classified retinopathy into stages 1 to 4 wherein 20 (53%) patients with stage 1 had dilations of small vessels; 12 (32%) patients with stage 2 disease had microaneurysm formation; 3 (8%) patients each with either stage 3 or 4 disease, respectively manifested AV anastomoses or ocular complications of vitreous hemorrhages, proliferative retinopathy and vision loss . The authors attributed the retinal vascular changes to decreasing blood flow in the retinal vasculature noting decreased intraocular pressure with disease progression. In contrast to type I TAK, hypertensive fundal changes predominated in patients with type III disease with 12 (86%) demonstrating hypertensive changes occurring in the fundus, and 2 (14%) manifesting hypertensive retinopathy.

Chun and colleagues [38], who reviewed medical records and FFA of 156 eyes from 78 patients with TAK, noted that the commonest ocular symptoms were subjective decrease of vision in 23 (29.5%) patients; amaurosis fugax in 20 (25.6%) patients; ocular pain in 9 (11.5%) patients; and metamorphopsia in 3 (4%) patients. Among 13 cases of retinopathy, 69% occurred in patients with TAK involving primarily the aortic arch and its branches, and among 25 patients with hypertensive retinopathy, 18 (72%) patients had involvement of the thoraco-abdominal aorta, its branches, and the aortic arch. Thus, patients with retinopathy were more likely to have carotid artery or aortic arch involvement, while those with hypertensive retinopathy were more likely to have involvement of the descending aorta.

The importance of staging retinopathy was highlighted by Chun and coworkers [38] who demonstrated that visual acuity (VA) dramatically worsened as patients progressed from stage 3 to stage 4 retinopathy. The best corrected VA in patients with Stage 1 to Stage 3 retinopathy ranged from 20/15 to 20/30, while those with stage 4 disease had VA ranging from 20/200 to hand motion alone. Causes of impaired VA in such patients included total cataract in 4 patients, neovascular glaucoma in 2 patients, vitreous hemorrhages in 1 patient, tractional retinal detachment in 3 patients, optic atrophy in 3 patients, and AION in 1 patient. Peter and coworkers [29] demonstrated an association between VA and retinopathy, noting a causal relation between uncorrected refractive error among 18 patients that was due to a cataract in 6 (33%) patients, grade 4 retinopathy in 4 (22%) patients, optic atrophy in 2 (11%) patients, hypertension with retinal detachment, longstanding papilledema, and retinal pigment changes of the fovea, and a posterior capsular opacity each in 1 (6%) patient. Although there was no correlation of patient age, duration of symptoms, history of limb claudication, presence of a carotid bruit, hemiplegia, or increased ESR or C-reactive protein (CRP) levels with the development of retinopathy, retinopathy was more frequent in those with significantly lower

blood pressures and non-recordable right upper limb blood pressures than in patients without retinopathy.

Ocular symptoms are typically a late manifestation of disease, with ophthalmic evaluation occurring on average 55 ± 69 months after disease onset. [29]. An ocular ischemic syndrome was the initial disease manifestation of TAK in three reported patients ranging in age from 14 to 42 years, of subacute or chronic progressive onset (43-45), in whom vascular imaging was crucial in the etiological diagnosis.

FFA is an important tool in determining the extent of ocular involvement in TAK [46], and when compared with indirect ophthalmoscopy in 31 eyes with TAK showed no additional changes in ten eyes without retinal vein dilation on indirect ophthalmoscopy. However, of 7 eyes with dilated retinal veins, FFA revealed additional abnormal findings such as microaneurysms, arteriovenous shunts, retinal neovascularization, and avascular areas important in grading the stages of retinopathy. Chun and colleagues (38) noted prolongation of arm-to-retina circulation time in all 21 (100%) eyes with retinopathy while 14 (67%) patients had delayed arteriovenous filling time. Similarly Uyama and Asayama [30] noted that arm to retinal time was delayed by 20 seconds on FFA in patients with retinopathy.

Kerr and colleagues [31] noted a 60% response rate to corticosteroids alone among 60 patients with TAK with an estimated time to remission of 22 months. In the steroid resistant patients, cytotoxic therapy employing methotrexate and cyclophosphamide induced remission in another 40% of patients. Jales-Neto and coworkers [47] found that combination corticosteroid and immunosuppressive therapy led to disease remission in 55% of adult patients, and in 24% of patients less than age 18 years. Among four patients with TAK treated with corticosteroids described by Ishikawa [48], one improved from stage 3 to stage 2 TAK, while another patient developed unilateral blindness, and two others, were stable. Pan-retinal photocoagulation is an adjunctive therapy used to treat cases of severe retinal ischemia [38], whereas antiplatelet agents reduced the frequency of arterial ischemic events in patients with TAK [49]. So noted and treated promptly with corticosteroids, the inflammatory process underlying ocular manifestations may lead to improvement, however arterial stenoses may require bypass surgery [50, 51].

MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

This systemic necrotizing vasculitis predominantly affects medium-sized arteries with an estimated annual incidence of 1.1 cases per 1,000,000 people in Australia [52] to 31 per 1,000,000 people in Sweden [53], and 77 per 1,000,000 people in the hepatitis-B virus (HBV) endemic area of Alaskan Eskimos [54]. The disorder is slightly more prevalent in males, with a male-to-female ratio of 1.7 to 1.9:1, and most predominant in patients 40 to 60 years of age, with an average age at onset of 47 years [55, 56]. The 2012 Revised CHCC [3] distinguished PAN from MPA, distinguishing it as a necrotizing arteritis of medium or small sized arteries without glomerulonephritis, or vasculitis in arterioles, capillaries or venules, and unassociated with antineutrophil cytoplasm antibodies (ANCA). The pathologic findings of PAN include hyaline-like necrosis in the media which rapidly spreads to the adventitia and intima, and

infiltration by neutrophils, eosinophils, lymphocytes and plasma cells. This is followed later by proliferation of fibroblasts that can thicken the intima and occlude vascular lumina [57].

Although ocular manifestations are not a part of the diagnostic criteria for PAN, they occur in 10% to 20 per cent of patients [58] either due to the direct effects of arteritis that results in vascular ischemia, or as a secondary effect of renovascular hypertension with subsequent retinal edema, transudates, hemorrhages and cystoid body formation [59]. The most common arteries affected are the posterior ciliary arteries and choroidal vessels, which can result in choroidal infarcts and exudative retinal detachments [59]. Conjunctival and anterior uveal involvement has also been reported [60]. Orbital involvement may result in exophthalmos, optic nerve involvement in visual loss, ocular vessel involvement in episcleritis, necrotizing scleritis, and corneal and scleral ulcers [61]. In an analysis of 393 patients with PAN [62], 42 (10.7%) patients had ophthalmologic manifestations of which blurred vision was the most common so noted in 13 of 42 (31%) patients, followed by conjunctivitis in 8 (19%) patients, retinal exudates in 8 (19%) patients, and retinal vasculitis in 7 (17%) patients. Other less common manifestations included uveitis in 5 (12%) patients, episcleritis in 4 (10%) patients, thrombosis in 4 (10%) patients, keratitis and optic neuropathy each in 3 (7.1%) patients, retinal hemorrhages in 2 (5%) patients, and oculomotor nerve palsy in 1 (2%) patient. A study on 348 patients with PAN [63] noted ophthalmologic manifestations in 30 (8.6%) patients, consisting of retinal vasculitis, retinal exudates, or both in 15 (4.3%) patients; conjunctivitis or keratitis in 12 (3.4%) patients, uveitis in 3 (0.8%) patients, and blurred vision in 2 (0.6%) patients. There was little difference in the frequency of ophthalmologic manifestations in those with or without HBV-related PAN, so noted respectively in 10% versus 7% of patients. Moreover, visual symptoms were the presenting manifestation of PAN in several reported patients, including one with thrombocytosis and acute blindness secondary to central retinal vein thrombosis [64], others with visual loss due to retinal vasculitis [59] and bilateral choroidal vasculitis [65], and another patient with dacryoadenopathy [66].

Reports of fundoscopic examination findings in patients with PAN are varied and include papilledema, macular star formation, cotton-wool spots, retinal or subhyaloid hemorrhages, retinal exudates, vascular occlusion of the central retinal artery, and irregularity of the retinal arteries with or without aneurysm formation [59]. Retinal fluorescein angiography may also be particularly helpful in the diagnosis and management of PAN. Acute multifocal choroidal ischemia is a common feature seen on fluorescein angiography in patients with PAN, yet very rare in the general population, presumably because the degree of vasculitis is sufficiently severe to affect the choroid [67]. Other common features on fluorescein angiography in PAN include retinal vasculitis with multiple arterioral and capillary occlusions [67].

Although there are few studies of the effect of corticosteroid treatment on the ocular manifestations of PAN, Nanjiani [58] reported treatment of bilateral optic neuritis, and circumscribed posterior choroiditis with serous retinal detachment with corticosteroids that improved systemic but not ocular manifestations. Akova and colleagues [68] described responsiveness of a spectrum of ocular findings including scleritis, peripheral ulcerative keratitis, nongranulomatous uveitis, retinal vasculitis, pseudotumor of the orbit, and central retinal artery occlusion in five patients, four of whom responded to combination corticosteroid and cyclophosphamide or azathioprine therapy.

Kawasaki Disease

This medium vessel vasculitis is one of commonest vasculitides in children with incidence rates varying from 8.39 per 100,000 children under age 5 per year in England [69] to 218.6 per 100,000 children under age 5 in Japan [70]. The disease occurs more often in males, with a male to female ratio of 1.3-1.6:1 [71, 72]. KD typically occurs in patients under 5 years of age, with a peak age of onset ranging from 9 to 11 months in Japan [70], and over 12 months in Canada and Britain [73, 74]. There are six diagnostic features of KD, five of which are needed for the diagnosis. They include fever of unknown origin lasting five days or more not responding to antibiotics; bilateral conjunctival hyperemia and indurated edema that spares the limbal region; orolabial lesions; redness and edema of palms and soles followed by fingertip desquamation; an erythematous polymorphous rash; and cervical lymph node enlargement [71].

Ocular involvement in KD is typified by bilateral conjunctival hyperemia and indurated edema that spares the limbal region; and conjunctivitis that occurs in 83% to 92% of patients [74]. The conjunctival lesion typically develops within a day or two of fever-onset and lasts up to several months [75]. Other ocular findings included bilateral injection of the bulbar conjunctiva so noted in up to 89% of patients, bilateral iridocyclitis in 78% of patients, superficial punctate keratitis in 22%, vitreous opacities and papilledema each in 11%, and subconjunctival hemorrhage in 6% of patients. Bulbar conjunctival injection typically occurs first, followed by acute iridocyclitis identified by inflammatory cells in the anterior chamber that reaches a maximum between the fifth and eighth day, thereafter diminishing after one month. Acute bilateral iridocyclitis is more common in children 4 years and older however the severity of iridocyclitis is generally independent of age [76**].** Burke and co-workers [77**]** noted that anterior uveitis was a predominant finding during the acute phase of illness. Other less common ocular findings in KD include disciform keratitis, so noted in a 10-year-old [78] and 11-year-old reported children [79], the latter of who presented with diffuse bilateral non-purulent conjunctival congestion, VA of 6/6 in the right eye and 6/5 in the left eye, and later developed cloudy vision. Ophthalmologic examination revealed that his vision was reduced to less than 6/60 in both eyes and that he had bilateral central stroma edema with localized keratitic precipitates. However, fundoscopy showed bilateral disc swelling without evidence of posterior segment inflammation. The latter, also rare, was similarly documented in several patients, including.

Posterior segment involvement in KD was documented in two patients with bilateral vitreous opacities and bilateral optic disc swelling [76], unilateral retinal exudates, macular and disc edema with severe visual loss [80] and in a patient with bilateral inner retinal ischemia diagnosed at postmortem examination [81]. Retinal vasculitis occurs rarely in KD due to selective inflammation of the blood-ocular barrier [76]. Several reported patients underwent FFA for retinal vasculitis, including one with retinal exudation, macular edema, and temporal disc swelling that showed no leakage [82], and another with bilateral acute anterior uveitis, in whom FFA showed disc edema and leakage with localized areas of perivascular sheathing suggestive of periphlebitis and vasculitis [83].

First line therapy for KD includes intravenous immune globulin (IVIg) therapy and aspirin. However corticosteroids and tumor necrosis factor (TNF) inhibitors may beneficial those who fail to respond to IVIg therapy [84, 85]. A few small series and case reports showed a favorable response of conjunctivitis and anterior uveitis respond to treatment with corticosteroids and

mydriatics [80], IVIg therapy and aspirin [83]. One other patient with disciform keratitis and bilateral disc swelling, without signs of posterior segment inflammation, treated with topical steroids every 2 hours, cyclopentolate 1% twice a day and oral acyclovir 200 mg five times a day, experienced rapid resolution of ocular signs and symptoms. His VA improved from 6/60 bilaterally to his baseline of 6/6 in the right eye and 6/5 in the left eye after three weeks of therapy [86]. However, since anterior uveitis can be self-limiting in 2 to 8 weeks, it can be difficult at times to ascertain the true impact of treatment on symptom resolution. Rennebohm [87] described six children with KD, five of whom developed anterior uveitis during the acute phase of KD. Both children treated with corticosteroids and cycloplegic drugs improved, as did the other three untreated children. Similarly, Puglise [75] described a 4-year-old child with KD who presented with bilateral swelling and hyperemia of the conjunctiva unresponsive to intense topical steroid therapy; however there was a reduction in conjunctival inflammation within one week of 30mg/kg of aspirin therapy and complete resolution in four weeks.

SMALL VESSEL VASCULITIS

Anca-Associated

Granulomatosis with Polyangiitis

This systemic necrotizing SVV is characterized by granulomatous inflammation of the upper and lower respiratory tract, with focal necrotizing glomerulonephritis. The disease shows a strong predominance for Caucasians, particularly those of northern European ancestry with a prevalence ranging from 23.7 cases per 1,000,000 people in France [88], to 63 cases per 1,000,000 people in the United Kingdom [89], and 95 cases per 1,000,000 people in Northern Norway [90]. It is slightly more common in men than in women with a 1.3 to 1.7:1 male to female ratio [62, 91], and typically occurs in the fourth and fifth decades of life [62, 88, 91]. The disease is rare in children, but when it occurs, it is four times more common in girls than boys [92]. The histopathology of GPA is characterized by a triad of multinucleated giant cell granulomatous inflammation, vasculitis, and necrosis [93].

The ACR [91] identified four diagnostic criteria for GPA, two of which must be present in order to make the diagnosis from among the following including, nasal or oral inflammation, an abnormal chest radiographic showing nodules, fixed infiltrates, or cavities, urinary sediment showing microhematuria or red cell casts, and granulomatous inflammation on biopsy. The presence of two or more criteria imparted a sensitivity of 88.2% and specificity of 92.0% for the diagnosis of GPA. Although serum ANCA level is not part of the ACR criteria, GPA is associated with ANCA, particularly c-ANCA, the presence of which had 99% specificity and 96% sensitivity for generalized GPA, and 67% sensitivity for the limited form [94]. Ocular findings are not part of the diagnostic criteria for GPA; however among patients with vasculitis [91], ocular inflammation, so noted as scleritis, episcleritis, and proptosis, had a sensitivity of 27.4% and a specificity of 96.9% for the diagnosis of GPA.

Ocular manifestations occur overall in 30% to 60% of patients with GPA [95-97], and are the presenting features in up to 16% of patients [97]. Ocular symptoms can due to primary inflammation or focal vasculitis that affects the anterior and posterior segments of the eye causing conjunctivitis, episcleritis, and keratitis, and optic nerve vasculitis; or as a result of the

contiguous spread of longstanding granulomatous sinusitis leading to proptosis, orbital pseudotumor and nasolacrimal duct obstruction. Vascular complications such as retinal artery occlusion can occur [98]. Frequent symptoms of orbital disease included ocular pain, epiphora and injection although proptosis, vision loss, diplopia and ophthalmoplegia occur [99, 100]. Rothschild and colleagues [62] noted ocular manifestations in 117 (34%) of 343 patients with GPA, exceeding the expected frequency of 11% for EGPA and 9% for MPA. Conjunctivitis was noted in 61 (51.2%) patients, followed by episcleritis in 46 (39.3%) patients, and orbital inflammatory disease in 23 (19.7%) patients. Other ocular manifestations also included blurred vision in 18 (15.4%) patients, uveitis in 9 (7.7%) patients, oculomotor nerve palsy in 5 (4.3%) patients, and sudden visual loss in 4 (3.4%) patients. Less common ocular manifestations were adnexal inflammation, scleritis, blepharitis, keratitis, optic neuropathy, retinal exudates and hemorrhages.

Hoffman and colleagues [96] noted ocular manifestations of GPA among 15% of 158 patients at presentation, and in 52% of those in the course of the illness. Conjunctivitis and dacrocystitis each occurred in 20% of patients; however, they were considered nonspecific features. Painful proptosis, often associated with visual loss due to optic nerve ischemia, and diplopia resulting from extraocular muscle entrapments, so noted in up to 2% of patients at onset of disease and in 15% throughout the course of illness, was a useful diagnostic feature typically caused by retro-orbital pseudotumor. Fauci and co-workers [97] identified proptosis in 15 of 49 (31%) patients with ocular involvement associated with GPA due to retro-orbital mass lesions.

Akikusa and co-workers [92] found eye involvement in 13 of 25 (52%) children with GPA at presentation and in 15 (60%) children over the course of their illness. Similar to adults, the commonest ocular manifestations were conjunctivitis in 14 (56%) patients, scleritis or episcleritis in 3 (12%) patients, and proptosis in 2 (8%) patients. Cabral and colleagues [101] reviewed the presenting clinical features of pediatric patients with GPA in three single- center cohorts and one multicenter cohort, noting ocular manifestations as common presenting features of GPA in children, with conjunctivitis occurring in up to 44% at presentation.

GPA is classified into classic and limited forms, the latter specifically excluding renal disease with a more favorable prognosis. Although both forms can have ocular manifestations of disease, Stavrou and colleagues [102] noted sight-threatening manifestations more often in 16 patients with classic GPA than 15 patients with limited GPA, further noting ocular manifestations in 13 (87%) limited GPA patients compared to 14 (89%) classic GPA patients. Moreover, 4 (27%) patients in the limited group experienced sight-threatening complications compared to 8 (50%) patients in the classical group.

Magnetic resonance imaging depicts mucosal inflammation and ulceration in the sinuses, nasal cavity and orbits in GPA with greater sensitivity than computed tomography (CT) and can aid in the determination of ocular involvement [103]. The serum ANCA test is useful in tracking patient responsiveness to systemic therapy. Shiuey and Foster [94] recognized that patients with GPA and non-normalizing serum ANCA levels after treatment often developed recurrent ocular despite apparent clinical remission. ANCA serology was further helpful in determining disease severity and future complications in patients who present with episcleritis [104], moreover those with positive ANCA serology were more likely to have ocular complications including keratopathy, visual acuity (VA) less than 20/50, and vascular pannus.

Fauci and colleagues [97] recommended remission induction treatment of GPA with 2mg/kg/day of oral cyclophosphamide and 1mg/kg/day of prednisone, followed by tapering of

prednisone to an alternate day administration, achieving complete remission rates of 93% for a mean duration of 48.2 months. Chan and colleagues [98] reported a patient with bilateral corneal ulcers and a VA reduced to 20/200 in the right eye and 20/70 in the left eye that was treated with 2 mg/kg/day of oral cyclophosphamide and 1mg/kg/d of prednisone. Two years later the VA in both eyes returned to 20/40, and the peripheral corneal ulcers healed although shallow peripheral corneal thinning remained. Foster and colleagues [105] studied a patient with GPA and progressive blurred vision, diplopia and increased supraorbital pressure, who was found to have a VA of 20/200 in the right eye, 20/40 in the left eye, 90% ophthalmoplegia in the left eye, and normal fundoscopic exam. The patient was treated with oral cyclophosphamide and prednisone, and one month later VA improved to 20/40 with complete resolution of ophthalmoplegia. Vischio and McCrary [106] who reported a 70-year-old man with left eye visual change, third nerve palsy and orbital mass compressing the optic nerve that was biopsied with proven GPA. The patient was treated with prednisone 40mg twice daily and cyclophosphamide 125mg daily, without visual improvement eleven weeks later. There is substantial ocular morbidity associated with GPA despite efficacious immunosuppressant therapy so noted in three enucleations among 140 patients [95]. Sadiq and colleagues [100] identified a subgroup of patients with GPA and orbital involvement with a poor prognosis evidenced by permanent visual loss in 43% of the patients.

Some patients with episcleritis, conjunctivitis, and anterior uveitis respond to topical therapy, but they should not be used because of secondary corneal thinning and perforation [107]. Although the surgical intervention is generally reserved for the performance of tissue biopsies, dacryocystorhinistomy was effective therapy for nasolacrimal duct obstruction, achieving symptomatic relief in 13 of 14 (93%) of patients [108].

Eosinophilic Granulomatosis with Polyangiitis

This systemic necrotizing small vessel vasculitis involves multiple organ systems, typically causing chronic rhinosinusitis, asthma, and eosinophilia. It is a rare disorder with an estimated annual incidence of 2.7 cases per 1,000,000 people and a period prevalence rate of 6.8 per million in those taking anti-asthma drugs [89, 109]. With most patients developing the disease in the fourth decade of life between age 14 and 74 years, EGPA has no gender predominance [62, 88, 110].

The ACR 1990 diagnostic criteria for EGPA [111] included six criteria, four of which were necessary from the following including, asthma, eosinophilia greater than 10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. The presence of four or more criteria yielded a sensitivity of 85% and a specificity of 99.7% for the diagnosis of EGPA. Although ANCA positivity is not part of the ACR's diagnostic criteria, it can be helpful in making the diagnosis in up to 70% of patients [88]. The characteristic changes of EGPA histopathology include necrotizing vasculitis and extra-vascular necrotizing granulomas with eosinophilic infiltrates; however, early cases may be characterized by tissue infiltration by eosinophils without overt vasculitis [112].

Ocular features of EGPA can involve all parts of the eye and orbit. Takanashi and co-workers [113] classified the ocular manifestations into two types, pseudotumor or orbital inflammatory and ischemic vasculitis types. Patients with the pseudotumor type typically present with a chronically red eye, dacryoadenitis, myositis, periscleritis, perineuritis, conjunctival granuloma, episcleritis, orbital abnormalities on imaging, and ANCA

seronegativity. Those with the ischemic vasculitis present with sudden visual loss, amaurosis fugax, anterior ischemic optic neuropathy, central retinal artery or branch retinal artery occlusion, normal orbital imaging, and ANCA seropositivity.

Among 270 patients with EGPA [62] 30 (11%) patients had ocular manifestations of which conjunctivitis was the most common so noted in 13 (43.3%) patients followed by blurred vision in 9 (30%) patients, oculomotor nerve palsy and sudden visual loss each in 4 (13.3%) patients. retinal vasculitis in 3 (12%) patients; orbital inflammatory disease, and retinal exudates each in 2 (6.7%) patients; and episcleritis, keratitis, uveitis, retinal thrombosis, and retinal exudates present each in 1 (3.3%) patient. Androudi and colleagues [114] described a patient with a 20 year history of severe steroid-dependent asthma, hematuria, pleuritis and sinusitis, who later developed uveitis and bilateral scleritis. Anterior ischemic optic neuropathy was reported by Lee and colleagues [115] in a 54- year-old man with bronchial asthma, allergic rhinitis, and sinusitis who presented with a sudden decrease in VA. Central retinal artery occlusion, another complication of EGPA, leading to sudden visual loss, was described among several other patients. Skrapari and colleagues [116] described a 50-year-old woman with left foot drop and painless visual loss in whom fundoscopy revealed central retinal artery occlusion. Kumano and co-workers [117] reported a 54-year-old woman with sudden loss of vision after tapering prednisolone from 30 mg to 10 mg per day, in whom central retinal artery occlusion was noted on FFA that showed delayed filling of the retinal and cilioretinal arteries, without leakage secondary to vasculitis. Hamann and Johansen [118] reported severe visual loss in association with central retinal artery occlusion evidenced by retinal whitening, macular cherry-red spot, combined with central retinal vein occlusion so noted by papilledema, retinal hemorrhages, and dilated and tortuous veins on Fundoscopy; fluorescein angiography revealed an absence of retinal filling.

Among 96 patients with EGPA described by Guillevin and colleagues [110] 3 (3.1%) patients presented with ophthalmic involvement. 2 had episcleritis, and 1 had bilateral exophthalmos. Koenig and co-workers [119] reported a patient with monocular blindness due to central retinal artery occlusion as the presenting feature of EGPA. McNab [120] described a 66-year-old woman with diplopia, foreign body sensation, redness and proptosis of the left eye, in whom orbital CT scan revealing increased density of the left orbital fat. In addition, Jordan and co-workers [121] reported two cases of EGPA who presented with dacryoadenitis and diffuse orbital inflammation. Takanashi and colleagues [113] recommended enhanced orbital imaging to look for inflammatory lesions. Fundoscopy is useful in identifying patients with central retinal artery occlusion.

The treatment of EGPA typically consists of corticosteroids and cyclophosphamide [122]; however plasma exchange can be added to treat patients with advanced renal disease, with expected survival rates approaching 90% [123]. There are no randomized, controlled studies of the efficacy of treatment on the ocular manifestations of EGPA. McNab [120] described a 66-year-old woman with orbital inflammation who responded rapidly and completely to an oral prednisolone taper starting at 50 mg. A patient with anterior ischemic optic neuropathy responded to treatment with 24 mg of methylprednisolone daily however after one month, VA improved from 20/50 to 20/25 in addition to improved respiratory symptoms. Followup fundoscopy revealed subsiding papilledema and splinter hemorrhages but Goldmann perimetry showed residual central visual field defect [115]. Central retinal artery occlusion generally carries a less favorable prognosis.

Microscopic Polyangiitis

This necrotizing small vessel vasculitis typically affects the kidney causing a pauci-immune focal necrotizing crescentic glomerulonephritis, and the lungs causing pulmonary capillaritis. Its annual incidence is 3.6 cases per million people [124], with a mean age of onset over 50 years, and slightly male predominance with a male to female ratio varying from 1 to 1.2:1 [62, 125]. The histopathology of MPA is similar to GPA and EGPA in that there is a necrotizing vasculitis; however, the absence of granulomatous inflammation distinguishes MPA from GPA, as does absence of asthma and eosinophilia from EGPA [126].

In 1990 the ACR developed criteria for diagnosing the systemic vasculitides, but it did not distinguish MPA from PAN. However, the 2012 revised CHCC distinguished the two defining MPA as a necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels, often associated with necrotizing glomerulonephritis and pulmonary capillaritis; granulomatous inflammation is absent [3]. Although the presence of ANCA is not part of the diagnostic criteria, up to 65% of patients are positive for pANCA [125, 127].

Ocular findings are not part of the diagnostic criteria for MPA, and are much less common in MPA than in other AAV. Nevertheless, ocular involvement can occur in up to 24% of patients with MPA most often presenting as episcleritis or conjunctivitis [128]. A study by Rothschild and colleagues [62] in 280 patients with MPA found that 25 (9%) had ocular manifestations. Of those with ocular manifestations, the most common was conjunctivitis occurring in 7 (28%), episcleritis occurring in 5 (20%), and blurred vision occurring in 4 (16%). Other less frequent ocular manifestations included retinal vasculitis in 3 (12%), retinal exudates, optic neuropathy, sudden visual loss and oculomotor nerve palsy in 2 (8%) patients each, and scleritis, keratitis, uveitis, retinal hemorrhage in 1 patient (4%) each. Other studies report less frequent ocular manifestations of disease, so noted in a study by Guillevin and colleagues [125] in a study of 85 patients that found only 1 patient (1.2%) with ocular involvement.

Although ocular signs and symptoms are rarely presenting features of MPA, there are patients who initially present with ocular involvement. Hara and colleagues [127] described a patient who presented with hyperemia and photophobia of the eyes and found to have limbal infiltration, iritis and scleritis due to MPA. Altaie and co-workers [129] reported an 80-year-old woman with MPA who presented with painless vision loss in the right eye, and was found to have optic neuritis. Darlington and co-workers [130] described a 16-year-old woman with the initial presentation of peripheral keratitis.

Episcleritis and conjunctivitis are the commonest ocular manifestations of MPA, and it is critical to distinguish between the two since episcleritis generally implies a worse prognosis. Alrashidi and colleagues [131] demonstrated the importance of recognizing anterior scleritis in the description of a patient with MPA with recurrent episodes of pain and redness for 7 years thought to be due to conjunctivitis. Eventually, the patient was diagnosed with episcleritis when she presented with severe ocular inflammation and vision loss, and slit lamp evaluation that demonstrated episcleritis. Thus, the authors suggest that a slit lamp evaluation should be done on patients with MPA to aid in the evaluation of the patient and determine appropriate treatment.

MPA is typically treated with corticosteroids and cyclophosphamide, and in severe cases plasmapheresis and IVIG have shown to be beneficial. If renal function is preserved, methotrexate may be added to induce remission. Maintenance therapy is recommended with

azathioprine [132]. A favorable response to treatment occurs in up to 79% of patients with 5-year survival rates ranging from 65% to 80% [128, 133].

Since ocular features in MPA are rare, the effects of treatment on ocular disease have been documented through single patient reports or small series. Mihara and co-workers [134] described two patients, one of whom had hypopyon iridocyclitis in the right eye, and ophthalmoscopy with retinal cotton-wool spots in the left eye, both of which responded to oral prednisolone, topical instillation of 1% atropine sulfate and subconjunctival injections of betamethasone.

The patient with bilateral scleritis and corneal infiltration responded to the betamethasone treatment. Altaei and co-workers [129] described a patient with initial VA of hand movement only in the right eye that improved to 6/9 in the right eye after 4 months of pulsed 100 mg/day of methylprednisolone followed by 60 mg/day of oral prednisolone and 100 mg/day of azathioprine.

IMMUNE COMPLEX MEDIATED

Hypocomplementemia Urticarial Vasculitis

HUV is a rare severe systemic form of urticarial vasculitis characterized by chronic non-pruritic urticarial lesions, angioedema, ocular inflammation, arthritis or arthralgia, obstructive lung disease, and glomerulonephritis. Its exact incidence is unknown, but it is twice more common in women than in men, and its peak incidence is seen in the fifth decade of life [135]. The histopathology of HUV is characterized by an interstitial neutrophilic infiltrate of the dermis, and a necrotizing vasculitis with immunoglobulin or C3 deposits in the blood vessels on immunofluorescence [136].

The diagnostic criteria for HUV were first described by Schwartz and colleagues [137]. The major criteria are urticaria for more than 6 months duration and hypocomplementemia. The minor criteria, two of which are required for diagnosis, were dermal venulitis on biopsy, arthralgia or arthritis, uveitis or episcleritis, mild glomerulonephritis, recurrent abdominal pain, and a positive C1q precipitin test by immunodiffusion, with reduced circulating C1q levels. Exclusion criteria included significant cryoglobulinemia, elevated anti-DNA antibody titer, high titer of antinuclear antibody (ANA), hepatitis B virus (HBV) antigenemia, decreased C-esterase inhibitor levels, and inherited complement deficiency. HUV and SLE share many clinical features, thus it is important to note that COPD and uveitis are typically found in HUV, but not SLE [138].

Ocular manifestations of HUV are found in up to 60% of patients. A study by Wisnieski and colleagues [138] in 18 patients with HUV found that 11 (61%) patients had ocular manifestations, 8 (44%) had conjunctivitis, episcleritis, and/or inflammation of the uveal tract, while 3 (16.6%) had scleral inflammation and photophobia. Davis and colleagues [139] found that 21% of patients had episcleritis or uveitis, while none with normocomplementemic urticarial vasculitis had ocular manifestations. Iridocyclitis, so noted in two patients by Corwin and Baum [140] was postulated to result from immune complex deposits. Thorne and colleagues [141] described a 67-year-old-man with eye pain, redness, rash, arthralgia and malaise later noted to have bilateral anterior scleritis without evidence of keratitis or uveitis,

and diagnosed with HUV. Mosawi and Hermi [142] described an 8-year-old boy with conjunctivitis who later developed episcleritis. The diagnosis of HUV is ultimately based on clinical presentation, laboratory findings, and tissue biopsy; however since ocular manifestations of disease are so pervasive, Wisnieski and co-workers [138] suggested that suspected patients should be screened for ocular inflammation with a slit lamp exam.

The treatment of HUV consists of dapsone and systemic corticosteroids, and nonsteroidal anti-inflammatory medication (NSAID) for symptomatic arthralgia and arthritis, and plasmapheresis in severe cases [135, 139]. Wisnieski and colleagues [138] studied 8 patients with C1q/HUV with conjunctivitis, episcleritis, and inflammation of the uveal tract, identifying three patients with scleral inflammation and noting that none developed chronic or irreversible ocular injury. All responded to prednisone and ophthalmic steroids. Thorne and colleagues [141] documented the response of scleritis to treatment in a 67 year-old-man with bilateral scleritis, who responded to 1 mg/kg/day of prednisone 1 mg/kg daily and 30 mg/kg/day of mycophenolate mofetil in six months. The response of iridocyclitis to cycloplegic and topical corticosteroids was shown by Corwin and Baum [140].

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is a small vessel vasculitis involving the skin, joints, peripheral nervous system and kidneys. The disease is more common in Southern Europe than in Northern Europe or Northern America, and the prevalence of essential mixed cryoglobulinemia is reported to be approximately 1 case per 100,000 people [143]. The mean age of onset of CV is in the fifth to sixth decade of life, with an age at onset of 27 to 78 years, and a female to male ratio of 1.3 to 3:1 [144-146]. The histopathology of CV is characterized by a leukocytoclastic vasculitis, B-lymphocyte expansion and tissue B-cell infiltrates [146].

The 2012 Revised CHCC defined CV as a vasculitis with cryoglobulin immune deposits affecting small vessels associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved [3]. Ocular signs and symptoms are neither part of the diagnostic criteria for CV, nor are they very common.

The first ocular manifestation of CV was likely described by Wintrobe and Buell [147] in a patient suffering from multiple myeloma that had bilateral thrombosis of the central retinal veins and visual impairment. Other ocular manifestations included anterior uveitis, scleritis, and peripheral ulcerative keratitis. Ryan and colleagues [148] described a 42-year-old woman with CV who had attacks of acute arthritis and urticarial lesions with painful red eyes and photophobia, later found to have 4+ cellular infiltrates and flare on slit-lamp examination consistent with anterior uveitis. Anterior uveitis was documented by Nicholson and Sobrin [149] in the description of a 40-year-old man with severe anterior uveitis associated with type II essential cryoglobulinemia. Scleritis and peripheral ulcerative keratitis were other manifestations so noted by Kedhar and co-workers [150] in a 49-year-old woman with necrotizing scleritis and peripheral ulcerative keratitis associated with Hepatitis C virus (HCV) infection.

Myers and colleagues [151] described in a 44-year-old man with chronic HCV-associated CV who developed sudden loss of vision in his left eye and abdominal pain. Fundoscopy revealed peripapillary cotton-wool spots and superficial retinal whitening in the macula. FFA revealed retinal vascular non-perfusion in the left macular and peripapillary region, but not in

the periphery, consistent with Purtscher retinopathy. The authors proposed that the retinopathy developed as a result of complement-mediated microembolism leading to vaso-occlusion. Sauer and co-workers [152] documented a patient with Purtscher-like retinopathy associated with HCV-associated CV with complaints of visual loss. Purtscher retinopathy and hypertensive retinopathy were described by Gorevic and colleagues [153] among 22 patients with CV, 14 (63.6%) of whom had hypertension, and 8 (36.4%) with hypertensive retinopathy; the latter likely resulted from CV-mediated, renovascular hypertension.

Central serous chorioretinopathy is another ocular complication of CV. Cohen and colleagues [154] reported two patients with CV who presented with serous retinal and retinal pigment epithelial detachments resembling central serous chorioretinopathy. The authors postulated that the increased protein content of the choroid in patients with CV caused an abnormal excess of interstitial fluid to accumulate in the subretinal pigment epithelium or subretinal space resulting in retinal pigment epithelial detachment.

The treatment of CV consists of corticosteroids plus an alkylating agent which is associated with induction of remission in up to 62% of patients. Rituximab plus corticosteroids has more recently been found to be beneficial producing induction of remission in up to 64% of patients. Though the combination of rituximab and corticosteroids is the most effective treatment for CV, it is associated with infection in 42% [145] of patient so treated. In those with HCV-associated CV, treatment of HCV with pegylated IFN and ribavirin in addition to rituximab is the optimal treatment for most [155]. Nicholson and Sobrin [149] described a patient with CV who presented with severe anterior uveitis who did not respond to corticosteroids but improved with plasmapheresis and rituximab. Kedhar and co-workers [150] found that necrotizing scleritis and peripheral ulcerative keratitis due to CV improved with high-dose prednisone, pegylated interferon, ribavirin, and cyclophosphamide. Myers and colleagues [151] described successful treatment of Purtscher retinopathy with plasmapheresis, prednisone and cyclophosphamide leading to improvement in left eye VA from 1/200 to 20/200, and resolution of retinal whitening, cotton-wool spots and retinal hemorrhages observed on fundoscopy in six months.

Central serous chorioretinopathy, another ocular manifestation of CV, responded to treatment with laser photocoagulation so noted by Cohen and colleagues [154] in two patients who achieved near normal VA in both eyes.

IgA Vasculitis

This small vessel vasculitis is characterized by IgA IC deposition, in addition to nonthrombocytopenic palpable purpura, abdominal pain and arthritis. It is one of the most common vasculitides in children, with an annual incidence rate between 10-18 per 100,000 children per year [156, 157]. IgAV has a peak incidence in those under age 6, is slightly more common in males, and more frequent during winter months [156-158]. The pathology of IgAV is characterized by infiltration of small blood vessels with polymorphonuclear leukocytes, and the presence of leukocytoclasia [156].

The ACR diagnostic criteria have found that the presence of two or more of the following criteria were 89.4% diagnostically sensitive and 88.1% specific for IgAV including, age at onset before 20 years, palpable purpura, acute abdominal pain, and biopsy showing granulocytes around arterioles or venules [159].

Ocular manifestations of IgAV are rare, but case reports have documented a range of ophthalmologic complications. Recurrent episcleritis was one of the first ocular complications of IgAV in a 14-year-old girl who developed photophobia and intermittent ocular pain 5 weeks after the onset of joint symptoms [160], ophthalmologic evaluation of whom revealed episcleritis and engorgement of the episcleral vessels.

The association between anterior uveitis and IgAV was first reported by Yamabe and colleagues [161] in the description of a patient with nephritis, anterior uveitis and keratitis later. Muqit and co-workers [162] described a 42-year-old man with HSP complicated by keratitis and granulomatous anterior uveitis. Erer and co-workers [163] reported a 39-year-old man with IgAV who presented with three episodes of anterior uveitis, one of which was bilateral, and unilateral episodes of each eye. Kaur and colleagues [164] documented bilateral anterior uveitis associated with IgAV in an 11-year-old boy with a 4 year history of eye pain and photosensitivity. Uveitis in IgAV is thought to be due to circulating IC, which reach the eye and deposit in uveal tissues. IC can deposit in vascular endothelial cells, pigmented epithelial cells, and corneal endothelial cells, expressing adhesion molecules that allows leukocytes to migrate to the uveal tissue and cornea causing injury [165].

Although IgAV is not typically associated with frank bleeding, bilateral subperiosteal orbital hematomas are a recognized complication so noted by Ma'luf and colleagues [166] in a 5- year-old-boy who presented with bilateral exophthalmos and bilateral upper eyelid ecchymosis.

Wu and colleagues [167] reported a 6-year-old girl who developed sudden vision loss, and later found on fundoscopy to have a cherry red spot with severe retinal edema of the macula and peripalliary area of the eyes, with disc edema and venous engorgement consistent with bilateral central retinal artery occlusion. Central retinal vein occlusion was reported in a 12-year-old boy with IgAV [168].

Other rare ocular manifestations include AION [169] and acute visual loss due to bilateral cystoid macular edema and cotton wool spots [170].

The treatment of IgAV varies with disease severity with milder cases responsive to supportive therapy and self-resolve in 6 to 16 weeks, and more severe involvement requiring systemic corticosteroids and IVIg [171]. Ocular manifestations of IgAV resolve with a combination of systemic and topical corticosteroids. A patient with episcleritis due to IgAV responded to corticosteroids, but had exacerbations of episcleritis whenever the alternate day prednisone dose was tapered to less than 30 mg (160). Erer and co-workers [163] described a patient with anterior uveitis who had three recurrent episodes of anterior uveitis, each which resolved within days of treatment with topical corticosteroids. Kaur and colleagues [164] reported on an 11-year-old male with anterior uveitis that responded to systemic prednisolone, topical steroids and homatropine eye drops.

AION-associated IgAV responds moderately well to corticosteroid treatment as noted by Chuah and Meaney (169) in the care of a 54-year-old man with AION whose VA improved from counting fingers to 6/36 with 4 mg of daily prednisolone. Cystoid macular edema and cotton wool spots were noted to respond to 60 mg of oral prednisone with resolution of the macular edema in two days [170].

VARIABLE VESSEL VASCULITIS

Behçet Disease

This disorder is characterized by relapsing aphthous ulcers of the mouth, eye and genitalia [172]. The most widely used diagnostic criteria of BD were formulated by the International Study Group (ISG) [173] that include recurrent oral ulcerations plus any two of genital ulceration, typical defined eye lesions, typical skin lesions, or a positive pathergy. Recurrent oral ulcerations are categorized as minor aphthous, major aphthous, and herpetiform ulcerations that recurred at least three times in a 12-month period. Recurrent genital ulcerations are defined as aphthous ulceration and scarring. Eye lesions were defined as anterior uveitis, posterior uveitis or cells in the vitreous on slit lamp examination; and retinal vasculitis. Compatible skin lesions included erythema nodosum, pseudofolliculitis, papulopustular lesions, and aceneiform nodules in post-adolescent patients not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitity was defined as positive when a sterile pustule developed after twenty four to forty-eight hours at the site of a needle prick to the skin [174]. Although the usual onset of BD is in the third or fourth decade of life, pediatric-onset cases have been described [175, 176]. Uluduz and colleagues [175] studied two large Istanbul BD cohorts totaling 728 patients, ascertaining and comparing pediatric-onset (26 patients) and adult adult-onset (702 patients)-neurological (NBD) that differed in male predominance and more frequent dural venous sinus thrombosis in pediatric patients compared to parenchymal neurological involvement in adults. Citirik and colleagues [176] described ocular findings in 34 pediatric patients that included panuveitis, posterior and anterior uveitis respectively in 53%, 32% and 15% of patients. Other ocular findings included cataracts in 59%, posterior synechiae in 24%, postoperative capsular opacification 24%, vitreous condensation after vitritis in 50%, optic atrophy in 30%, cystoid macular edema 15%, narrowed or occluded retinal vessels after retinal phlebitis and branched retinal occlusions in 6%, neovascularization of the disk and phthisis bulbi each in 3% of patients. Arai and colleagues [177] described the postmortem findings in a young man with BD with relapsing unilateral uveitis, sensorineural hearing loss, slight fever, and progressive CNS and autonomic nervous system involvement that included multifocal brainstem and cerebellar necrotic foci, perivascular neutrophilic inflammation, and perivasculitis.

Cortical venous sinus thrombosis (CVST) in BD most commonly presents with symptoms and signs of increased intracranial pressure with a rarity of venous infarcts. Prothrombosis when present, is presumed to commence as an endothelial disturbance. The treatment of BD-related CVST includes consideration of anticoagulation and corticosteroids alone or in association with another immunosuppressant agent.

Cogan Syndrome

Morgan and Baumgartner [178] described a 26-year-old man with recurrent pain, spasm and redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis and explosive Menière disease was made however in retrospect this patient may have been the first

reported case of CS associated with nonsyphilitic interstitial keratitis (IK). Vestibuloauditory symptoms were later described by Cogan [179]. Haynes and colleagues [180] set forth diagnostic criteria for typical CS according to the definitions established by Cogan [179] in a review of 30 patients seen at the National Eye Institute of the National Institutes of Health (NIH) by Cogan [179, 181] with symptoms of IK that developed abruptly and gradually resolved, associated with photophobia, lacrimation, and unilateral or bilateral eye pain. Such symptoms tended to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and frequently progressive hearing loss that characteristically occurred before or after the onset of IK. However within one to six months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of one to three months, certainly no longer than two years.

Gluth [182] reviewed a cohort of CS seen at the Mayo Clinic between 1940 and 2002. The commonest symptoms at presentation were sudden hearing loss in 50%, balance disturbance in 40%, ocular irritation I n32%, photophobia in 23%, tinnitus in 13%, and blurred vision in 10%). Specifically noted inflammatory eye findings that occurred in the course of disease included interstitial keratitis in 77%, iritis or uveitis in 37%, oscillopsia in 25%, scleritis or episcleritis in 23%, and conjunctivitis in 10%.

Most patients with CS (58%) were treated with corticosteroids with an overall favorable response in both vestibuloauditory and ophthalmologic manifestations, with the remainder demonstrating only ophthalmologic (23%) or vestibuloauditory improvement (19%) alone (98). Other therapies included methotrexate, cyclophosphamide, azathioprine, entanercept, hydroxchloroquine, and IVIg therapy. Surgical cochlear implantation can led to objective and subjective benefits with improved hearing recognition.

SINGLE ORGAN VASCULITIS

Primary CNS Vasculitis

Adult [183] and childhood isolated CNS angiitis [184], primary angiitis of the CNS [185], adult [186] and childhood PCNSV [187]; granulomatous angiitis of the brain (GAB) (188) and granulomatous angiitis of the nervous system (GANS) [189], are equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS of diverse cause and clinicopathologic expression.

The diagnosis of PACNS [185], like IACNS [183] relies upon the presence of the classic angiographic features of beading in cerebral angiographic studies or the histopathologic features of angiitis in brain and meningeal vessels in the absence of systemic vasculitis or another cause for the observed findings. Affected patients with PACNS present with headache of gradual onset accompanied by either focal neurological signs or diffuse cognitive changes, so noted respectively in those with involvement of either large named arteries or small meningeal and distal terminal cortical vessels. The clinical course can be rapidly progressive over days to weeks, or insidiously over weeks to months, with seemingly prolonged periods of stabilization.

Younger and colleagues [188] described symptoms and signs in four patients with GAB alone or in association with concomitant neurosarcoidosis, varicella zoster virus (VZV) infection, and Hodgkin lymphoma, and reviewed the clinical and laboratory findings in 74 additionally-proven cases. Mental change, headache, fever, focal weakness, and visual changes, were the commonest symptoms and signs at onset respectively in 58%, 54%, 21%, 15%, 9% at presentation, and in 78%, 54%, 21%, 42%, and 12% during the course of the illness. Visual symptoms included diplopia, amaurosis fugax, blurring of vision, and contiguous involvement of the eye in those with V1 dermatomal VZV lesions. Hemiparesis, quadriparesis, and lethargy were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis followed by combination chemotherapy employing corticosteroids and cyclophosphamide.

Cupps and colleagues [183] noted neuro-ophthalmological involvement in two of four patients with IACNS. Patient 1 had transient hemifield visual loss accompanied by headaches before the angiographic diagnosis of IACNS with involvement of named cerebral vessels, followed several months later after commencement of combination immunosuppressant therapy by a one-week period of altered VA. Patient 3 had a unilateral fundus Roth spot, with markedly decreased VA and normal pupillary response before diagnostic cerebral angiography of IACNS showed narrowing of named cerebral vessels, followed months later after commencement of combination immunosuppressant therapy by occipital headaches, transient decreased visual acuity and a starburst image in the central visual field.

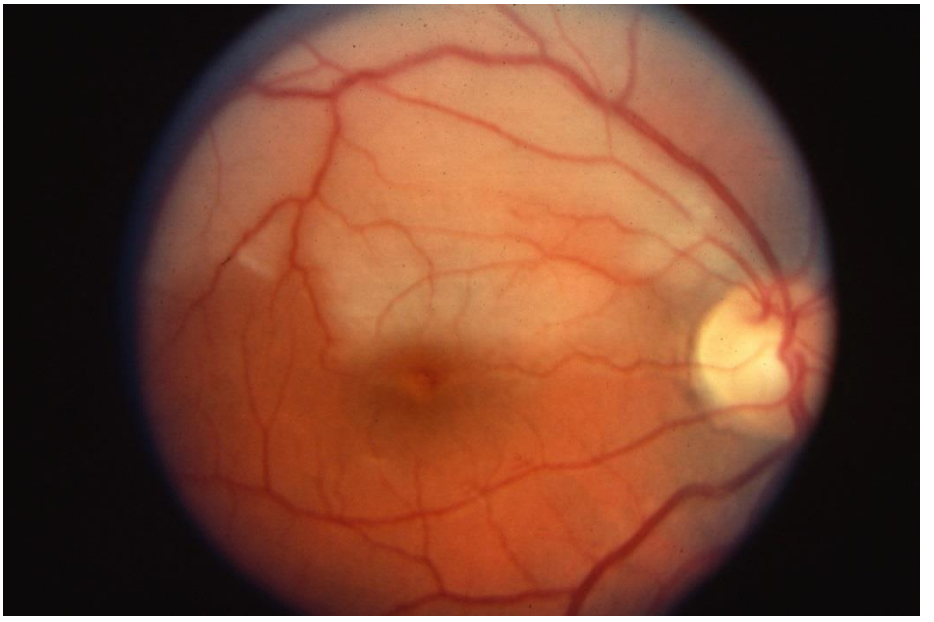


Figure 2. Branch retinal artery occlusion in a patient with isolated CNS vasculitis.

Calabrese and Mallek [185] reported eye signs in 15% of literature cases with angiographically or pathologically defined PACNS but in none of 8 Cleveland Clinic patients. Among 70 patients with angiographically-defined and 31 patients with pathologically-verified PCNSV described by Salvarani and colleagues [186], hemiparesis, unilateral numbness, blurred vision and decreased acuity were most common in those with angiographically-defined

PCNSV, although persistent neurological deficit or stroke and headache were the commonest initial findings overall in 68% of patients. A granulomatous pattern of inflammation was seen most often in those with altered cognition and at an older age. Lanthier and coworkers [184], who described histologically-proven IACNS in two children, had one child (Case 2) with bilateral optic disk swelling and persistent conjugated gaze-evoked nystagmus at presentation. Among four children with angiographically-negative childhood PACNS described by Benseler and colleagues [187] one child (Patient 3) was noted to have gaze-evoked nystagmus. (Figure 2)

CONCLUSION

Ophthalmologic and neuro-ophthalmologic manifestations of primary systemic and isolated CNS vasculitis typically arise in association with ischemic vascular disease of the CNS. Although uncommon, such manifestations may be the first clue to underlying ischemic disease due to primary or secondary involvement of visual and eye movement pathways warranting further evaluation for CNS vasculitis.

REFERENCES

[1] Galetta SL. Vasculitides. Chapter 44. In, CN McGhee, ed. *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. Lippincott Williams & Wilkins: Philadelphia, 2008; 2333-2426.

[2] Jennette JC, Falk RJ, Andrassay K, et al. Nomenclature of systemic vasculitides. Proposal of an international conference. *Arthritis Rheum.* 1994; 37:187-192.

[3] Jennette JC, Falk RJ, Bacon PA. 2012 Revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* 2013; 65:1-11.

[4] Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PRES endorsed consensus criteria for the classification of childhood vasculitides. *Ann. Rheum. Dis.,* 2006; 65:936-941.

[5] Ruperto N, Ozen S, Pistorio A, et al. EULAR/PINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: Overall methodology and clinical characterization. *Ann. Rheum. Dis.,* 2010; 69:790-797.

[6] Salvarani C, Gabriel SE, O'Fallon WM, et al. The incidence of giant cell arteritis in Olmsted, County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann. Intern. Med.,* 1995; 123:192-194.

[7] Baldursson O, Steinsson K, Björnsson J, et al. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. *Arthritis Rheum.* 1994, 37:1007-1012.

[8] Weyand CM, Liao YJ, Goronzy JJ. The immunopathology of giant cell arteritis: diagnostic and therapeutic implications. *J. Neuroophthalmol.,* 2012; 32:259-265.

[9] Gonzalez-Gay MA, Blanco R, Rodriguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum.* 1998; 41:1497-1504.

[10] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* 1990; 33:1122-1128.

[11] Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. *Ann. Intern. Med.,* 1990; 129:345-352.

[12] Weyand CM, Goronzy JJ. Medium-and large-vessel vasculitis. *N Engl J Med* 2003; 349:160-169.

[13] Fraser JA, Weyand CM, Newman NJ, et al. The treatment of giant cell arteritis. *Rev. Neurol. Dis.,* 2008; 5:140-152.

[14] Hayreh SS, Podhajsky P, Zimmerman B. Ocular manifestations of giant cell arteritis. *Am. J. Ophthalmol.,* 1998; 125:509-520.

[15] Huston KA, Hunder GG, Lie JT, et al. Temporal arteritis: a 25-year epidemiologic, clinical, and pathologic study. *Ann. Intern. Med.,* 1978; 88:162-167.

[16] Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis. *Arthritis Rheum.* 2003; 48:3532-3537.

[17] Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. *Am. J. Ophthalmol.,* 1998; 125:521–526.

[18] Prieto-González S, Arguis P, García-Martínez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann. Rheum. Dis.,* 2012; 71:1170–1176.

[19] Guyer DR, Miller NR, Auer Cl, et al. The risk of cerebrovascular and cardiovascular disease in patients with anterior ischemic optic neuropathy. *Arch. Ophthalmol.,* 1985; 103:1136-1142.

[20] Hayreh SS. Anterior ischaemic optic neuropathy. Differentiation of arteritic from non-arteritic type and its management. *Eye,* 1990; 4:25-41.

[21] Hayreh SS. Anterior ischaemic optic neuropathy II. Fundus on ophthalmoscopy and fluorescein angiography. *Br. J. Ophthalmol.,* 1974, 58:964-980.

[22] Galetta SL. Vasculitis. In: Miller NR, Newman NJ, Biousse V, et al., eds. *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. Vol 2. 6th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005: 2347-2365.

[23] Ho AC, Sergott RC, Regiollo CD, et al. Color Doppler hemodynamics of giant cell arteritis. *Arch. Ophthalmol.,* 1994; 112:938–945.

[24] Salvarani C, Cantini F, Boiardi L, et al. Medical progress: Polymyalgia rheumatic and giant cell arteritis. *N. Engl. J. Med.,* 2002; 347: 261–271.

[25] Nesher G, Berkun Y, Mates M, et al. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum.* 2004; 50:1332–1337.

[26] Aiello PD, Trautmann JC, McPhee TJ, et al. Visual prognosis in giant cell arteritis. *Ophthalmology,* 1993; 100:550–555.

[27] Danesh-Meyer H, Savino PJ, Gamble GG. Poor prognosis of visual outcome after visual loss from giant cell arteritis. *Ophthalmology,* 2005; 112:1098-103.

[28] Liu GT, Glaser JS, Schatz NJ, et al. Visual morbidity in giant cell arteritis: Clinical characteristics and prognosis for vision. *Ophthalmology,* 1994; 10: 1779–1785.

[29] Peter J, David S, Danda D, et al. Ocular Manifestations of Takayasu arteritis: a cross-sectional study. *Retina,* 2011; 31:1170-1178.

[30] Uyama M, Asayama K. Retinal Vascular Changes in Takayasu's Disease (Pulseless Disease), Occurrence and Evolution of the Lesion. *Documenta Ophthalmologica Proceedings Series,* 1976; 9:549-554.

[31] Kerr GS, Hallahan CW, Giordana J, et al. Takayasu Arteritis. *Ann Intern Med* 1994; 120:919-929.
[32] Watts R, Al-Taiar A, Mooney J, et al. The epidemiology of Takayasu arteritis in the UK. *Rheumatology,* 2009; 48:1008-1011.
[33] Dreyer L, Faurschou M, Baslund B. A population-based study of Takayasu's arteritis in eastern Denmark. *Clin. Exp. Rheumatol.,* 2011; 29:S40-S42.
[34] Nasu T. Takayasu's truncoarteritis in Japan: A statistical observation of 76 autopsy cases. *Pathol. Microbiol.* 1975;43:140–146.
[35] Lande A, Bard R, Roosi P, et al. Takayasu's arteritis. A worldwide entity. *NY State J. Med.,* 1976; 32:379-392.
[36] Arend WP, BA Michel, Hunder GG, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* 1990;33:1129-1134.
[37] Koszewski B. Branchial Arteritis or Aortic Arch Arteritis. A New Inflammatory Arterial Disease (Pulseless Disease): Critical Review. *Angiology,* 1958; 9:180-186.
[38] Chun YS, Park SJ, Park IK, et al. The clinical and ocular manifestations of Takayasu arteritis. *Retina,* 2001; 21:132-140.
[39] Sagar S, Kar S, Gupta A, et al. Ocular changes in Takayasu arteritis in India. *Jpn. J. Ophthalmol.,* 1994; 38:97–102.
[40] Kiyosawa M, Baba T. Ophthalmological findings in patients with Takayasu disease. *Int. J. Cardiol.,* 1998; 66:S141–S147.
[41] Takayasu M. A case with peculiar changes of the central retinal vessels. *Acta. Soc. Ophthalmol. Jpn.* 1908; 12:554–557.
[42] Kaushik S, et al. Retinal arterial occlusion in Takayasu's arteritis. *Indian J. Ophthalmol.,* 2005; 53:194-196.
[43] Shailaja S, Vivek G, Shetty R, et al. 'Eye is a window the pulse': bilateral ocular ischaemic syndrome as a presenting manifestation of Takayasu arteritis. *BMJ Case Reports,* 2013.
[44] Demir MN, Hazirolan D, Altiparmak UE, et al. Takayasu's disease and secondary ocular ischemic syndrome. *J. Pediatr. Ophthalmol. Strabismus,* 2010; 47:54-57.
[45] Pelegrin T, Mesquida M, Rey A, et al. Blind runner. *Surv. Ophthalmol.* 2012; 57:486-494.
[46] Baba T, Itakura K, Tanaka R, et al. Importance of fluorescein angiographic study in evaluation early retinal changes in Takayasu disease. *Jpn. J. Ophthalmol.,* 1999:43:546-552.
[47] Jales-Neto LH, Levy-Neto M, Bonfa E, et al. Juvenile-onset Takayasu arteritis: peculiar vascular involvement and more refractory disease. *Scand. J. Rheumatol.,* 2010; 39:506-510.
[48] Ishikawa K. Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). *Circulation,* 1978: 57:27-35.
[49] de Souza SW, Machado NP, Pereira VM, et al. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. *Circ. J.,* 2010; 74:1236-1241.
[50] Leonard TJK, Sanders MD. Ischaemic optic neuropathy in pulseless disease. *Br. J. Ophthal.,* 1983; 67:389-392.
[51] Lewis JR, Glaser JS, Schatz NJ, et al. Pulseless (Takayasu) Disease with Ophthalmic Manifestations. *Journal of Clinical Neuro-Ophthalmology,* 1993; 13:242-249.

[52] Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. *Intern. Med. J.,* 2008; 38:816-23.

[53] Mohammad AJ, Jacobsson LT, Mahr AD. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. *Rheumatology,* 2007; 46:1329-1337.

[54] McMahon BJ, Heyward WL, Templin DW, et al. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow up. *Hepatology,* 1989; 9:97-101.

[55] Bae YD, Choi HJ, Lee JC, et al. Clinical features of polyarteritis nodosa in Korea. *J. Korean Med. Sci.,* 2006; 21:591-595.

[56] Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: A capture-recapture estimate. *Arthritis Rheum.* 2004; 51:92-99.

[57] Goar EL, Smith LS. Polyarteritis Nodosa of the Eye. *Trans Am. Ophthalmol. Soc.,* 1951; 49:37-46.

[58] Nanjiani MR. Ocular manifestations of polyarteritis nodosa. *Brit. J. Ophthalmol*., 1967; 51:696-697.

[59] Morgan C, Foster S, D'Amico D, et al. Retinal vasculitis in polyarteritis nodosa. *Retina,* 1986; 6:205-209.

[60] Purcell JJ, Birkenkamp R, Tsai CC. Conjunctival lesions in periarteritis nodosa. A clinical and immunopathologic study. *Arch. Ophthalmol.,* 1984; 102:736-738.

[61] Cogan DG. Corneoscleral lesions in periarteritis nodosa and Wegener's granulomatosis. *Trans Am. Ophthalmol. Soc.,* 1955; 53:321-344.

[62] Rothschild PR, Pagnoux C, Seror R, et al. Ophthalmologic Manifestations of Systemic Necrotizing Vasculitides at Diagnosis: A Retrospective Study of 1286 Patients and Review of the Literature. *Semin. Arthritis Rheum.* 2013;43:507-514.

[63] Pagnoux C, Raphaèl S, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa. A systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French vasculitis study group database. *Arthritis Rheum.* 2010; 62:616-626.

[64] Leung AC, McLay A, Boulton-Jones JM. Polyarteritis presenting with thrombocytosis and central retinal vein thrombosis. *Scott. Med. J.,* 1987; 32:24-6.

[65] Pinto Ferreira F, Faría, A, Ganhão F. Periarteritis nodosa with initial ocular involvement. *J. Fr. Ophthalmol.,* 1995*;* 18:788-793.

[66] MacClure GM. Polyarteritis nodosa with an unusual ocular presentation. *Brit. J. Ophthal.,* 1968; 52:141-148.

[67] Binaghi M, Kamoun MN, Coscas KG. Fluorescein angiography in the diagnosis of periarteritis nodosa. *J. Fr. Ophtalmol.,* 1984; 7:19-30.

[68] Akova YA, Jabbur NS, Foster CS. Ocular presentation of polyarteritis nodosa. Clinical course and management with steroid and cytotoxic therapy. *Ophthalmol.* 1993;100:1775-1781.

[69] Harnden A, Mayon-White R, Perera R, et al. Kawasaki disease in England: ethnicity, deprivation, and respiratory pathogens. *Pediatr. Infect. Dis. J.,* 2009; 28:21-24.

[70] Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. *J. Epidemiol.,* 2012; 22: 216–221.

[71] Ayusawa M, Sonobe T, Uemura S, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr. Int.,* 2005; 47:232-234.
[72] Yim D, Curtis N, Cheung M. Update on Kawasaki disease: Epidemiology, aetiology and pathogenesis. *J. Paediatr. Chil. Health,* 2013; 49:704-708.
[73] Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. *BMJ,* 2002; 324:1424–1425.
[74] Lin YT, Manlhiot C, Ching JC, et al. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. *Pediatr. Int.,* 2010; 52: 699–706.
[75] Puglise J, Rao N, Weiss R, et al. Ocular features of Kawasaki's disease. *Arch. Ophthalmol.,* 1982; 100:1101-1103.
[76] Ohno S, Miyajima T, Higuchi M, et al. Ocular manifestations of Kawasaki's disease (mucocutaneous lymph node syndrome). *Am. J. Ophthalmol.,* 1982; 93:713-717.
[77] Burke MJ, Rennebohm RM. Eye involvement in KD. *J. Pediatr. Ophthalmol. Strabismus,* 1981; 18:7-11.
[78] Offret H. Disciform keratitis and Kawasaki's disease. *J. Fr. Ophtalmol.,* 1993; 16:114-116.
[79] Kadyan A, Choi J, Headon MP. Disciform keratitis and optic disc swelling in KD: an unusual presentation. *Eye,* 2006; 20:976-977.
[80] Jacob JL, Polomeno RC, Chad Z, et al. Ocular manifestations of KD (mucocutaneous lymph node syndrome). *Can. J. Ophthalmol.,* 1982; 17:199-202.
[81] Font RL, Mehta RS, Streusand SB, et al. Bilateral retinal ischemia in Kawasaki disease. Postmortem findings and electron microscopic observations. *Ophthalmol.* 1983; 90:569-577.
[82] Verghote M, Roussea E, Jacob J, LaPointe N. An uncommon clinical sign in mucocutaneous lymph node syndrome. *Acta. Paediatr. Scand.,* 1981; 70:591-593.
[83] Anand S, Yang TC. Optic disc changes in KD. *J. Ped. Ophthalmol. Strabismus.* 2004:41:177-179.
[84] Son MB, Gauvreau K, Burns JC, et al. Infliximab for intravenous immunoglobulin resistance in KD: a retrospective study. *J. Pediatr.,* 2011; 158:644.
[85] Dominguez SR, Anderson MS. Advances in the treatment of KD. *Curr. Opin. Pediatr.* 2013; 25:103-109.
[86] Kadyan A, Choi J, Headon MP. Disciform keratitis and optic disc swelling in Kawasaki disease: an unusual presentation. *Eye,* 2006; 20:976-977.
[87] Rennebohm RM, Burke MJ, Crowe W, et al. Anterior uveitis in Kawasaki's disease. *Am. J. Ophthalmol.,* 1981; 91:535-537.
[88] Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: A capture-recapture estimate. *Arthritis Rheum.* 2004; 51:92-99.
[89] Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum.* 2000;43:414–419.
[90] Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. *Arthritis Rheum.* 2000;43:2481–2487.
[91] Leavitt R, Fauci A, Bloch D, et al. The American college of rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis and Rheum.* 1990; 33:1101-1107.

[92] Akikusa JD, Schneider R, Harvey EA, et al. Clinical features and outcome of pediatric Wegener's granulomatosis. *Arthritis and Rheum.* 2007; 57:837-844.
[93] McDonald J, Edwards R, Wegener's granulomatosis- a triad. *JAMA,* 1960; 1*73*:1205–1209.
[94] Shiuey Y, Foster CS. Peripheral ulcerative keratitis and collagen vascular disease. *Int. Ophthalmol. Clin.* 1998; 38:21-32.
[95] Bullen CL, Liesegang TJ, McDonald TJ, et al. Ocular complications of Wegener's granulomatosis. *Ophthalmology,* 1983; 90:279-290.
[96] Hoffman G, Kerr G, Leavitt R, et al. Wegener Granulomatosis: an analysis of 158 patients. *Ann. Int. Med.,* 1992; 116:488-498.
[97] Fauci AS, Haynes BF, Katz P, et al. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann. Int. Med.,* 1983; 98:76-85.
[98] Chan A, Li E, Choi P, et al. Unusual eye signs in Wegener's granulomatosis. *Hong Kong Med. J.,* 2007; 13:241-242.
[99] Perry SR, Rootman J, White VA. The clinical and pathological constellation of Wegener granulomatosis of the orbit. *Ophthalmology,* 1997; 104:683–694.
[100] Sadiq SA, Jenning CR, Jones NS, et al. Wegener's granulomatosis: the ocular manifestations revisited. *Orbit,* 2000; 19:253–261.
[101] Cabral D, Uribe A, Benseler S, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. *Arthritis and Rheum.* 2009; 60: 3413-3424.
[102] Stavrou P, Deutsch J, Rene C, et al. Ocular manifestations of classical and limited Wegener's granulomatosis. *Q. J. Med.,* 1993; 86:719-25.
[103] Muhle C, Reinhold-Keller E, Richter C, et al. MRI of the nasal cavity, the paranasal sinuses, and orbits in Wegener's granulomatosis. *Eur. Radiol.,* 1997; 7:566–570.
[104] Hoang L, Lim L, Vaillant B. Antineutrophil cytoplasmic antibody-associated active scleritis. *Arch. Ophthalmol.,* 2008; 126:651-655.
[105] Foster W, Greene S, and Millman B. Wegener's granulomatosis presenting as ophthalmoplegia and optic neuropathy. *Otolaryngol. Head Neck Surg.,* 1995; 112:758-62.
[106] Vischio J, McCrary C. Orbital Wegener's granulomatosis: a case report and review of the literature. *Clin. Rheumatol.* 2008; 27:1333-1336.
[107] Pakrou N, Selva D, Leibovitch I. Wegener's Granulomatosis: Ophthalmic manifestations and management. *Semin Arthritis Rheum.* 2006; 35:284-292.
[108] Kwan ASL, Rose GE. Lacrimal drainage surgery in Wegener's granulomatosis. *Br. J. Ophthalmol.,* 2000; 84:329-331.
[109] Martin RM, Wilton LV, Mann RD. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: retrospective analysis of 58 prescription-event monitoring cohort studies. *Pharmacoepidemiol. Drug. Saf.* 1999; 8:179-89.
[110] Guillevin L, Cohen P, Gayraud M. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine,* 1999; 78:26-37.
[111] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990; 33:1094-100.
[112] Churg A. Recent advances in the diagnosis of Churg-Strauss syndrome. *Mod. Pathol.* 2001; 14:1284.

[113] Takanashi T, Uchida S, Arita M, et al. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome. Report of two cases and review of the literature. *Ophthalmology,* 2001; 108:1129-1133.
[114] Androudi S, Iaccheri B, Brazitikos P. Bilateral chronic anterior uveitis and neuro-ophthalmologic manifestations in a patient with Churg-Strauss syndrome: an unusual ocular presentation. *Ocul. Immunol. Inflamm.* 2004; 12:59-63.
[115] Lee JE, Lee SU, Kim SY, et al. Anterior ischemic optic neuropathy in a patient with Churg-Strauss syndrome. *Korean J. Ophthalmol.,* 2012; 26:469-472.
[116] Skrapari I, Kagkelari E, Charitatos E, et al. Acute painless monocular visual loss due to central retinal artery occlusion in a patient with Churg-Strauss vasculitis. *Clin. Rheumatol.* 2008; 27:125-127.
[117] Kumano Y, Yoshida N, Fukuyama S, et al. Central retinal artery occlusion in a patient with ANCA-negative Churg-Strauss syndrome. *Clin. Ophthalmol.* 2012; 6:1225-1228.
[118] Hamann S, Johansen S. Combined central retinal artery and vein occlusion in Churg-Strauss syndrome: case report. *Acta Ophthalmol. Scand,* 2006; 84:703-706.
[119] Koenig M, Maillard N, Lévy M, et al. Monocular blindness as the first symptom of Churg-Strauss syndrome. *Presse Med.,* 2008; 37:235-238.
[120] McNab A. Orbital inflammation in Churg-Strauss syndrome. *Orbit,* 1998; 17:203-205.
[121] Jordan N, Verma H, Ekbote A. Dacryoadenitis and diffuse orbital inflammation: unusual first presentation of Churg-Strauss syndrome. *Orbit,* 2011; 30:160-161.
[122] Bosch X, Guilabert A, Espinosa G, et al. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. *JAMA,* 2007; 298:655-669.
[123] Moosig F, Bremer JP, Hellmich B, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann. Rheum. Dis.,* 2013; 72:1011-1017.
[124] Watts R, Jolliffe V, Carruthers D, et al. Effect of classification on the incidence of polyarteritis nodosa and microscopic polyangiitis. *Arthritis and Rheum.* 1996; 39:1208-1212.
[125] Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis. Clinical and laboratory findings in eighty-five patients. *Arthritis and Rheum.* 1999; 42:421-430.
[126] Jennette JC, Thomas DB, Falk RJ. Microscopic polyangiitis (microscopic polyarteritis). *Semin. Diagn Pathol.,* 2001; 18:3-13.
[127] Hara A, Ohta S, Takata M, et al. Microscopic polyangiitis with ocular manifestations as the initial presenting sign. *Am. J. Med. Sci.,* 2007; 334: 308-310.
[128] Savage C, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. *Quarterly Journal of Medicine,* 56:467-483.
[129] Altaie R, Ditzio F, Fahy GT. Microscopic polyangitis presenting with sub-acute reversible optic neuropathy. *Eye,* 2005; 19:363-365.
[130] Darlington JK, Mannis MJ, Segal WA, et al. Peripheral nonulcerative keratitis as a presenting sign of microscopic polyangiitis. *Cornea,* 2001; 20:522-524.
[131] Alrashidi S, Yousef Y, Krema H. Visual loss from scleritis in C-ANCA positive microscopic polyangiitis. *BMJ Case Reports,* 2013: June 10.
[132] Villiger P, Guillevin L. Microscopic polyangiitis: Clinical presentation. *Autoimmunity Reviews,* 2010; 9:812-819.

[133] Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, et al. Overall survival, renal survival and relapse in patients with microscopic polyangiitis: a systematic review of current evidence. *Rheumatology*, 2011; 50:1414-1423.

[134] Mihara M, Hayasaka S, Watanabe K, et al. Ocular manifestations in patients with microscopic polyangiitis. *Eur. J. Ophthalmol.*, 2004; 15:138-142.

[135] Grotz W, Baba H, Becker J, et al. Hypocomplementemic urticarial vasculitis syndrome. An interdisciplinary challenge. *Dtsch. Arztebl. Int.*, 2009; 106:756-763.

[136] Mehregan D, Hall M, Gibson L. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J. Am. Acad. Dermatol.*, 1992; 26:441-448.

[137] Schwartz HR, McDuffie FC, Black LF, et al. Hypocomplementemic urticarial vasculitis: association with chronic obstructive pulmonary disease. *Mayo Clin. Proc.*, 1982; 57:231-238.

[138] Wisnieski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome: clinical and serologic findings in 18 patients. *Medicine (Baltimore)*, 1995; 74:24-41.

[139] Davis M, Daoud M, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. *J. Amer. Acad. Dermatol.*, 1998; 38:899-905.

[140] Corwin JM, Baum J. Iridocyclitis in two patients with hypocomplementemic cutaneous vasculitis. *Am. J. Ophthalmol.*, 1982; 94:111-113.

[141] Thorne J, Hernandez M, Rencic A, et al. Severe scleritis and urticarial lesions. *Am. J. Ophthalmol.*, 2002; 134:932-934.

[142] Adnan Al Mosawi ZA, Ahmed Al Hermi BE. Hypocomplementemic urticarial vasculitis syndrome in an 8 year old boy: a case report and review of literature. *Oman. Med. J.* 2013; 28: 275-277.

[143] Ferri C. Mixed cryoglobulinemia. *Orphanet. J. Rare Dis.*, 2008; 3:25.

[144] Casato M, Saadoun D, Marchetti A, et al. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological test. *J. Rheumatol.*, 2005; 32:484-488.

[145] Terrier B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood*, 2012; 119:5996-6004.

[146] Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin. Arthritis Rheum.* 2004; 33:355-374.

[147] Wintrobe M, Buell M. Hyperproteinemia associated with multiple myeloma. With report of a case in which an extraordinary hyperproteinemia was associated with thrombosis of the retinal veins and symptoms suggesting Raynaud's disease. *Jour. Am. Med. Assn.*, 1932; 99:1411-1414.

[148] Ryan LM, Kozin F, Eiferman R. Immune complex uveitis: a case. *Ann. Intern. Med.*, 1978; 88:62-63.

[149] Nicholson L, Sobrin L. Anterior uveitis secondary to type II essential cryoglobulinemia. *J. Ophthalmic. Inflamm. Infect.* 2013; 3:56.

[150] Kedhar SR, Belair ML, Jun AS, et al. Scleritis and peripheral ulcerative keratitis with hepatitis C virus-related cryoglobulinemia. *Arch. Ophthalmol.*, 2007; 125:852-853.

[151] Myers JP, Di Bisceglie AM, Mann ES. Cryoglobulinemia associated with Purtscher-like retinopathy. *Am. J. Ophthalmol.,* 2001; 131:802-804.
[152] Sauer A, Nasic X, Zorn F, et al. Cryoglobulinemia revealed by a Purtscher-like retinopathy. *Clin. Ophthalmol.* 2007; 1:555-557.
[153] Gorevic P, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am. J. Med.,* 1980; 69:287-308.
[154] Cohen SM, Kokame GT, Gass JD. Paraproteinemias associated with serous detachments of the retinal pigment epithelium and neurosensory retina. *Retina,* 1996; 16:467-473.
[155] Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. *Curr. Opin. Rheumatol.* 2013; 25:10-18.
[156] Calviño MC, Llorca J, García-Porrúa C, et al. Henoch-Schönlein Purpura in Children from Northwestern Spain. A 20-year Epidemiologic and Clinical Study. *Medicine,* 2001; 80:279-290.
[157] Peru H, Soylemezoglu O, Bakkaloglu SA, et al. Henoch Schonlein purpura in childhood: clinical analysis of 254 cases over a 3-year period. *Clin. Rheumatol.* 2008; 27:1087-1092.
[158] Trapani S, Micheli A, Grisolia F, et al. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin. Arthritis Rheum.* 2005; 35:143-53.
[159] Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura *Arthritis Rheum.,* 1990; 33:1114-1121.
[160] Lorentz WB, Weaver RG. Eye involvement in anaphylactoid purpura. *Am. J. Dis. Child,* 1980; 134:524-525.
[161] Yamabe H, Ozawa F, Fukushi K, et al. IgA nephropathy and Henoch-Schönlein purpura nephritis with anterior uveitis. *Nephron,* 1099; 50:368-370.
[162] Muqit MMK, Gallagher MJ, Gavin M, et al. Henoch-Schonlein purpura with keratitis and granulomatous anterior uveitis. *Br. J. Ophthalmol.,* 2005; 89:1221-1222.
[163] Erer B, Kamali S, Cingu K, et al. Recurrent anterior uveitis in Henoch Schonlein's vasculitis. *Rheumatol. Int.,* 2010; 30:1377-1379.
[164] Kaur S, Maheshwari A, Aneja S, et al. Henoch-Schönlein purpura with uveitis: an unusual case and review of literature. *Rheumatol. Int.,* 2012; 32:4057-4059.
[165] Chan C, Li Q. Immunopathology of uveitis. *Brit. J. Ophthalmol.,* 1998; 82:91-96.
[166] Ma'luf RN, Zein WM, El Dairi E, et al. Bilateral subperiosteal orbital hematomas and Henoch-Schönlein purpura. *Arch Ophthalmol* 2002; 120:1389-1399.
[167] Wu TT, Sheu SJ, Chou LC, et al. Henoch-Schonlein purpura with bilateral central retinal artery occlusion. *Br. J. Ophthalmol.,* 2002; 86:351-352.
[168] Barton CH, Vaziri ND. Central retinal vein occlusion associated with hemodialysis. *Am. J. Med. Sci.,* 1979; 277:39-47.
[169] Chuah J, Meaney T. Anterior ischaemic optic neuropathy secondary to Henoch-Schönlein Purpura. *Eye,* 2005; 19:1028.
[170] Nicholson L, Mathews D. Bilateral cystoid macular oedema and cotton wool spots associated with Henoch-Schonlein purpura. *BMJ Case Rep.,* 2013; Published online.
[171] Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. *Ann. Intern. Med.,* 1994; 120:476-84.

[172] Behcet H, Matteson EL. On relapsing, aphthous ulcers of the mouth, eye and genitalia caused by a virus. 1937. *Clin. Exp. Rheumatol.,* 2010; 28(Suppl 60):S2-S5.
[173] International Study Group for Behçet's Disease. *Lancet,* 1990; 335:1078-1080.
[174] Sobel JD, Haim S, Shafrir A, et al. Cutaneous hyper-reactivity in Behçet disease. *Dermatologica,* 1973; 146:350-356.
[175] Uluduz D, Kürtüncü M, Yapici et al. Clinical characteristics of pediatric-onset neuro-Behçet disease. *Neurology,* 2011; 77:1900-1905.
[176] Citirik M, Berker N, Songur MS, et al. Ocular findings in childhood-onset Behcet disease. *JAAPOS,* 2009; 13:391-395.
[177] Arai Y, Kohno S, Takahashi Y, et al. Autopsy case of neuro-Behcet's disease with multifocal neutrophilic perivascular inflammation. *Neuropathology,* 2006; 26:579-585.
[178] Morgan RF, Baumgartner CJ. Meniere's disease complicated by recurrent interstitial keratitis: Excellent results following cervical ganglionectomy. *West J. Surg.,* 1934; 42:628.
[179] Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. *Arch. Ophthal.,* 1945; 33:144-149.
[180] Haynes BF, Kaiser-Kupfer MI, Mason P, et al. Cogan's syndrome: Studies in thirteen patients, long-term follow-up, and a review of the literature. *Medicine,* 1980; 59:426-441.
[181] Norton EWD, Cogan DG. Syndrome of nonsyphylitic interstitial keratitis and vestibuloauditory symptoms. A long-term follow-up. *Arch. Ophthalmol.,* 1959; 61:695-697.
[182] Gluth MB, Baratz KH, Matteson EL, et al. Cogan syndrome: A retrospective review of 60 patients throughout a half century. *Mayo Clin. Proc.,* 2006; 81:483-488.
[183] Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospsective diagnostic and therapeutic experience. *Am. J. Med.,* 1983; 74:97-105.
[184] Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. *Neurology,* 2001; 56:837-842.
[185] Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine,* 1988; 67:20-39.
[186] Salvarani C, Brown RD Jr., Calamia KT et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann. Neurol.,* 2007; 62:442-451.
[187] Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children. *Arthritis Rheum.* 2005; 52:2159-2167.
[188] Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain. An inflammatory reaction of diverse etiology. *Arch. Neurol.,* 1988; 45:514-518.
[189] Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. *Neurol. Clin.,* 1997; 15:821-834.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 5

THE BLOOD-BRAIN BARRIER

David S. Younger*, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health
City University of New York, New York, NY, US

ABSTRACT

There has been extraordinary research in the blood-brain barrier over the past decade. Once considered a static anatomical barrier to the traffic of molecules in and out of the central nervous system when fully developed in adults, and otherwise irrelevant to neuroscience and disease, the blood-brain barrier is now known not only to be fully functional in development, but vital in cerebrovascular angiogenesis. The cellular components and other molecular constituents of the blood-brain barrier, contained in a neurovascular unit, protect the central nervous system from injury and disease by limiting the passage of toxins, pathogens, and inflammatory effectors of the immune system. Blood-brain barrier breakdown has been recognized as an important factor in a variety of primary neurological diseases however such disturbances while common to primary and vasculitis of the central nervous system, has yet to be critically analyzed. The chapter provides a comprehensive review of the blood-brain barrier in health and disease, with special consideration to the pathogenesis of central nervous system vasculitis. This chapter reviews the history, neurodevelopment, ultrastructure, function, and clinicopathologic correlation and relevance to central nervous system vasculitis.

Keywords: blood-brain barrier, blood-nerve barrier, systemic vasculitis

*Corresponding Author's Email: youngd01@nyu.edu

INTRODUCTION

The past decade has witnessed an expansion of knowledge in the properties possessed by the blood-brain barrier (BBB) in health and disease as summarized in several excellent recent reviews [1-5]. In essence, the neurovascular unit of the BBB is comprised of capillary vascular and neural cells, extracellular matrix components, and a variety of immune cells that mediate local immunity. The schematized and electron microscopic (EM) appearance of cerebral capillaries in the BBB shown in Figures 1 and 2, demonstrate layers of pericytes adherent to the abluminal or parenchymal surface of endothelial cells, together surrounded by a layer of basal lamina comprised of extracellular matrix protein molecules. The end feet of neighboring astrocyte processes ensheath the blood vessels. Monolayers of adjacent endothelial cells that form tight junctions (TJ) strands shown in Figure 1, connecting adjacent endothelial cells by adhesions of transmembrane occludin, claudin, and junctional associated molecules [JAM] across the intercellular space while cytoplasmic scaffolding and regulatory proteins such as zona occludens type 1 and 2 [ZO-1, ZO-2] provide linkage to the actin cytoskeleton and initiate several signaling mechanisms via protein-protein interactions. Endothelia BBB cells are also linked by adherens junctions composed of vascular endothelial (VE)-cadherin, which mediates cell-cell adhesion interactions, linking adherens junctions to the actin cytoskeleton via catenins [2, 3]. Perivascular macrophages that reside between astrocyte endfeet and the vessel wall, mast cells associated with specific regions of the CNS; resident microglia that act as antigen presenting cells (APC), and circulating leukocytes that can penetrate the intact BBB via interactions with endothelial adhesion molecules (CAM] to mediate bidirectional crosstalk between immune cells and endothelium for normal surveillance, constitute the extended neurovascular unit (NVU) [2].

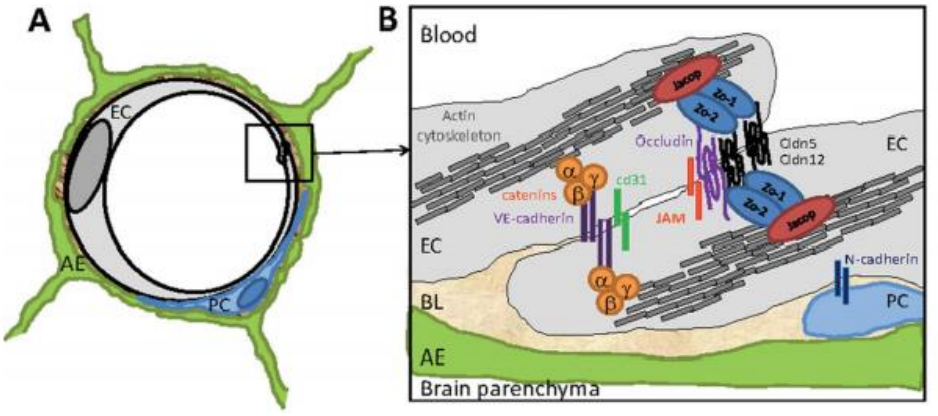


Figure 1. A. Cross-section schematic representation of a capillary in the human blood-brain barrier over an endothelial tight junction. B. The insert shows the molecular composition of tight and adherens junctions. See text for details. Reproduced from [1], with permission of the publisher.

Breakdown or disruption of the BBB accompanies a variety of inflammatory and autoimmune, neoplastic, infectious, and neurodegenerative central nervous system (CNS) disorders, notably stroke, multiple sclerosis, brain trauma, human immune virus, infection, and Alzheimer disease. These disorders are associated with the abnormal entry of plasma components, immune molecules and cellular elements that leads to further neural dysfunction

and varying degrees of irreversible neural degeneration. Although there is little known about the role of BBB breakdown in primary and secondary CNS vasculitis, future progress could lead to improved understanding of primary and secondary forms of CNS vasculitis [6] with the prospect of even improving the outcome two potentially devastating disorders, childhood and adult primary angiitis of the CNS (PACNS) [7-9]. According to Weiss and colleagues [10] further understanding of the BBB could envision the use of new therapeutic strategies that bypass it, taking advantage of the selective expression of membrane bound proteins expressed by brain endothelia cells or circulating leukocytes to target new drugs, as well as improve the effectiveness of conventional systemic immunosuppression. This chapter reviews the history, neurodevelopment, ultrastructure, function, and clinicopathologic correlation and relevance to CNS vasculitis.

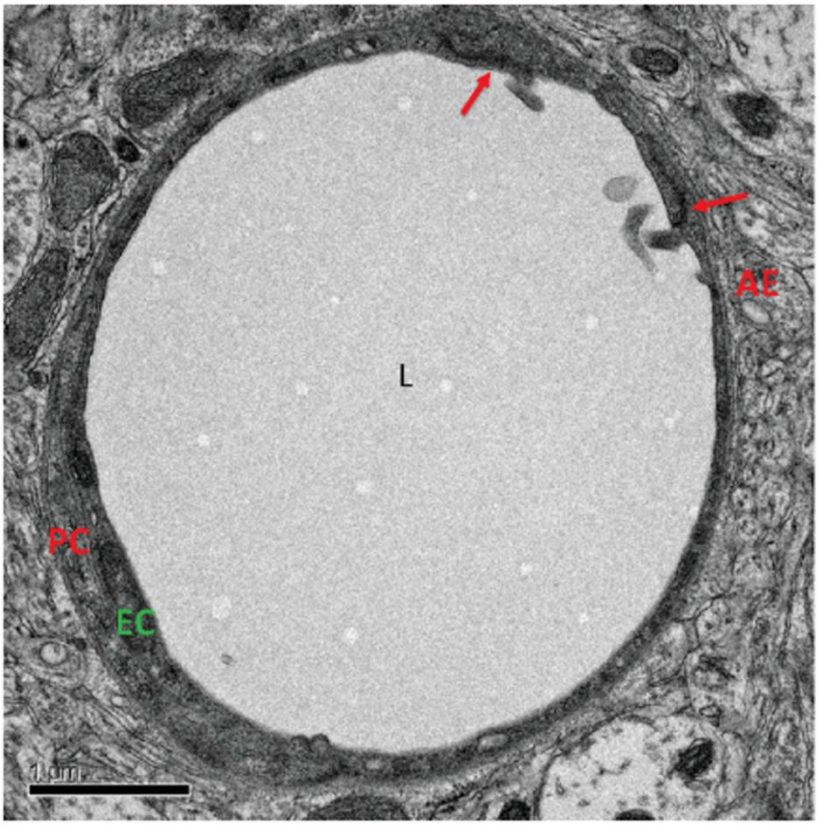


Figure 2. Electron micrograph of a capillary in the adult murine blood-brain barrier. Endothelial cells are held together by tight junctions (red arrow). Reproduced from [1], with permission of the publisher.

HISTORICAL BACKGROUND

In 1885, Ehrlich [11] provided the first suggestion of the presence of a barrier when a parenteral injection of vital dye into the bloodstream of mice penetrated practically every systemic organ except the brain turning them dark purplish-blue, leaving the brain and spinal cord pale white-yellow. Ehrlich himself thought that this difference was due to a low binding

affinity. The existence of a barrier at the level of the cerebral vessels was postulated by Bield and Kraus [12] and later by Goldman [13] and Lewandowsky [14] at the turn of the twentieth century, who jointly interpreted their experience in favor of a true BBB, later termed *Blut-Hirn-Schranke*. In 1967, Reese and Karnovsky [15] demonstrated a structural barrier to an intravenous injection of horseradish peroxidase (HRP) demonstrating exogenous peroxidase to the lumina of blood vessels and in some micropinocytotic vesicles within endothelial cells, but none beyond the vascular endothelium. The relatively scarce number of vesicles was a morphological feature of a functioning BBB. Their findings localized at a fine structural level a barrier composed of the plasma membrane and the cell body of endothelial cells and TJ between adjacent cells of the cerebral cortex. In 1969, EM studies by Brightman and Reese [16] in the mouse conclusively demonstrated endothelial and epithelia TJ that occluded the interspaces between blood and parenchyma or cerebral ventricles, constituting the ultrastructural basis for the blood-brain and blood-cerebrospinal fluid barriers. Feder [17] noted active exclusion of the small electron-dense tracer microperoxidase by intact TJ after parenteral injection supplementing the findings of Reese and Karnovsky [15]. Nagy and colleagues [18] examined fracture faces of cerebral endothelium in normal and hyperosmolar mannitol-treated rat brains to elucidate the organization of TJ in various segments of the cerebral vascular bed and the structural basis of BBB opening in hyperosmotic conditions. Their findings provided no direct evidence for the structural basis of BBB opening in hyperosmolar mannitol-treated rat brains noting extended TJ regions in capillaries and postcapillary venues. Shivers and coworkers [19] studied isolated rat brain capillaries employing freeze-fracture images of interendothelial ZO revealing complex arrays of intramembrance ridges and grooves characteristic of TJ. The ZO of these capillary endothelial cells were considered very tight.

NEURODEVELOPMENT

In contrast to the neuronal development, the vascular system undergoes blood vessel formation through the two distinct processes, vasculogenesis and angiogenesis. The former commences with endothelial differentiation from angioblasts to vascular plexuses, while the latter is associated with sprouting of new vessels from existing ones. Both vasculogenesis and angiogenesis are influenced by vascular endothelial growth factor (VEGF), a major attractive molecule for extending blood vessels especially endothelial tip cells [20], as well as by other molecules, blood flow and contact with surrounding tissues. Found at the growing end of extending vessels, the shaft of extending endothelial tip cells is composed of an endothelial cell chain made of stalk cells similar to the axon growth cone and its associated axonal shaft. *In vivo* imaging employing green fluorescent protein (GFP) depicts the advancing endothelial tip cell navigating the environment and sprouting from existing vasculature [21]

Several experimental observations have suggested the importance of the neurodevelopment of the BBB [5]. First, there are shared molecular and cellular mechanisms in both neurogenesis and angiogenesis [22, 23]. Four major families of axon guidance ligand-receptor pairs include Slit/Robo, semaphoring/plexin/neuropilin, Netrin/Unc5/DCC, and Ephrin/Eph, together mediating complex cellular navigational programs within axons as both chemoattractants and repellents, and directing the angiogenic tip cells toward its final destination.

Neuropilin-1 is necessary for endothelial tip cell guidance in the developing central nervous system [24]. Moreover, axonal terminal arborization parallels vessel sprouting. Similar to hypoxic tissue that secretes VEGF via hypoxia-inducible factor (HIF), a transcription factor that promotes cell survival through the downstream activation of numerous genes including *VEGF* [25]. Axonal terminals devoid of synaptic input secrete nerve growth factor (NGF), the expression of which is down-regulated when innervation occurs.

Second, there is co-regulation of these two systems in developing embryonic and adult brains [22, 26; 27]. Stubbs and colleagues [26] found that blood vessels provided a supporting niche in regions of adult neurogenesis. The investigators [26] employed Tbr2-GFP transgenic mice that served as a correlate for the expression of the intermediate progenitor cell (IPC) T-box transcription factor Tbr2, to examine the proximity of dividing cells in the subventricular (SVZ) and ventricular zone (VZ) of the shaking rat Kawasaki and reeler mutant mouse in relation to blood vessels throughout neurogenesis. Their findings which included the extension of neuritis toward and along labeled blood vessels supported the notion of vascular-neuronal interactions in development. Javaherian and coworkers [27], who likewise studied IPC in the SVZ of embryonic Swiss Webster mouse cortices, employed confocal microscopy to image the vast network of capillaries in the SV and SVZ. The authors [27] noted that Tbr2 cells divided near vascular branch-points suggesting endothelial tip cells contributed to the neurogenic niche for IPC, with ectopic overexpression of VEGF-A in a pattern that followed that of blood vessel development. These findings indicated that the developing cortical vasculature provided a microenvironment within the SVZ in which IPC accumulated and divided during neurogenesis.

Third, a structural and functional BBB complete with TJ appear as soon as cerebral vessels penetrate the CNS parenchyma [28, 29]. Johansson and colleagues [28] explained that the widely held view that the BBB was immature during development stemmed from teleological interpretations and experimental observations of high cerebrospinal fluid (CSF) protein levels in fetal CSF and the apparent passive passage of biomarkers during development. Instead, the blood-CSF barrier, like the BBB is functionally and morphologically mature from very early in development. The authors maintain that inconsistent terminology used in the literature such as leaky, immature, and developing, used to describe the barrier gives a connotation of TJ that are more permeable that their adult counterparts without evidence to support this concept. Mølgård and Saunders [30] noted well-formed complex TJ across cerebral endothelial cells in human embryos and fetuses by freeze fracture and thin section EM by 8 weeks of age, commensurate with the differentiation of brain capillaries. Efflux transporters are likewise expressed in cerebral endothelial and choroid plexus epithelial cells early in the fetal and postnatal rats [31]. Ballabh and colleagues [32] studied the expression and quantification of endothelial TJ molecules including claudin-5, occluding, and JAM by immunohistochemistry and Western blot analysis in blood vessels of germinal matrix, cortex, and white matter of fetuses and premature infants gestational age 16 to 40 weeks. The authors [32] noted no significant decrease in the expression of the endothelial TJ molecules claudin-5, occludin, and JAM-1 as a function of gestational age in germinal matrix compared with cortex and white matter suggesting that they were unlikely to be responsible for germinal matrix fragility and vulnerability to hemorrhage in premature infants. These findings are consistent with the concept that TJ molecules develop and perhaps mature early during human gestation. Ballabh and colleagues [33] observed that a paucity of TJ or pericytes coupled with incomplete coverage of blood vessels by astrocyte end-feet, could instead account for the observed fragility of blood vessels in the germinal matrix of premature infants. Braun and colleagues [34] found that

pericytes coverage and density that was less in the germinal matrix vasculature than in the cortex or white matter in human fetuses, premature infants, and premature rabbit pups. Although VEGF suppression significantly enhanced pericyte coverage in germinal matrix, it remained less than in other brain regions.

NEUROBIOLOGY AND CELLULAR INTERACTIONS

Endothelial Cell Interactions

The existence of the endothelial cell was first surmised by William Harvey, and first observed by Marcello Malpighi in blood capillaries using compound microscopy in the nineteenth century, and later by EM in the mid-twentieth century, revealing the presence of plasmalemmal vesicles or caveolae. The ability to culture EC later permitted even more detailed investigation of their activation and function *in vivo*. Derived from mesoderm via the differentiation of hemangioblasts and angioblasts, there are a few protein/mRNA marker candidates including platelet/endothelial cell adhesion molecule (PECAM)-1 in monocytes and VE-cadherin in fetal stem cells. Endothelial cells of the BBB not only provide a physical barrier between the systemic circulation and the brain, but assure the selective inward passage of ions, nutrients, and neuropeptides via specialized transport mechanisms. Sodium, potassium, chloride, hydrogen, bicarbonate and calcium ions are transported across the BBB via transporters located mainly along the luminal surface of endothelial cells including, the sodium and potassium adenosine triphosphate (ATP)- dependent transport pump, the sodium-potassium-chloride cotransporter (NKCC), sodium-proton, chloride-bicarbonate, and sodium calcium exchanges that assure optimal levels of brain electrolyte levels and intracellular pH. The transport of essential nutrients is assured by members of the soluble carriers (SLC) superfamily, located variably along the luminal and abluminal membrane including, glucose transporter-1 (GLUT1), monocarboxylic acid-1 (MCT-1); excitatory, organic acid (OAT), cation (OAC), amine and choline transporters (CTL1), respectively to transport lactate and ketone bodies as alternative energy neuronal sources, and sodium-independent or dependent removal of glutamate, aspartate, glutamine, histidine, and asparagine from the interstitial compartment of the brain. Other specific carrier-mediated transporters mediate the passage of transferrin, low-density lipoproteins, leptin, immunoglobulin G (IgG), insulin, and growth factors via receptor-mediated transcytosis via binding of the protein to specific receptors on the endothelial cell surface following by endocytosis of the ligand-receptor complex with passage across the cytoplasm and exocytosis at the opposite side of the cell [35] and via the formation of caveolae or vesicle formation for the transport of macromolecules [36]. Transmigration of cellular elements across endothelial cells of the BBB during inflammation including leukocytes, neoplastic cells, and pathogenic viruses, bacteria and yeasts, investigated in experimental animal models utilizing HRP, highlighted the role of caveolae as mini-transporters of the CNS [36]. Unique systems of modified caveolae that fuse together forming transendothelial cell channels and later vesiculo-canalicular or vesiculo-tubular structures (VTS) or vesiculo-vacuolar organelles (VVO), appear to be an important gateway to the CNS in damaged endothelial cell populations [36]. Transportation of potentially toxic endogenous or xenobiotic lipid-soluble nonpolar molecules from the brain to the blood are accomplished

by transporters located along the luminal membrane such as the ATP binding cassette (ABC) transporter P-glycoprotein 1 (P-gp or Pgp) (multidrug resistance protein 1 [MDR1] or ATP-binding cassette sub-family B member 1 [ABCB1]) respectively important in the distribution of CNS tumor drug therapy [37] and the active efflux of the anti-human immunodeficiency virus type 1 (HIV1) nucleoside drug abacavir at the BBB [38-40]; and breast-cancer resistance protein (BCRP) and multidrug resistance related protein (MRP) 1, 2, 4 and 5 efflux transporter pumps that serve as defense mechanisms and determinate bioavailability and concentration of many CNS drugs important in the treatment of CNS cancers [41] such as the novel tyrosine kinase inhibitor dasatinib [42], and the efflux transportation of the protease inhibitor lopinavir that contributes to its poor oral bioavailability in the treatment of HIV1 [43]. The neuroinflammation and progression of damage associated with focal cerebral ischemia appears to be modulated by upregulation of other MRP protein molecules that activate Toll-like receptor (TLR) signaling contributing to neuroinflammation and progression of ischemic cerebral damage [44].

Transendothelial migration of circulating leukocytes involves a multistep process. Leukocyte adhesion molecules (LAM) expressed on the surface of EC initiate binding of leukocytes as a beginning step in the in their entry in brain tissue which later includes rolling adhesion to EC, firm adhesion, and transmigration. Although less well understood, the molecular mechanism is believed to involve endothelial CAM including CD99, platelet ECAM (PECAM-1)/CD31, vascular CAM-1 (VCAM-1) (important in firm adhesion); junctional adhesion molecule-1; expression of leukocyte adhesion molecules E- and P-selectin (rolling adhesion); cytokine responsiveness so noted *in situ* and in cell culture [45, 46] and expression of the integrins alpha4- and beta-2. Inflamed capillary endothelia support transmigration of different subsets of leukocytes. There are two routes for leukocytes to pass through endothelial cell, the so called paracellular route, or through the endothelial cell itself or transcellular route. The BBB with its abundance of TJ complexes relies primarily on the transcellular route as it does for solute and fluid transport. Neutrophil recruitment is partially dependent ICAM-1, and expresses L-selectin and lymphocyte function-associated antigen (LFA)-1 but not chemokine C motif receptor 7 (CCR7), which may explain why granulocytes roll but do not arrest for transmigrate in high endothelial venules (HEV).

Pericyte Interactions

Brain endothelial cells are exposed to a myriad of pericyte interactions [47] in the regulation of brain angiogenesis, endothelial cell TJ formation, as well as the differentiation, microvascular vasodynamic capacity, structural stability, and neuroimmunologic network operations of the intact BBB [48]. Rouget [49] first ascribed capillary contractility to pericytes but Zimmermann [50] named the cell and described its morphologic aspects. The presence of smooth muscle cells in association with pericytes and the absence of a smooth muscle layer from capillaries and postcapillary venues influenced early views ascribing contractile properties to narrow capillaries hence regulate microvascular flow even though a number of subsequent experimental studies failed to substantiate it [51, 52]. Smooth muscle actin was conclusively demonstrated in pericytes by immunocytochemistry employing smooth muscle α-actin isoform specific antibodies and immunogold labelling in conjunction with EM noting that

smooth muscle α-actin expression in capillaries was limited exclusively to pericytes and not present in endothelial cells [53]. Since the histochemical localization of smooth muscle α-actin is demonstrated in precapillaries and not in midcapillaries, it has been suggested that smooth muscle α-actin containing capillaries are involved in contractility and the control of capillary blood flow in the BBB [54].

Unlike other perivascular cells, they lie within the microvessel basal lamina and contribute to its formation. Typical CNS pericytes are flattened or elongated, stellate-shaped solitary cell with multiple cytoplasmic processes encircling the capillary endothelium and contacting a large abluminal vessel area. Brain pericytes are characterized by granular deposits present in lysosomes that strongly react with acid phosphatase, a finding that led to consideration of a phagocytic role [55]. They rapidly phagocytose an intravenous injection of HRP which can be employed as a pericytes histochemical stain. The number of granular lysosomes in brain pericytes increases with disruption of the BBB. Several other markers have been employed in the identification of pericytes including, smooth muscle α-actin (SMA), desmin, polydendrocytes (NG2 cells), platelet-derived growth factor receptor (PDGFR)-β, aminopeptidase A and N, regulator of G-protein signaling 5 (RGS5) and the promoter trap transgene *XlacZ4* [56].

An active role of pericytes in the BBB was inferred from the localization of γ-glutamyl transpeptidase (GGTP) in brain capillary endothelial cells and pericytes, both *in vivo* and *in vitro* [57]. This heterodimeric glycoprotein distributed on the external surface of the cell catalyzes the transfer of γ-glutamyl from glutathione to accept peptides and functionally appears to be concerned with transport of large neutral amino acids across the BBB. Detectable amounts of GGTP are found in other regions of the brain with an intact BBB but not in those that lack one such as the median eminence. Abnormal platelet derived growth factor (PDGF)-B and PDGF-β signaling plays a critical role in the recruitment of pericytes to newly formed vessels, and when deficient, as in knockout of *pdgfb* and *pdbfrb*, leads to perinatal death due to vascular dysfunction with associate vascular leakage and hemorrhage.

Pericyte-endothelia cell signaling factors have been identified. Sphingosine-1-phosphate (SIP) signaling triggers cytoskeletal, adhesive, and junctional changes, affecting cell migration, proliferation, and survival [58]. Angiopoietin-Tie2 signaling in the vascular wall involved in reciprocal communication between endothelial cell and pericytes, such as may be seen in *ang1*- or *tie*2-null mice deficient in Ang1, leads to defective angiogenesis and poorly organized BM, with reduced coverage and detachment of pericytes. Conversely, overexpression of Ang1 leads to expanded and stabilized, leakage resistant microvasculature [59, 60].

The importance of CNS pericytes has been underscored by their proposed role in neuroimmunological networks associated with BBB function. First, CNS pericytes may be actively involved in the regulation of leukocyte transmigration, antigen presentation, and T-cell activation. They constitutively express low levels of VCAM-1 and ICAM-1, which have costimulatory activity in main histocompatibility cell (MHC)-class II dependent antigen presentation; leukocytes cluster on pericytes in culture [48] suggesting a role in inflammation. Smooth muscle pericytes present antigen *in vivo* and differentially activate Th1 and Th2 CD4-T cells. Moreover, CNS pericytes produce a number of immunoregulatory cytokines including interleukin (IL) 1β, IΛ–6, and granulocyte-macrophage colony stimulatory factor (GM-CSF) [61]. Transforming growth factor (TGF)-β produced in an active form in pericytes/endothelial cocultures, may function as an endogenous immunoregulator at the BBB [62]. It is therefore of

interest that TFG-β1 inhibits cytokine-induced CNS endothelial cell activation in isolated rat CNS microvessels [63]. To further emphasize the importance of pericyte interactions in association with endothelial cells, there are no known genetic human diseases due to pericyte deficiency.

Astrocyte Interactions

The intimate relationship of astrocytes and blood vessels was appreciated by Cajal [64] and Golgi [65] in the late nineteenth century. Since then, ultrastructural studies have shown that astrocytic endfeet in the perivascular astroglial sheath leads to a complete covering of brain microvessels [66]. Signaling at the gliovascular interface is facilitated by astrocyte-specific proteins and channels in astrocyte endfeet including, acquaporin-4, connexin 43, purinergic receptors, and potassium channels [67]. Moreover, ultrastructural studies have demonstrated that processes of vasoactive neurons for the regulation of cerebrovascular tone, in particular those expressing noradrenaline, synapse onto astrocytes rather than directly onto blood vessels [68]. Altogether, these findings support the observation that astrocytes one of the more numerous cells in the CNS, are important determinants of the intact BBB and crucial as well for ionic homeostasis, neurotransmitter uptake, synapse formation, and neurodevelopment. Zhang and Barres [69] have reviewed the differences in astrocyte morphology, developmental origin, gene expression profile, physiological properties, function and response to injury and disease. Two essential roles of astrocytes, in neurovascular coupling and the regulation of lymphocyte trafficking across the BBB have been extensively studied.

All signaling molecules targeted to the cerebral vasculature must first act on, or pass through astrocytes in order to reach smooth muscle cells in the vessel wall. It is now recognized that neurotransmitter-mediated signaling has a key role in regulating cerebral blood flow, and that much of this control is mediated by astrocytes [70]. Moreover, cerebral blood flow may be controlled by capillaries as well as by arterioles. The glial and neuronal control of cerebral blood flow has been studied in brain slices [71]. Koehler and colleagues [72] demonstrated that electrical field stimulations in brain slices led to an increase in intracellular calcium in astrocyte cell bodies, which when transmitted to perivascular end-feet, was followed by a decrease in vascular smooth muscle calcium oscillations and arteriolar dilation.

The increase in astrocyte calcium after neuronal activation was in part mediated by activation of metabotropic glutamate receptors. Calcium signaling *in vitro* was influenced by adenosine acting on A2B receptors and by epoxyeicosatrienoic acids (EET) shown to be synthesized in astrocytes. Moreover, prostaglandins, EET, arachidonic acid, and potassium ions are candidate mediators of communication between astrocyte end-feet and vascular smooth muscle. Astrocytes appear to be capable of transmitting signals to pial arterioles on the brain surface to ensure adequate blood flow to feeding arterioles. Therefore these cells play an important role in the coupling of dynamic changes in cerebral blood flow in association with neuronal activity.

Koehler and colleagues [72] provided insight into the morphological aspects of neurovascular coupling at the capillary level of the BBB. At least one astrocyte endfoot process contacts a blood vessel and those abutting capillaries and larger vessels express connexin-43 and purinergic P2Y receptors, which together permit Ca^{2+} increases to be transmitted 60 μm or more along the abluminal side of the vessel wall. Astrocytic cells are therefore in a unique

position for sensing neuronal activity, integrating that information, and communicating with blood vessels in brain parenchyma. While neurons do not directly innervate intraparenchymal vascular smooth muscle, subpopulations of GABAergic interneurons come into close contact with astrocyte foot processes and elicit vasodilation. Such neurons might modulate vascular function through stimulation of nitric oxide (NO) synthase (NOS) activity, release of vasoactive peptides, or an astrocyte signaling mechanism.

Hudson and coworkers [73] studied trafficking of peripheral blood mononuclear cells (PBMC) across feline brain endothelial cells (FBEC) in cell culture system after the addition of combinations of different configurations of astrocytes and microglia in a model of feline immunodeficiency virus.

The addition of astrocytes to FBEC significantly increased the adherence of PBMC which was suppressed by the addition of microglia, whereas the latter alone had no effect on PBMC adherence. Whereas all PBMC showed some level of trafficking across FBEC, monocytes and B cells were significantly increased if astrocytes were present. The exposure of astrocytes notably increased the percentage of trafficking CD8 T-cells from 24% to 64%, while microglia led to a significant reversal in the preferential trafficking of CD8 cells in the presence of astrocytes. Astrocytes are capable of secreting various cytokines and chemokines in the upregulation of adhesion molecules and T-cell ligands in intact endothelial cells such as ICAM, VCAM, E-selectin, and PECAM. Human cocultured human endothelial cells and astrocytes increase the expression of ICAM-1 due to inflammatory activation by hypoxia *in vitro* [74].

Other studies have demonstrated that astrocytes are a source of IL-6, TNF-α, and MCP-1 which contribute to the CNS inflammatory response [75]. Trafficking of PBMC along the endothelial cell of the BBB is a complex mechanism that involves major subsets of immune cells and relies heavily on astrocyte, microglia and endothelial cell interactions, moreover, astrocytes appear to be an active factor in the recruitment of immune cells, while microglia appear to curtail this activity.

IMPLICATIONS FOR CEREBRAL VASCULITIS

There is an extensive literature of BBB biology in health and in widely differing neurological disorders including stroke [76], epilepsy [77], multiple sclerosis [78], Alzheimer disease [79], motor neuron disease [80], Parkinson disease [81], trauma [82], glioblastoma [83], HIV encephalitis [84] and systemic lupus erythematosus (SLE) [85]. Between 40 and 70% of patients with SLE have involvement of the central nervous system (CNS) [86], yet unlike systemic and primary CNS vasculitides, the role of the BBB in CNS lupus has been the subject of intense study employing animal models and human clinical data.

The BBB is crucial because it maintains the brain internal milieu constant, allowing optimal neuronal function. Loss of BBB integrity leads to influx of inflammatory cells, and molecules such as autoantibodies causing brain injury. Earlier studies using the well-established MRL/*lpr* mouse model that reflects the events that occur in human CNS lupus, revealed loss of BBB integrity with worsening disease [87, 88] due to chronic activation of the complement cascade with the generation of the anaphylatoxins, C3a and C5a, and aggravated C5a/C5aR signaling. In cell culture, C5a causes neuronal cells to become apoptotic, and binds to two receptors, the G-coupled, C5aR1 and the alternate receptor, C5aR2 [89]. C5a/C5aR1

signaling mediates a number of biological processes, including chemotaxis and degranulation of mast cells, basophils, neutrophils and eosinophils. It increases vascular permeability, generation of reactive oxygen species, and enhances production of cytokines from monocytes and macrophages. Whether C5a/C5aR signaling is protective or neurotoxic depends upon the setting with increases in circulating C5a leading to poor outcomes in CNS lupus [89].

Hopkins and colleagues [90] measured levels of complement anaphylatoxin split products, C3a and C5a, in the circulation of patients with SLE who were followed serially. Means complement levels were significantly higher during periods of lupus flare compared to those during a stable period, with the highest levels seen in patients with CNS involvement. Pathologic specimens from two cases who died during an acute lupus flare revealed neutrophils occluding the cerebral and systemic intestinal vessels.

C5a also contributes to cellular apoptosis in lupus [91] wherein treatment with the C5aRant, inhibiting C5a/C5aR signaling results in significant and substantial decreases in brain pathology in MRL/*lpr* mice, leaving upstream potentially protective complement activation events intact. There was evidence for a relationship between complement activation, inflammation and neuronal viability in lupus brain tissue. C5aR1 is present predominantly on blood myeloid cells, but is also constitutively expressed on several brain cell types including endothelial cells, which contribute to BBB integrity. Such studies shows the possible neuroprotective role for C5aR antagonists in MRL/lpr mice, and indicates a potential future avenues of research for systemic and primary CNS vasculitides.

CONCLUSION

There has been extraordinary research in the blood-brain barrier over the past decade. Once considered a static anatomical barrier to the traffic of molecules in and out of the CNS, the BBB of children and adults is now recognized to be fully functional and vital to both cerebrovascular angiogenesis and normal homeostatic maintenance. The cellular components and other molecular constituents of the blood-brain barrier, contained in the NVU protect the CNS from injury and disease by limiting the passage of toxins, pathogens, and inflammatory effectors of the immune system. The implications of BBB disruption in cerebral vasculitis have yet to be appreciated, however comparisons to CNS lupus may lead to a better understanding of the neural mechanisms involved in disease pathogenesis and BBB integrity, and efficacious neuroprotective treatment strategies.

REFERENCES

[1] Daneman R. The blood-brain barrier in health and disease. *Ann. Neurol.* 2012; 72:648-672.

[2] Benarroch EE. Blood-brain barrier. *Neurology* 2012; 78:1268-1276.

[3] Hawkins BR, Davis TP. The blood-brain barrier/Neurovascular unit in health and disease. *Pharmacol. Rev.* 2005; 57:173-185.

[4] Weiss N, Miller F, Cazaubon S, et al. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim. Biophys. Acta* 2009; 1788:842-857.

[5] Neuwelt EA, Bauer B, Fahlke C, et al. Engaging neuroscience to advance translational research in brain barrier biology. *Nat. Rev. Neurosci.* 2011; 12:169-182.
[6] Younger DS. Adult and childhood vasculitis of the nervous system. Chapter 14. *Motor Disorders,* 3rd Ed. DS Younger, Ed, David S. Younger MD PC: New York, 2013; 235-280.
[7] Twilt M, Benseler SM. The spectrum of CNS vasculitis in pediatrics and adults. *Nat. Rev. Rheumatol.* 2011; 8:97-107.
[8] Hajj-Ali RA, Singhal AB, Benseler S, et al. Primary angiitis of the CNS. *Lancet Neurol.* 2011; 10:561-572.
[9] Salvarani C, Brown RD Jr., Calamia KT et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann. Neurol.* 2007; 62:442-451.
[10] Weiss N, Miller F, Cazaubon S, et al. Implications of the blood-brain barrier in neurological diseases: part II]. *Rev. Neurol.* 2009; 165:1010-1022.
[11] Ehrlich P. The requirement of the organism for oxygen. An analytical study with the aid of dyes [English translation]. In, Himmelweit F, Marquardt M, Dale H, Eds. *The Collected Papers of Paul Ehrlich*. London: Pergamon Press; 1957; 433-496.
[12] Bield A, Kraus B, Über eine bisher unbekannte toxische Wirkung der Gallensauren auf das Zentralnervensystem. [About a hitherto unknown toxic effect of bile acids on the central nervous system.] *Zhl Inn. Med.* 1898; 19:1185-1200.
[13] Goldmann EE. Vitalfarbung am Zentral-nervensystem. [Vital coloring on the central nervous system.] Abh Preuss Akad Wissensch. *Physkol Mathem Klasse* 1913; 1:1-60.
[14] Lewandowsky M. Zür lehre der cerebrospinal flüssigkeit. Z für Klinische. [Zür teaches the cerebrospinal fluid. Z for Clinical.] *Med 1900*; 40.
[15] Reese TS, Karnovsky MJ. Fine structural localization of a blood-brain barrier to exogenous peroxidase. *J. Cell Biol.* 1967; 34:207-217.
[16] Brightman MW, Reese TS. Junctions between intimately apposed cell membranes in the vertebrate brain. *J. Cell Biol.* 1969; 40:648-677.
[17] Feder N. Microperoxidase: an ultrastructural tracer of low molecular weight. *J. Cell Biol.* 1971; 51:339-343.
[18] Nagy Z, Peters H, Huttner I. Fracture faces of cell junctions in cerebral endothelium during normal and hyperosmotic conditions. *Lab. Invest* 1984; 50:313-322.
[19] Shivers RR, Betz AL, Goldstein GW. Isolated rat brain capillaries possess intact, structurally complex, interendothelial tight junctions: freeze-fracture verification of tight junction integrity. *Brain Res.* 1984; 324:313-322.
[20] Gerhardt H, Golding M, Fruttiger M, et al. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J. Cell Biol.* 2003; 161:1163-1177.
[21] Lawson ND, Weinstein BM. In vivo imaging of embryonic vascular development using transgenic zebrafish. *Dev. Biol.* 2002; 248:307-318.
[22] Tam SJ, Watts RJ. Connecting vascular and nervous system development: angiogenesis and the blood-brain barrier. *Annu. Rev. Neurosci.* 2010; 33:379-408.
[23] Carmeliet P, Tessier-Lavigne M. Common mechanisms of nerve and blood vessel wiring. *Nature* 2005; 436:193-200.
[24] Gerhardt H, Ruhrberg C, Abramsson A, et al. Neuropilin-1 is required for endothelial tip cell guidance in the developing central nervous system. *Dev. Dyn.* 2004; 231:503-509.
[25] Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat. Med.* 2003; 9:677-684.

[26] Stubbs D, DeProto J, Nie K, et al. Neurovascular congruence during cerebral cortical development. *Cerebral Cortex* 2009; 19:i32-i41.
[27] Javaherian A, Kriegstein A. A stem cell niche for intermediate progenitor cells of the embryonic cortex. *Cerebral Cortex* 2009; 19:i70-i77.
[28] Johansson PA, Dziegielewska KM, Liddelow SA, et al. The blood-CSF barrier explained: when development is not immaturity. *Bioassays* 2008; 30:237-248.
[29] Ek CJ, Dziegielewska KM, Stolp H, et al. Functional effectiveness of the blood-brain barrier to small water soluble molecules in developing and adult opossum (*Monodelphis domestica*). *J. Comp. Neurol.* 2006; 496:13-26.
[30] Møllgård K, Saunders NR. The development of human blood-brain and blood-CSF barriers. *Neuropathol. Appl. Neurobiol.* 1986; 12:337-358.
[31] Ek CJ et al. Efflux mechanisms at the developing brain barriers: ABC-transporters in the fetal and postnatal rat. *Toxicol Lett.* 2010; 197:51-59.
[32] Ballabh P, Hu F, Kumarasiri M, et al. Development of tight junction molecules in blood vessels of germinal matrix, cerebral cortex, and white matter. *Pediatr Res.* 2005; 58:791-798.
[33] Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview. Structure, regulation, and clinical implications. *Neurobiol. Dis*. 2004; 16:1-13.
[34] Braun A, Xu H, Hu F, et al. Paucity of pericytes in germinal matrix vasculature of premature infants. *J. Neurosci.* 2007; 27:12012-12024.
[35] Kreuter J. Drug delivery to the central nervous system by polymeric nanoparticles: What do we know? *Adv. Drug Deliv. Rev.* 2013; Aug 24 [Epub ahead of print].
[36] Lossinsky AS, Shivers RR. Structural pathways for macromolecular and cellular transport across the blood-brain barrier during inflammatory conditions. *Histol. Histopathol.* 2004; 19:535-564.
[37] Dai H, Marbach P, Lemaire M, et al. Distribution of ST1-571 to the brain is limited by P-glycoprotein-mediated efflux. *J. Pharmacol. Exp. Ther.* 2003; 304:1085-1092.
[38] Shaik N, Giri N, Pan G, et al. P-glycoprotein-mediated active efflux of the anti-HIV1 nucleoside abacavir limits cellular accumulation and brain distribution. *Drug Metab. Dispos* 2007; 35:2076-2085.
[39] Zhang C, Kwan P, Zuo Z, et al. The transport of antiepileptic drugs by P-glycoprotein. *Adv. Drug Deliv. Rev.* 2012; 64:930-942.
[40] Aronica E, Sisodiya SM, Gorter JA. Cerebral expression of drug transporters in epilepsy. *Adv. Drug Deliv. Rev.* 2012; 64:919-929.
[41] Kerb R, Hoffmeyer S, Brinkmann U. ABC drug transporters: hereditary polymorphisms and pharmacological impact in MDR1, MRP1 and MRP2. *Pharmacogenomics* 2001; 2:51-64.
[42] Chen Y, Agarwal S, Shaik NM, et al. P-glycoprotein and breast cancer resistance protein influence brain distribution of dasatinib. *J. Pharmacol. Exp. Ther.* 2009; 330:956-963.
[43] Agarwal S, Pai D, Mitra AK. Both P-gp and MRP2 mediate transport of lopinavir, a protease inhibitor. *Int. J. Pharm.* 2007; 339:139-147.
[44] Ziegler G, Prinz V, Albrecht MW, et al. Mrp-8 and -14 mediate CNS injury in focal cerebral ischemia. *Biochim. Biophys. Acta* 2009; 1792:1198-1204.
[45] Petzelbauer P, Bender JR, Wilson J, et al. Heterogeneity of dermal microvascular endothelial cell antigen expression and cytokine responsiveness in situ and in cell culture. *J. Immunol.* 1993; 151:5062-5072.

[46] Milstone DS, O'Donnell PE, Stavrakis G, et al. E-selectin expression and stimulation by inflammatory mediators are developmentally regulated during embryogenesis. *Lab. Invest.* 2000; 80:943-954.
[47] Armulik A, Abramssson A, Betsholtz C. Endothelial/pericytes interactions. *Circ. Res.* 2005; 97:512-523.
[48] Balabanov R, Dore-Duffy P. Mini-Review. Role of the CNS microvascular pericytes in the blood-brain barrier. *Journal of Neuroscience Research* 1998; 53:637-644.
[49] Rouget C. Mémoire sur le développement, la structure et les propriéties physiologiques des capillaires sanguins et lymphatiques. [Memory on the development, structure and physiological properties of blood and lymphatic capillaries.] *Arch. Physiol. Normale Pathol.* 1873; 5:603-661.
[50] Zimmerman K. Die feinere Bau der Blutcapillaren. [The finer construction of the blood capillaries] *Anat. Entwickl* 1923; 68:29-109.
[51] Diaz-Flores LR, Gutierrez H, Varela N, et al. Microvascular pericytes: A review of their morphological and functional characteristics. *Histol. Histopathol.* 1991; 6:269-286.
[52] Tilton RG. Capillary pericytes: Perspectives and future trends. *J. Electon Microsc. Tech.* 1991; 19:327-344.
[53] Bandopadhyay R, Orte C, Lawrenson JG, et al. Contractile proteins in pericytes at the blood-brain and blood-retinal barriers. *J. Neurocytol.* 2001; 30:35-44.
[54] Boado RJ, Pardridge WM. Differential expression of α-actin mRNA and immunoreactive protein in brain microvascular pericytes and smooth muscle cells. *J. Neurosci. Res.* 1994; 39:430-435.
[55] Farrell CR, Steward PA, Farrell CL, et al. Pericytes in human cerebral microvasculature. *Anat. Rec.* 1987; 218:466-469.
[56] Gerhardt H, Betsholtz C. Endothelial-pericyte interactions in angiogenesis. *Cell Tissue Res.* 2003; 314:15-23.
[57] Frey AB, Meckelein H, Weiler-Guttler B, et al. Pericytes of the brain microvasculature express γ-glutamyl transpeptidase. *Eur. J. Biochem.* 1991; 202:421-429.
[58] Allende ML, Proia RL. Sphingosine-1-phosphate receptors and the development of the vascular system. *Biochim. Biophys. Acta* 2002; 1582:222-227.
[59] Suri C, McClain J, Thurston G, et al. Increased vascularization in mice overexpressing angiopoietin-1. *Science* 1998; 282:468-471.
[60] Thurston G, Suri C, Smith K, et al. Leakage-resistant blood vessels in mice trangenically overexpressing angiopoietin-1. *Science* 1999; 286:2511-2514.
[61] Fabry Z, Fitzsimmons K, Herlein J, et al. Production of cytokines interleukin 1 and 6 by murine brain microvessel endothelium and smooth muscle pericytes. *J. Neuroimmunol.* 1993; 47:23-34.
[62] Dore-Duffy P, Balabanov R, Rafols J, et al. The recovery phase of acute experimental autoimmune encephalomyelitis in rats corresponds to development of endothelial cell unresponsiveness to interferon gamma activation. *J. Neurosci. Res.* 1996; 44:223-234.
[63] Dore-Duffy P, Balabanov R, Washington R, et al. Transforming growth factor-β1 inhibits cytokine-induced CNS endothelial cell activation. *Mol. Chem. Neuropathol.* 1994; 22:161-175.

[64] Ramon y Cajal S. Algunas conjeturas sobre el mecanismo anatomico de la ideacion, asociacion y atencion. [Some conjectures about the anatomical mechanism of ideation, association and attention.] *Rev. Med. Cir. Pract.* 1895; 36:497-508.

[65] Golgi C. *Sulla fina anatomia degli organi central del sistema nervosa*. [*On the fine anatomy of the central organs of the nervous system.*] 1986; Milan: Hoepli

[66] Mathiisen TM, Lehre KP, Danbolt NC, et al. The perivascular astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. *Glia* 2010; 58:1094-1103.

[67] Price DL, Ludwig JW, Mi H, et al. Distribution of rSlo Ca2+-activated K+ channels in rat astrocyte perivascular endfeet. *Brain Res.* 2002; 956:183-193.

[68] Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *J. Appl. Physiol.* 2006; 100:1059-1064.

[69] Zhang Y, Barres BA. Astrocyte heterogeneity: an underappreciated topic in neurobiology. *Curr. Opin. Neurobiol.* 2010; 20:588-594.

[70] Petzold GC, Murthy VN. Role of astrocytes in neurovascular coupling. *Neuron* 2011; 71:782-797.

[71] Attwell D, Buchan AM, Charpak S, et al. Glial and neuronal control of brain blood flow. *Nature* 2010; 468:232-243.

[72] Koehler RC, Gebremedhin D, Harder DR. Role of astrocytes in cerebrovascular regulation. *J. Appl. Physiol.* (1985); 2006; 100:307-317.

[73] Hudson LC, Bragg DC, Tompkins MB, et al. Astrocytes and microglia differentially regulate trafficking of lymphocyte subsets across brain endothelial cells. *Brain Res.* 2005; 1058:148-160.

[74] Zhang W, Smith C, Howlett D, et al. Inflammatory activation of human brain endothelial cells by hypoxic astrocytes in vitro is mediated by IL-1beta. *J. Cereb. Blood Flow Metab* 2000; 20:967-978.

[75] Dong Y, Benveniste EN. Immune function of astrocytes. *Glia* 2001; 36:180-190.

[76] Jiao H, Wang Z, Liu Y, et al. Specific role of tight junction proteins claudin-5, occluding, and ZO-1 of the blood brain barrier in a focal cerebrovascular ischemic insult. *J. Mol. Neurosci.* 2011; 44:130-139.

[77] Oby E, Janigro D. the blood-brain barrier and epilepsy. *Epilepsia* 2006; 47:1761-1774.

[78] Alvarez JI, Cayrol R, Prat A. Disruption of central nervous system barriers in multiple sclerosis. *Biochim. Biophys. Acta* 2011; 1812:252-264.

[79] Bowman GL, Kaye JA, Moore M, et al. Blood-brain barrier impairment in Alzheimer disease: stability and functional significance. *Neurology* 2007; 68:1809-1814.

[80] Garbuzova-Davis S, Haller E, Saporta S, et al. Ultrastructure of blood-brain barrier and blood-spinal barrier in SOD1 mice modeling ALS. *Brain Res.* 2007; 1157:126-137.

[81] Faucheux BA, Bonnet AM, Agid Y, et al. Blood vessels change in the mesencephalon of patients with Parkinson's disease. *Lancet* 1999; 353:981-982.

[82] Tompkins O, Shelef I, Kaizerman I, et al. Blood-brain barrier disruption in post-traumatic epilepsy. *J. Neurol. Neurosurg. Psychiatry* 2008; 79:774-777.

[83] Ishihara H, Kubota H, Lindberg RL, et al. Endothelial cell barrier impairment induced by glioblastoma and transforming growth factor beta2 involves matrix metalloproteinases and tight junction proteins. *J. Neuropathol. Exp. Neurol.* 2008; 67:435-448.

[84] Roberts TK, Buckner CM, Berman JW. Leukocyte transmigration across the blood-brain barrier: perspectives on neuroAIDS. *Front Biosci.* 2010; 15:478-536.

[85] Huizinga TW, Diamond B. Lupus and the central nervous system. *Lupus* 2008; 17:376–379.
[86] Mahajan SD, Tutino VM, Redae Y, et al. C5a induces caspase-dependent apoptosis in brain vascular endothelial cells in experimental lupus. *Immunology* 2016; 148:407-419.
[87] Jacob A, Hack B, Chen P, Quigg RJ, Alexander JJ. C5a/CD88 signaling alters blood–brain barrier integrity in lupus through nuclear factor-κB. *J Neurochem* 2011; 119:1041–1051.
[88] Jacob A, Hack B, Chiang E, et al. C5a alters blood–brain barrier integrity in experimental lupus. *FASEB* J 2010; 24:1682–1688.
[89] Mahajan SD, Tutino VM, Redae Y, et al. C5a induces caspase-dependent apoptosis in brain vascular endothelial cells in experimental lupus. *Immunology* 2016; 148:407-419.
[90] Hopkins P, Belmont HM, Buyon et al. Increased levels of plasma anaphylatoxins in systemic lupus erythematosus predict flares of the disease and may elicit vascular injury in lupus cerebritis. *Arthritis Rheum* 1988; 31:632–641.
[91] Jacob A, Hack B, Bai T, Brorson JR, et al. Inhibition of C5a receptor alleviates experimental CNS lupus. *J Neuroimmunol* 2010; 221:46–52.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 6

NEUROIMAGING OF CNS VASCULITIS

Eytan Raz[1], MD PhD, Adam J. Davis[1], MD and David S. Younger[2,*], MD, MPH, MD

[1]Department of Radiology, Division of Interventional Neuroradiology
Division of Interventional Neuroradiology
New York University School of Medicine, New York, NY, US;
[2]Department of Neurology, Division of Neuroepidemiology,
New York University School of Medicine,
College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health,
City University of New York, New York, NY, US

INTRODUCTION

Vasculitis is a term used to describe a diverse spectrum of diseases characterized by inflammation of the blood vessels that may progress to ischemic injury of the central nervous system (CNS) resulting in a myriad of focal and generalized neurologic symptoms. The injury is usually secondary to mural changes resulting in vessel stenosis or occlusion. Endothelial inflammation promotes intraluminal coagulation and thrombosis [1]. Perivascular inflammatory changes and edema contribute to the pathologic picture. Arterial and venous components may be involved separately or together and dural sinuses may be affected. Generalized inflammatory processes may produce a secondary encephalitis or myelitis. Although the CNS vasculitides can have a wide range of clinical, radiographic and pathologic manifestations, they also resemble more common non-inflammatory and occlusive vascular and connective tissue diseases. The radiological aspects of CNS vasculitis have evolved in the past decade [2]. No one single imaging modality is sufficient or preeminent. A combination of studies is typically required for a confident diagnosis of CNS vasculitis.

* Corresponding Author's Email: youngd01@nyu.edu

OVERVIEW AND CLASSIFICATION

With an estimated worldwide incidence of 20 per million for eosinophilic granulomatosis with polyangiitis (EGPA) also known as Churg-Strauss syndrome, 10 per million for granulomatosis with polyangiitis (GPA), 2.6 per million for Takayasu arteritis (TAK), and 0.9 per million for polyarteritis nodosa (PAN) [3, 4], and only a fraction of patients presenting with CNS involvement, it is important for clinicians to be familiar with clinical and neuroradiologic presentation of vasculitis. This is especially important in young and middle aged adults where the prevalence of atherosclerotic disease is low [5, 6].

The historical aspects of the classification of the vasculitides are reviewed elsewhere [7, 8]. Early classification schemes were based upon pathological parameters such as large, medium, or small vessels size; location of the vessel such as the aortic arch, pulmonary, abdominal, or skin; caliber of vessels including muscular artery, arteriole, venule, vein or combination thereof; histopathological characteristic of the inflammatory cell infiltrate whether polymorphonuclear, mononuclear, eosinophilic, giant cell or epithelioid cell types; location of the vascular inflammation such as intimal, media, elastic lamina, adventitial, or panarteritis; and the presence of immune complexes.

Cupps and Fauci [9] summarized the advances of the preceding decades recognizing several clinicopathologic categories for the vasculitides. The PAN group of systemic necrotizing vasculitis comprised classic PAN and the small vessel vasculitis EGPA. Hypersensitivity vasculitis comprised serum sickness, Henoch-Schönlein purpura, now termed IgA vasculitis (IgAV), and cryoglobulinemic vasculitis. GPA was separated from PAN and EGPA. The giant cell arteritis (GCA) category comprised temporal arteritis, now termed GCA, and TAK, recognized more for the unique location of vasculitic involvement and inflammatory giant cell composition.

To illustrate the clinical importance placed on the angiographic manifestations of the PAN group of primary systemic vasculitides, Citron and colleagues [10] described multi-organ arteritis including the CNS in a highly publicized report of fourteen Los Angeles multidrug abusers. The drug closest to a common denominator was intravenous use of methamphetamine by all but two patients and exclusively by one. Acute vessel lesions of fibrinoid necrosis of the media and intima with infiltration by polymorphonuclear cells, eosinophils, lymphocytes and histiocytes, followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for PAN. However substantiation of necrotizing arteritis was present in only four of the fourteen patients. Citron and Peters [11] responded to the criticism from Baden [12] that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers, with the countering opinion that evidence of aneurysms, noted in thirteen of the fourteen patients, was ample proof of arteritis.

The contribution of angiography to CNS vasculitis commenced with the identification of angiographic beading and a sausage-like appearance of cerebral vessels at sites of presumed arteritis, first described in GCA by Hinck and coworkers [13] in 1964. Cupps and Fauci (14) established the utility of cerebral angiography in the diagnosis of histologically-proven isolated angiitis of the CNS or primary angiitis of the CNS (PACNS) in 1983. As giant cells and epithelioid cells, usually found at postmortem examination in such patients were an inconsistent finding in a meningeal and brain biopsy and therefore considered unnecessary for antemortem

diagnosis, Moore and colleagues [15] considered angiography necessary for diagnosis noting that normal cerebral angiograms had shown postmortem evidence of CNS vasculitis affecting only small vessels. This prevailing opinion was shared by Calabrese and Mallek [16] who proposed criteria for the diagnosis of primary angiitis of the central nervous system (PACNS), and Hajj-Ali and Calabrese who later separated PACNS from the reversible cerebral vasoconstrictive syndrome (RCVS), characterized instead by transient nonvasculitic narrowing of intracranial vessels [17].

By 1990, Hunder and colleagues [18] on behalf of the American College of Rheumatology (ACR) noted that the goal in classification was to identify sets of sensitive criteria that recognized a high proportion of patients with a particular form of vasculitis, while specifically excluding a high proportion of those with other diseases. Although highly specific and sensitive classification criteria might prove useful in the depiction of patients for epidemiologic studies and therapeutic trials, such criteria might not necessarily include the full spectrum of manifestations of a particular vasculitic disease, which was instead the role of formal diagnostic criteria. Lie [19] noted that while a definitive diagnosis of vasculitis almost invariably required histological documentation, the interpretation of a diagnostic tissue sample was subject to variables as diverse as the pathologist's experience, tissue selection, sample size, chronological age of the disease, and any prior treatment at the time of the biopsy. The angiographic appearance of aneurysms or occlusions of visceral arteries not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes, were useful in the classification of PAN [20] with a sensitivity of 73.5% and specificity of 89.2%. The angiographic features of narrowing, aneurysm, or occlusion of the aorta or its primary branches, were employed in the classification of TAK [21] with sensitivities and specificities of 85.5% and 81.2%, 20.3% and 95.9%, and 51.6% and 86.1%, respectively. In the same 1990 volume of the journal, Arthritis and Rheumatism, the ACR Subcommittee on Classification of Vasculitis noted no diagnostic features of angiography useful in the classification criteria of EGPA [22], GPA [23], hypersensitivity vasculitis [24], IgAV [25], or GCA [26].

Jennette and colleagues [27, 28] held two Chapel Hill Consensus Conferences (CHCC) beginning in 1994 [27] and again in 2012 [28], establishing the nomenclature or nosology of systemic vasculitides. However, different from the ACR Subcommittee on Classification of Vasculitis [18], Jennette and colleagues [27, 28] incorporated prevailing knowledge about etiology, pathogenesis, pathology, demographics, and clinical manifestations, and employed a model of the predominant caliber of involved vessel that delineated the three major categories of systemic vasculitis including large size vessel vasculitis (LVV), medium size vessel vasculitis (MVV), and small sized vessel vasculitis (SVV) types, adding further distinctions as to the structural and functional characteristics of particular vascular beds, as well as the known biochemical and functional properties that rendered them susceptible to vasculitic injury. With about twenty-six recognized vasculitides in the 2012 revised CHCC, many of which demonstrate overlap in affected involved arteries, coupled with advances in the neuroradiologic techniques for discerning CNS involvement, there has been heightened interest in imaging the cerebral vasculature.

Küker [29] differentiated the entities of extracranial LVV, and intracranial MVV and SVV noting that vasculitic involvement of the internal carotid (ICA), common carotid (CCA), M1 and A1 segments of the middle (MCA) and anterior cerebral arteries (ACA), intracranial vertebral and basilar arteries, and P1 segment of the posterior cerebral artery (PCA), generally

regarded as intracranial LVV, would instead be considered systemic MVV by 2012 Revised CHCC nomenclature [28].

Moreover, vasculitic involvement along arterial vessels distal to the MCA bifurcation as well as communicating vessels such as the anterior (AComm) and posterior communicating (PComm) arteries, were still considered MVV systemically although intracranial. They may not be demonstrable along with intracranial LVV by magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) or computed tomographic angiography (CTA), and may require conventional angiography (CA) for luminal irregularity to be visualized.

The smallest muscular arteries and arterioles within the brain parenchyma, as well as, the capillaries and proximal venules, all considered intracranial SVV by their lumen size corresponding to a caliber of 200 to 500 microns or less [30, 31], and considered beneath the resolution of invasive and non-invasive neuroimaging, require tissue biopsy to diagnose vasculitic involvement. The radiologic findings of CNS vasculitis may be similar to nonvasculitic inflammatory vasculopathies such as systemic lupus erythematosus (SLE), and other non-inflammatory vasculopathies such as atherosclerosis and spontaneous dissection in association with connective tissue disease and infection.

Examples of the neuroradiographic imaging of systemic LVV due to TAK and GCA (Figures 1-3), MVV in association with PAN (Figure 4), SVV related to EGPA (Figure 5), SLE (Figure 6), Behçet disease (BD) (Figure 7), PACNS (Figures 8-9), human immunodeficiency virus (HIV) (Figure 10), and RCVS (Figure 11) are all shown at the end of the chapter.

NEURORADIOLOGIC APPROACH TO CNS VASCULITIS

Küker [29] described three steps in the diagnostic evaluation of CNS vasculitis beginning with the demonstration of brain lesions by T_2- and diffusion and perfusion-weighted MRI, followed by the delineation of underlying vascular pathology by 1.5 Tesla (T) MRA to study the entire course of the carotid and vertebral arteries, as well as the circle of Willis. Time-of-flight (TOF) MRA sequences permits detection of more subtle stenoses and improves spatial resolution, as well as mural thickness in basal brain arteries with MRA source images; moreover, MRI may discern mural enhancement. Conventional angiography with digital subtraction (DSA) is employed to evaluate medium-sized and small-sized brain vessels, the status of cerebral hemodynamics, and assess brain perfusion.

Gomes [32] divided available neuroimaging studies into three groups including those that investigated the brain parenchyma, vessel lumen and vessel wall. Parenchymal findings, while least specific, were necessary to detect the presence of disease as well as to follow progression and remission status. Vessel lumen abnormalities, while highly suggestive for systemic vasculitis when present, were considered nonspecific and insensitive in the diagnosis of intracranial SVV.

Parenchymal Imaging

The MRI findings of CNS vasculitis have been previously described [33-36], the commonest of which are T_2/fluid attenuation inversion recovery (FLAIR) hyperintense lesions

secondary to ischemia distributed throughout subcortical and deep white matter, the deep grey nuclei and the cortices. The MCA territory was the commonest involved in CNS vasculitis [37, 38]. Diffusion weighted imaging (DWI) helps to distinguish acute, subacute and chronic ischemia and is thus mandatory. Lesions are frequently bilateral and of differing ages. Involvement of multiple vascular territories or lesions within a frankly non-vascular territorial distribution may be clues to the diagnosis of CNS vasculitis although they can also be seen in association with thrombophilic and cardiogenic multiple embolic process that produce ischemia. Ischemic lesions were present in up to one-half of patients with PACNS [35]. Nonspecific white matter changes, which may be the only finding in symptomatic patients [39, 40], would be unlikely findings of atherosclerotic hypertensive disease in young patients, yet sometimes difficult to distinguish from CNS demyelinating disease.

Intraparenchymal and subarachnoid hemorrhages may be presenting or associated radiographic features of CNS vasculitis [41] although they occur less commonly than ischemic lesions so noted in up to 40% of patients with PACNS as compared to hemorrhage that occurred in only 4% to 12% of patients [42-44]. There is uncertainty regarding the significance of microscopic hemorrhage in patients with CNS vasculitis. T_2-weighted gradient-echo MRI, which depicts chronic blood or hemosiderin products as regions with marked signal intensity loss (susceptibility effect), was useful in demonstrating multiple silent petechial hemorrhages scattered throughout both cerebral hemispheres located in cortical-subcortical regions in a patient with stereotypic tingling spells in the right hand followed by acute mutism due to histological-proven PACNS. Brain CT showed a small hematoma in the left parietal lobe and 1.5 T T_1-weighted, turbo spin-echo T_2-weighted, and fluid-attenuated inversion recovery brain MRI demonstrated acute hemorrhage in the left parietal lobe as well as subacute hemorrhage in the right frontal lobe [42]. However, T_2-weighted gradient-echo images showed multiple small hemorrhages scattered throughout the cerebral hemispheres located in the cortical-subcortical regions sparing the basal ganglia, thalamus, and brain stem. Conversely, neither large nor small silent cortical hemorrhages were found among 25 patients with intracranial vasculitis employing T_2*-weighted MRI [45].

Leptomeningeal enhancement by MRI was noted in up to 9% of patients with PACNS [34, 44] often in association with cognitive disturbances, normal MRA and catheter angiography (CA), granulomatous angiitis histopathology and small vessel involvement [44].

Delayed perfusion and reduced cerebral blood volume may be seen on brain CT and MRI in patients with cerebral vasculitis [34, 45, 46]. Magnetic resonance spectroscopy (MRS) reveals elevated glutamate and glutamine levels and reduced N-acetyl aspartate content in cerebral vasculitis [46, 47], and absence of a choline peak [46-47].

High Resolution Magnetic Resonance Imaging

High resolution MRI (hrMRI) employing gadolinium enhanced fat-saturation T_1 spin echo techniques provides useful information of possible inflammatory changes in those with suspected systemic LVV. More recently the use of vessel wall imaging has increased due to the multiple applications in vivo such as the differentiation between atherosclerosis and vasculitis, the visualization of intracranial dissection and to determine which aneurysm has ruptured in patients with acute subarachnoid hemorrhage and multiple aneurysms. The arterial wall enhancement in patients with vasculitis is probably related to contrast leakage from the lumen

into the arterial wall given the increased permeability of the endothelium; it is also possible that the presence of dilated neovessels in the wall is responsible for the increased contrast enhancement. It is important to keep in mind that there may be a discordance between the MRI findings and the clinical vasculitis activity [48]. In 26 patients with TAK and 16 healthy subjects so studied [49], contrast-enhanced T_1-weighted spin echo MRI using small fields of view and thin slices showed enhancement of thickened aortic wall compared with myocardium suggested active TAK. The degree of disease activity was concordant with laboratory measures of disease activity in 88.5% of patients, including erythrocyte sedimentation rates and C-reactive protein. The measured signal intensity of the aortic wall relative to that of myocardium during the early phase of contrast-enhanced MRI, which was significantly correlated with serological markers of inflammation, provided a useful assessment of disease activity in TAK. Notably T_2-weighted signal intensity changes were less sensitive than enhanced images. In sixty-four consecutive patients with suspected GCA, Bley and colleagues [50a] assessed mural thickness, lumen diameter, and mural contrast-enhancement scores by T_1-weighted spin-echo images with sub-millimeter in-plane spatial resolution. Their findings demonstrated that evaluation of the mural inflammatory MRI signs for diagnosing vasculitis resulted in a sensitivity of 80.6% and a specificity of 97%, in comparison to histologic results alone which demonstrated a sensitivity of 77.8% and specificity of 100%. Some positive MRI results were associated with biopsy-negative histopathology for GCA presumably due to sampling errors with skip lesions predominating in the tissue biopsy. Among GCA patients who received treatment with corticosteroids <10 days, sensitivity of hrMRI ranged from 81% to 85% while others receiving corticosteroids >10 days demonstrated a sensitivity of 33%. Notwithstanding, hrMRI still should provide sensitive and specific information when neuroimaging is performed within days following the initiation of immunosuppressive treatment. Additionally, in GCA, Geiger et al. demonstrated how mural contrast enhancement of the ophthalmic arteries can be demonstrated using a 3-T MRI examination and they showed that it is a common finding in patients with GCA with suspicious ophthalmic arteries involvement.

High-resolution MRI findings of intracranial vasculitis include concentric and asymmetric vessel wall thickening, an eccentric or narrowed vessel lumen and vessel wall enhancement. Enhancement may be limited to the vessel wall or extend to adjacent leptomeninges. Kuker and colleagues [50b] reported that 25 of 27 (92.5%) children and adults patients with a diagnosis of cerebral vasculitis affecting large brain vessels secondary to various etiologies demonstrated mural thickening, 23 of whom had abnormal mural enhancement confirmed in more than one plane of imaging. The authors contended that for intracranial large vessel disease, direct vascular wall inflammatory wall changes provided greater specificity than indirect luminal imaging findings and perhaps exceeded that of tissue biopsy. Obusez and coworkers ([50c] suggested that the degree and persistence of vessel wall enhancement helped to differentiate PACNS and RCVS in a cohort of 26 patients with respectively confirmed diagnoses. Whereas mural enhancement was less prominent in RCVS and resolved in nearly all patients restudied at mean followup of 3.5 months, those with PACNS demonstrated an increased degree of vessel wall enhancement with persisted over a mean followup of 13.5 months.

An additional role of wall imaging MRI is to help selecting the appropriate target for biopsy in cases of suspected vasculitis [48].

Indirect Vessel Imaging Techniques

Indirect imaging techniques that characterize changes in the vessel lumen leading to ischemia, infarction and hemorrhage in cerebral vasculitis can be obtained by MRA, CTA and CA, however these do not provide direct evidence of the associated underlying mural and perivascular inflammation. Catheter angiography provides up to 0.2 mm of spatial resolution and 0.5 to 0.25 seconds of temporal resolution in a typical study, exceeding MRA and CTA [30]. The spatial resolution of multi-detector CTA, which is dependent on detector row thickness, is approximately 0.4 to 0.75 mm. CA provides detailed information regarding hemodynamics that is generally absent from both CTA and MRA. Dynamic 320-section CTA provides limited hemodynamic information with a temporal resolution of 1 second and a spatial resolution of 0.5mm [51]. Indices for MRA spatial resolution are even less precise than these other techniques.

Magnetic Resonance Angiography

This non-invasive non-ionizing indirect vessel wall imaging study does not require intravenous contrast administration for the assessment of intracranial stenoses and vascular occlusions in suspected CNS vasculitis. MRA may overestimate vascular stenosis secondary to diminished signal intensity from vessel tortuosity and slow flow. The more subtle finding of intracranial vessel irregularity is more difficult to assess due to lower spatial resolution. Among nine arteries from 14 young patients with clinical and radiological suspicion of cerebral vasculitis, the sensitivity for detecting a stenosis by three-dimension (3D) TOF MRA or DSA varied from 62% to 79% for MRA, and 76% to 94% for DSA. The specificity for detecting a stenosis varied from 83% to 87% for MRA, and 83% to 97% for DSA. Using the criterion of >2 stenoses in two or more separate vascular distributions as a true positive criterion for cerebral vasculitis, the false positive rate for MRA and DSA were comparable [52]. When more than two stenoses were noted on MRA, DSA is unlikely to add further diagnostic precision in a given patient with suspected cerebral vasculitis, but yet might be useful when MRA was normal or disclosed <3 stenoses [52].

Computed Tomography Angiography

Indirect vessel wall imaging employing CTA has been used in TAK, GCA, PAN and CNS vasculitis. The efficacy of CTA in TAK, a chronic idiopathic LVV that primarily affects large vessels such as the aorta and its major branches, as well as the pulmonary and coronary arteries, is well established [53]. Non-specific inflammation of involved vessels leads to concentric wall thickening, fibrosis and thrombus formation. These produce the characteristic neuroradiologic findings of focal stenosis, occlusion, dilatation and luminal irregularity with a characteristic distribution and severity of involvement. The relative sensitivity and specificity of CTA for TAK was respectively 93% to 95% and 98% to 100% [54]. The salient CTA features of TAK include mural thickening, luminal changes, collateral vessels, and other findings usually with respect to the pulmonary and coronary arteries. In the early stages of TAK mural inflammatory changes may precede luminal contour changes, an important advantage of CTA as compared with DSA.

CTA is useful in patients with GCA in whom LVV occurs in 25% of patients [55], especially in those with confirmed biopsy pathology to screen for the presence of stenosis,

dissection, and aneurysms, as well as to assess the extent of arterial involvement and to monitor vascular lesions for signs of progression [56]. Intramural leaky microvessels which give rise to delayed enhancement of the arterial wall are consistent with, but not specific for inflammatory vasculopathy. Moreover, generally irreversible wall thickening and increased intra-wall blood pooling despite immunosuppressant treatment should not be employed to assess the inflammatory burden or disease activity [56]. Aneurysm formation along gastrointestinal, renal arteries and other systemic medium sized vessels so noted on CTA, particularly in the absence of aortic involvement, are useful neuroradiologic signs of PAN in the differential diagnosis of GCA [57, 58].

An entity considered by some to be part of the GCA spectrum, and often diagnosed with a CTA of the neck, is carotidynia, a clinical entity described first in 1927, which manifests with tenderness and pain at the neck at the level of the carotid bifurcation. The two clinical signs of carotidynia are not specific, and other causes of neck pain can have the same clinical presentation. This entity is thought to be caused by perivascular inflammation as proved by the common coexistence of increase of the erythrocyte sedimentation rate or C-reactive protein as well as ipsilateral lymph node enlargement and pharyngeal or laryngeal inflammation, as well as biologic findings, with a mild increase of the erythrocyte sedimentation rate or C-reactive protein. The findings on CT are presence of a perivascular infiltration, defined as soft amorphous tissue replacing the fat surrounding the carotid artery.

A relationship with GCA has not been demonstrated but in a series of 47 patients, 8 patients had an autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylarthritis, Graves disease, Sjögren syndrome, or Hashimoto thyroiditis, often presenting during clinical relapse of the primary autoimmune disease [59]. A new name for the condition was recently proposed, TransIent Perivascular Inflammation of the Carotid artery (TIPIC) syndrome [59].

CTA also provides useful assessment of stenotic, dilated and focally occluded vessels of the circle of Willis in the 2nd and 3rd order branches of the ACA, MCA and PCA involved by CNS vasculitis. However the resolution of luminal irregularity is less well appreciated on CTA compared with CA, since the former modality which is less dynamic, and requires the inference of collateral flow and angio-architecture from opacified vessels. The radiation dose penalty, which is slightly greater than a routine head CT, makes CTA suitable as an initial screening modality for CNS vasculitis in adults, but less desirable in children and young adults. CT readily identifies abnormal mural thickening as defined by thickness >1 mm in 93% of patients with clinical evidence of TAK along the ascending aorta, aortic arch, and descending thoracic aorta [53]. Up to 73% of patients with TAK so studied demonstrated changes within the cervicocerebral vessels, most commonly the arch and descending thoracic aorta, brachiocephalic artery and common carotid artery where wall thickening varied from 1 mm to 10 mm. Once considered the gold standard for detecting abnormal vasculature, CA may be falsely negative in the early stages of TAK [47, 53]. This is an important consideration as the disease is most effectively treated with immunosuppressive therapy during the earliest phase of the illness; a time when CA may be non-diagnostic. CTA is an excellent option in these circumstances as it provides not only information regarding luminal abnormalities, including stenosis, occlusion, aneurysmal dilatation and contour irregularities similar to CA, but direct diagnostic findings including wall thickening, calcification and abnormal enhancement [47, 53]. While nonspecific to the cerebrovascular circulation, Yamada and colleagues [54] demonstrated a sensitivity and specificity of 95% and 100% respectively, for CTA in the diagnosis of TAK, with claims of positive correlation of vessel wall changes to the

histopathologic findings [47]. Heterogeneous mural enhancement and an inner concentric low attenuation ring that enhanced at delayed imaging likewise demonstrated a positive correlation with the acute phase of histopathologic findings of vascularization and intimal swelling in the tunica media.

Catheter Angiography

Although CA has been the gold standard for diagnosis of cerebral vasculitis, it occupies a less important role compared to MRA and CTA in the initial evaluation of suspected patients. The classical angiographic features of CNS vasculitis are multifocal luminal narrowing, vascular contour irregularity and vascular dilatations with the appearance of a string of beads often along multiple vessels and in differing vascular territories, although ectasia and normal luminal diameter may also occur. The affected vessel may demonstrate a smooth or irregular luminal contour and vascular stenosis which is classically a discrete short segment or elongated. The size of the vessels affected and the distribution of lesions within each of the vessels varies with the vasculitic etiology and may be a clue to the proximate cause. Extracranial large vessel narrowing and undulation of long segments with variable luminal angiographic involvement occurs in GCA, while variable intracranial skull based and medium cortical vessel involvement occurs in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), SLE and PACNS. There is no predilection for vessel branch points in PACNS in contrast to atherosclerosis and hypertensive disease [59]. Luminal narrowing along vascular regions of laminar flow disruption and high shear stress in the ICA bulb, petro-cavernous junction and cavernous segments suggests atherosclerosis. However, multifocal stenosis and luminal irregularity within the same vessel segment with intervening normal vessel contours, and isolated stenosis within separate vascular territories and otherwise normal vessel contours favors vasculitis. Multiple emboli generally present with more obstructive than stenotic lesions, and tends not to occur as discretely along multiple vascular territories or in tandem along the same vessel in contrast to CNS vasculitis. Angiographic features that favor medium vessel vasculitic involvement due to systemic vasculitis and autoimmune disease in contrast to PACNS include abrupt vascular truncation, occlusion and microaneurysm formation [60]. The collateral circulation should be investigated and quantified by CT and MR perfusion imaging in patients with severe luminal narrowing and vascular occlusion of medium and large vessels as should abnormal cerebral hemodynamics typified by slow anterograde flow, diminished distal luminal size, and prolonged circulation time. Vascular dissection which rarely occurs in intracranial vasculitis is much more common in the extracranial vasculature in GCA.

The sensitivity of CA for PACNS is reportedly 40% to 100% [34, 35, 38, 40, 59-63] and the specificity no higher than 37% for CA in the diagnosis of PACNS [64]; however they may vary depending upon the particular clinical, radiographic and histopathologic definitions employed. Vasculitic small vessel involvement is typically beneath the resolution of CA. Children with so-called angiography negative, biopsy positive, small vessel (SV)-childhood PACNS (cPACNS) [65] who present with negative angiography and a positive MRI, are generally considered to be candidates for cerebral and leptomeningeal biopsy to confirm the presence of vasculitis.

There is a poor correlation between neuroradiologic findings on MRI and CA in PACNS [38, 60]. Whereas two-thirds of lesions detected by MRI showed a CA lesional correlate, only 44% of those detected by CA were conversely identified by MRI. Furthermore, the correlation

of 41 territories involved by MRI subsequently studied by CA was 15%, whereas among 50 vascular territories involved by CA, a correlate was found in 34% of MRI studies.

The risk of transient neurological injury is 10% and permanent morbidity occurs in about 1% of patients undergoing CA for the evaluation of CNS vasculitis [66]. Intravenous corticosteroids administered prior to CA may ameliorate the risk of injury and reduce complications.

NUCLEAR MEDICINE IMAGING MODALITIES

Positron Emission Tomography

Nuclear Medicine evaluation of neurovasculitis remains promising but problematic. Conceptually the ability to monitor metabolic activity within the vessel wall should be a good indicator of inflammatory activity. ^{18}fluorodeoxygluscose positron emission tomography (FDG-PET) has been the best studied radionuclide for this indication, particularly in systemic LVV. One meta-analysis [67] demonstrated a wide variability of diagnostic sensitivity for TAK ranging from 28% to 100% while the range of specificity was 50% to 100%. Fused PET and CT images provide superior anatomic localization and improved sensitivity and specificity of 91% and 89% for TAK. A greater diagnostic sensitivity of 80% and specificity of 89% in those studied by FDG-PET were noted for GCA [68]. Nonetheless, the specificity of FDG-PET is degraded by the presence of atherosclerosis as active inflammatory plaques may produce false positive findings [69]. The utility of FDG-PET for monitoring disease activity in these patients may be problematic. Some patients with TAK deemed inactive by clinical criteria may in fact demonstrate biopsy-proven active inflammation [70]. Studies indicate that FDG-PET is a sensitive and helpful diagnostic study for identifying patients with subclinical active disease, with 83% of biopsy-proven GCA patients demonstrating positive or concordant lesions by FDG-PET imaging [71]. The sensitivity and specificity of FDG-PET in the identification of active vasculitic disease compared with clinical signs and laboratory criteria led to respective rates of 100% and 89% [72].

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) employs multiplanar nuclear medicine imaging for the investigation of regional CNS perfusion abnormalities. It provides direct information about the pathophysiology and cerebral metabolism in cerebral vasculitides at the level of capillary endothelium in the blood-brain barrier (BBB) microcirculation beyond the resolution of MRA, CTA, and CA [73, 74].

There are claims of the utility of brain SPECT imaging in the clinical diagnosis and management of cerebral vasculitis associated with SLE [75, 76], Kawasaki disease [77], IgAV [78], neurological BD [79], GPA [80], and brain irradiation [81, 82]. Apart from the direct impact of vascular narrowing and occlusion resulting from necrotizing arteritis and vascular infiltration, other explanations for an abnormal brain SPECT include circulating immune complexes on the BBB [83], and neurotoxic effects of antibodies and brain antigenic targets

[81], glial cell interactions [82], and pathogenic hypersensitivity responses to brain antigens released during vascular-mediated tissue necrosis [82].

The results of brain SPECT imaging were described in one patient with histologically-verified cerebral vasculitis [84]. This 71-year-old man with later-proven granulomatous angiitis of the brain underwent Tc-99m hexamethylpropyleneamine oxime (HMPAO) brain SPECT three weeks after onset of CNS disease. There was irregular radiotracer uptake throughout both cerebral hemispheres with scattered multiple areas of hypoperfuision, further demonstrated in surface volumetric images. Postmortem examination showed fibrinoid necrosis, inflammatory cells, mainly lymphocytes, histiocytes and a few multinucleated giant cells involving medium-to-small meningeal and parenchymal vessels with intramural vascular deposits of amyloid, without systemic vasculitis. Although there was no specific mention of the correlation of the SPECT findings with anticipated BBB involvement, the authors [88] attributed the observed cortical hypoperfusion to focal narrowing and occlusion of small- and medium-sized cerebral arteries.

Color Doppler Ultrasonography

Color Doppler ultrasonography (CDU) and color duplex imaging provide direct imaging and evaluation of superficial arteries and their vessel walls. They have been most extensively studied in systemic LVV such as GCA and TAK. This non-invasive methodology which lacks exposure to ionizing radiation can be easily administered and repeated to monitor disease activity and response to treatment. It provides a high resolution imaging of the walls of deep-seated vessels as compared with MRI, detecting wall thickness and edema the latter of which produces a hypoechoic signal on CDU as a halo sign. In a meta-analysis of 998 patients with 17 studies, the sensitivity of the halo sign for biopsy-proven GCA was only 75%, but specificity was 83%. Concentric homogeneous mural thickening, stenosis and occlusion of the aorta and brachiocephalic branches are typical CDU features of GCA and TAK [69, 85, 86], which may be differentiated from atherosclerotic disease by the absence of plaque formation, concentric long segment involvement and location. Ultrasonography revealed subtle mural changes characterized by a homogenous, circumferential mid-echoic wall thickening within the subclavian and carotid arteries in the early stages of TAK preceding abnormalities detected by CA [87], with overall greater wall thickness of the CCA and ICA in the vasculitic vessels compared to controls. The CCA intima to medial thickness ratio was increased in patients with TAK compared with normal control [88] yielding respective sensitivity and specificity rates of 82% and 70%.

The wall diameters of common, frontal and parietal division of the superficial temporal artery were significantly greater in patients with GCA than in symptomatic patients without the disease as well as asymptomatic age-matched controls [89]. A hypoechoic halo surrounding a patent vessel lumen was found in 73% of biopsy proven vasculitis patients but not in symptomatic patients without GCA and asymptomatic controls. The histopathologic finding of mural cellular infiltration did not correlate with a hypoechoic halo albeit attributed to edema. The halo disappeared at a mean of 16 days following effective treatment. Similar findings are present in the occipital arteries [90] although the sensitivity is less when compared with the superficial temporal arteries. The halo examination is a useful exam for symptomatic patients

presenting with nuchal pain, occipital headache or occipital scalp tenderness, especially when occipital artery involvement may be the only imaging manifestation of the disease.

CONCLUSION

The neuroimaging evaluation of vasculitis may seem complex and nonspecific, particularly for PACNS and the primary systemic autoimmune vasculitides. When all imaging modalities including those that provide parenchymal, luminal and mural evaluation are brought to bear on a given patient with suspected vasculitis, the entire constellation of findings typically brings clarity to the situation. The largest single series of PACNS [35] demonstrated that 77% of CT, 97% of MRI, 59% of MRA and 90% of CA studies were ultimately positive in comparison to 62% of positive brain biopsies. While each individual modality may be nonspecific, combining CNS parenchymal and peripheral vascular radiological studies with serological and histopathologic studies in clinically suspected patients, should assure the accurate diagnosis of systemic and nervous system vasculitis in virtually all true cases.

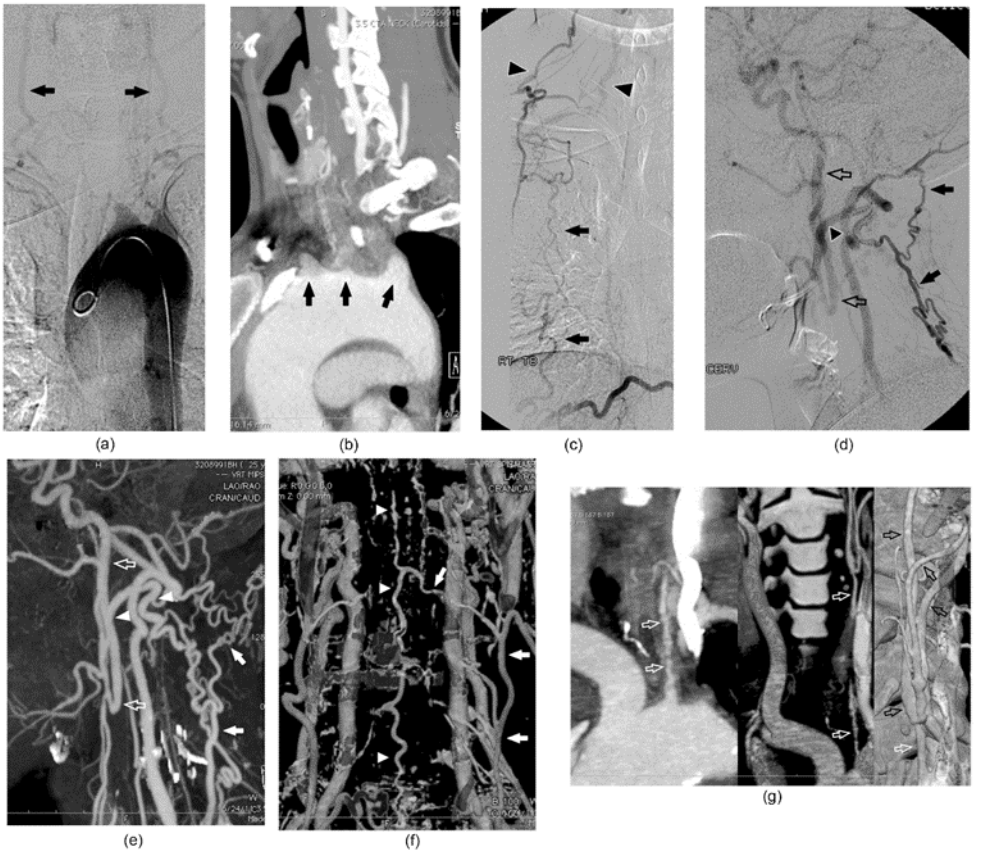


Figure 1. (Continued).

Figure 1 (a-g). Takayasu Arteritis and collateral circulation in two patients, both with vascular insufficiency. Patient 1: figures 1a-f; Patient 2: 1g. (a and b) Complete occlusion of the great vessels arising from the aortic arch on CA and CTA with residual stumps of the brachiocephalic, common carotid and left subclavian arteries (black arrows). (c) Extensive collaterals to the cephalic circulation via the intercostal arteries (black arrows) to the deep cervical and vertebral artery (black arrowheads). (d) Distal deep cervical branches (black arrows) with opacification of the occipital artery (black arrowhead) via retrograde flow filling the internal carotid artery (black outline arrows). (e) Collateral circulation by CTA although flow dynamics are absent (deep cervical artery, white arrows; occipital artery, white arrowheads; internal carotid artery, white outline arrows). (f) Very small vasculature provides clinically significant collateral circulation from the ascending cervical artery, vertebral artery, and spinal radicular artery (white arrows) via the anterior spinal artery (white arrowheads) to the intracranial circulation. (g) Isolated involvement of the left common carotid artery beginning at the origin and extending the length of the vessel. Note the severe continuous long segment luminal narrowing characteristic of the disease (g) Left, maximum intensity projection; middle, volume rendered image, outlined white arrows). The internal and external carotid arteries imaged by CTA (right, volume rendered image, outlined black arrows) are diminished in caliber with otherwise smooth lumina and normal morphology resulting from decreased flow than the effect of vasculitic involvement. Abbreviations: CA, catheter angiography; CTA, computed tomographic angiography. Courtesy of Adam Davis, MD.

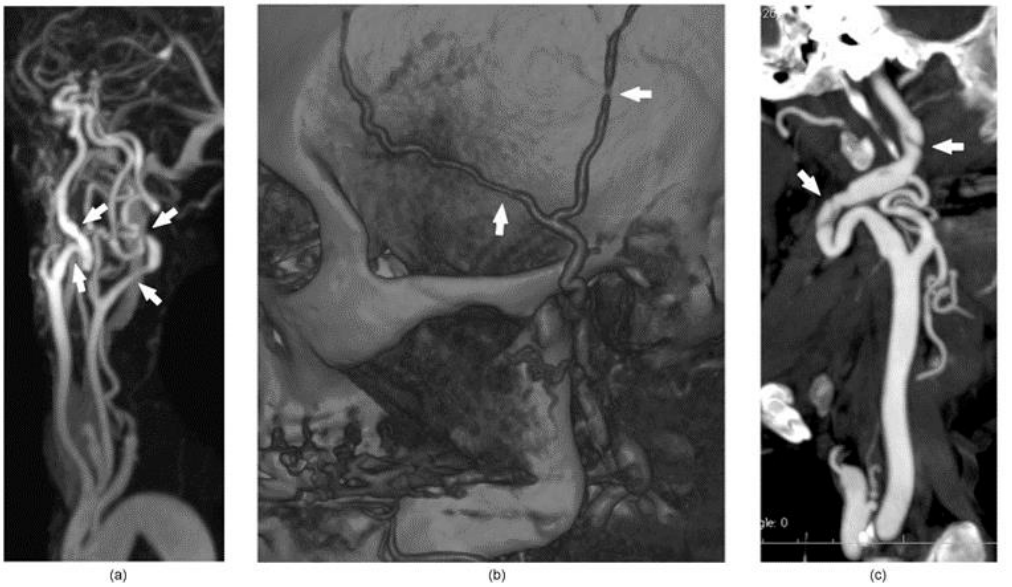


Figure 2 (a-c). Giant Cell Arteritis. Patient with severe worsening headache, diplopia and jaw pain. (a) At presentation, MRA demonstrates multifocal luminal narrowing and contour irregularity within bilateral internal carotid arteries (white arrows). (b) CTA volume rendering reveals multifocal short segment luminal narrowing of the superficial temporal arteries (white arrows). (c) Maximum intensity projection images of the internal carotid arteries with intraluminal linear defects (white arrows) are consistent with dissection. Abbreviations: MRA, magnetic resonance angiography; CTA, computed tomographic angiography. Courtesy of Adam Davis, MD.

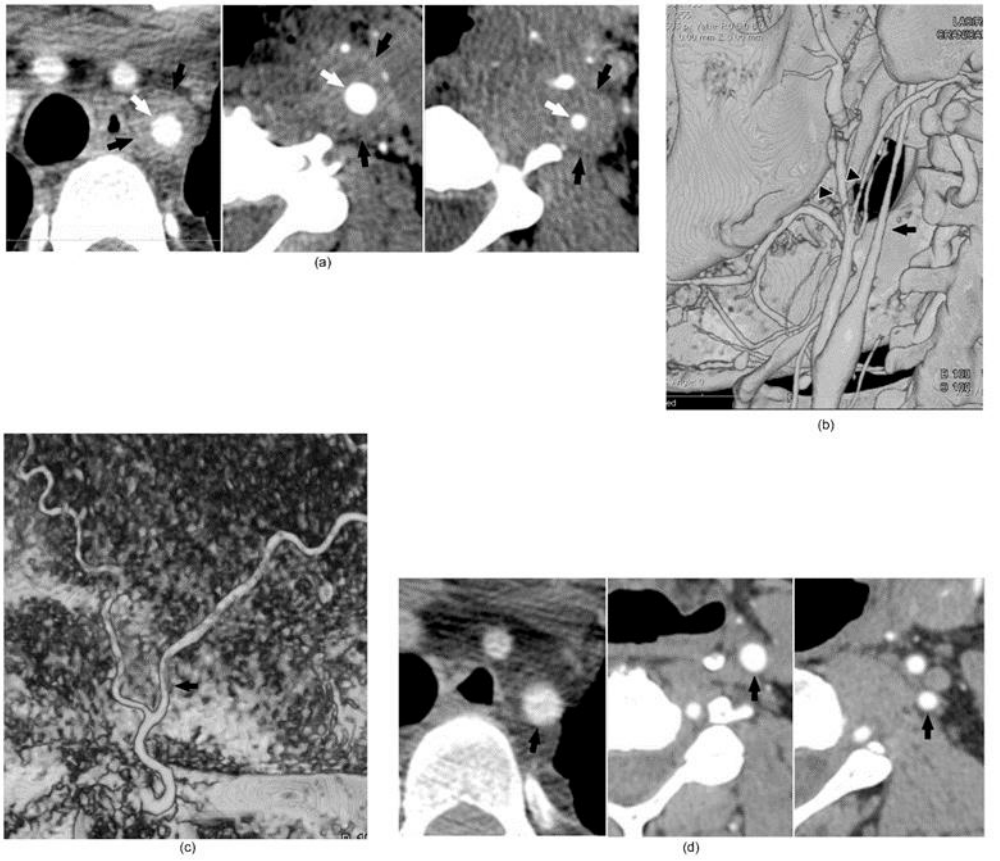


Figure 3 (a-d). Large vessel vasculitis with features of Takayasu arteritis and giant cell arteritis. (a) Marked mural thickening with heterogeneous enhancement within the bilateral cervical vasculature shown left to right: left subclavian, common carotid, and internal carotid arteries. The black arrows indicate the outer wall contour, normally a barely imperceptible margin, while the white arrows indicate the enhancing, narrowed vessel lumen with an appearance consistent with Takayasu arteritis. (b) CTA volume rendering with long segment smooth narrowing of the left internal carotid artery (black arrow) with more localized narrowing along the external carotid artery branches (arrowheads) typically found with giant cell arteritis. (c) CTA volume rendering narrowing of the superficial temporal artery (black arrow) as would be expected in giant cell arteritis. (d) Resolution of mural thickening within the left subclavian, common carotid and internal carotid arteries after treatment with corticosteroids. Abbreviations: CTA, computed tomographic angiography. Courtesy of Adam Davis, MD.

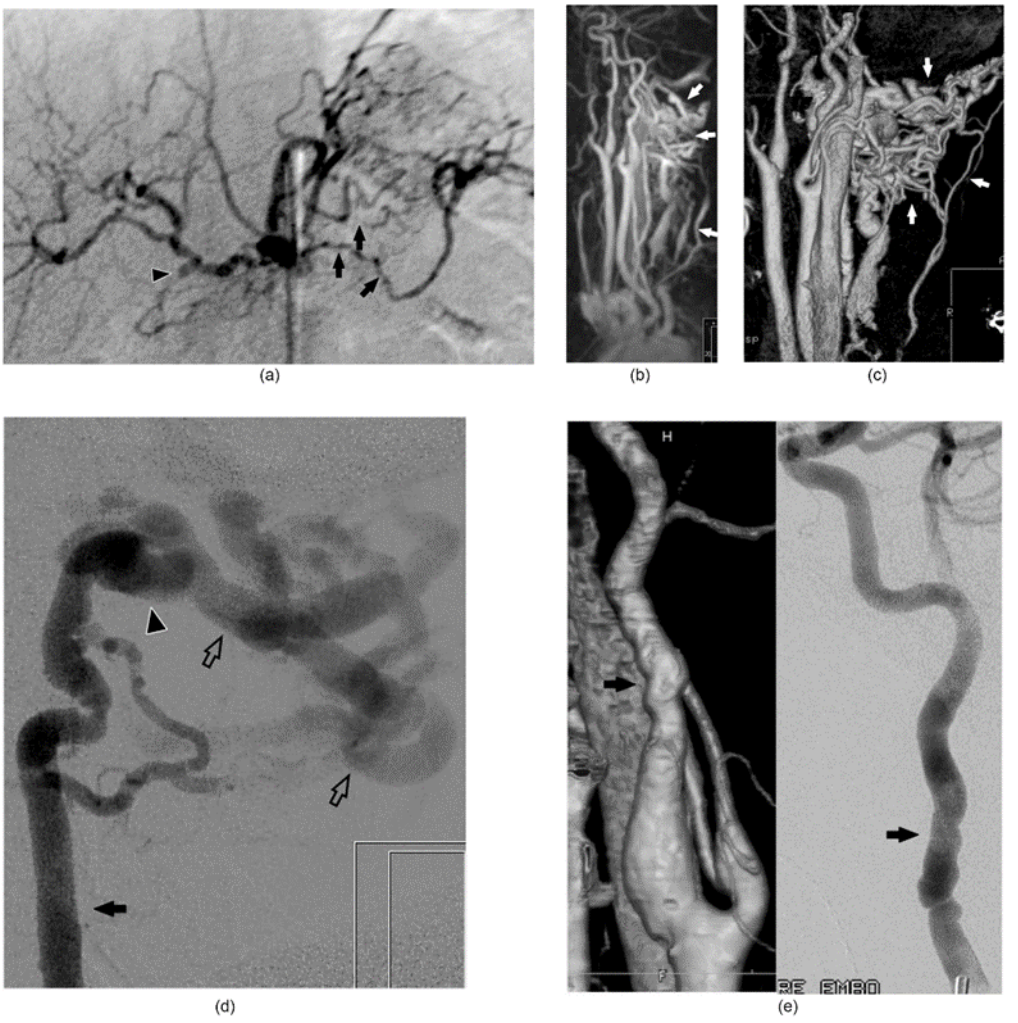


Figure 4 (a-e). Polyarteritis nodosa. (a) CA of the celiac axis performed five years prior to presentation with multifocal luminal narrowing (black arrows) and aneurysmal dilatation of the hepatic and splenic arteries (black arrowhead). (b and c) MRA and CTA reveal a collection of prominent, tortuous vasculature at the posterior cervical space enveloping the distal left vertebral artery. Prominent draining veins are noted (white arrows). (d) The left vertebral artery (black arrow) is the site of arteriovenous shunting (black arrowhead) into a dilated, tortuous draining vein confirming the diagnosis of an arteriovenous fistula. (e) CTA and CA (left and right respectively) demonstrate a discrete region of luminal irregularity and narrowing within the proximal cervical segment of the internal carotid artery (black arrows) which in isolation could be confused with fibromuscular dysplasia. Abbreviations: CA, catheter angiography; MRA, magnetic resonance angiography; CTA, computed tomographic angiography. Courtesy of Adam Davis, MD.

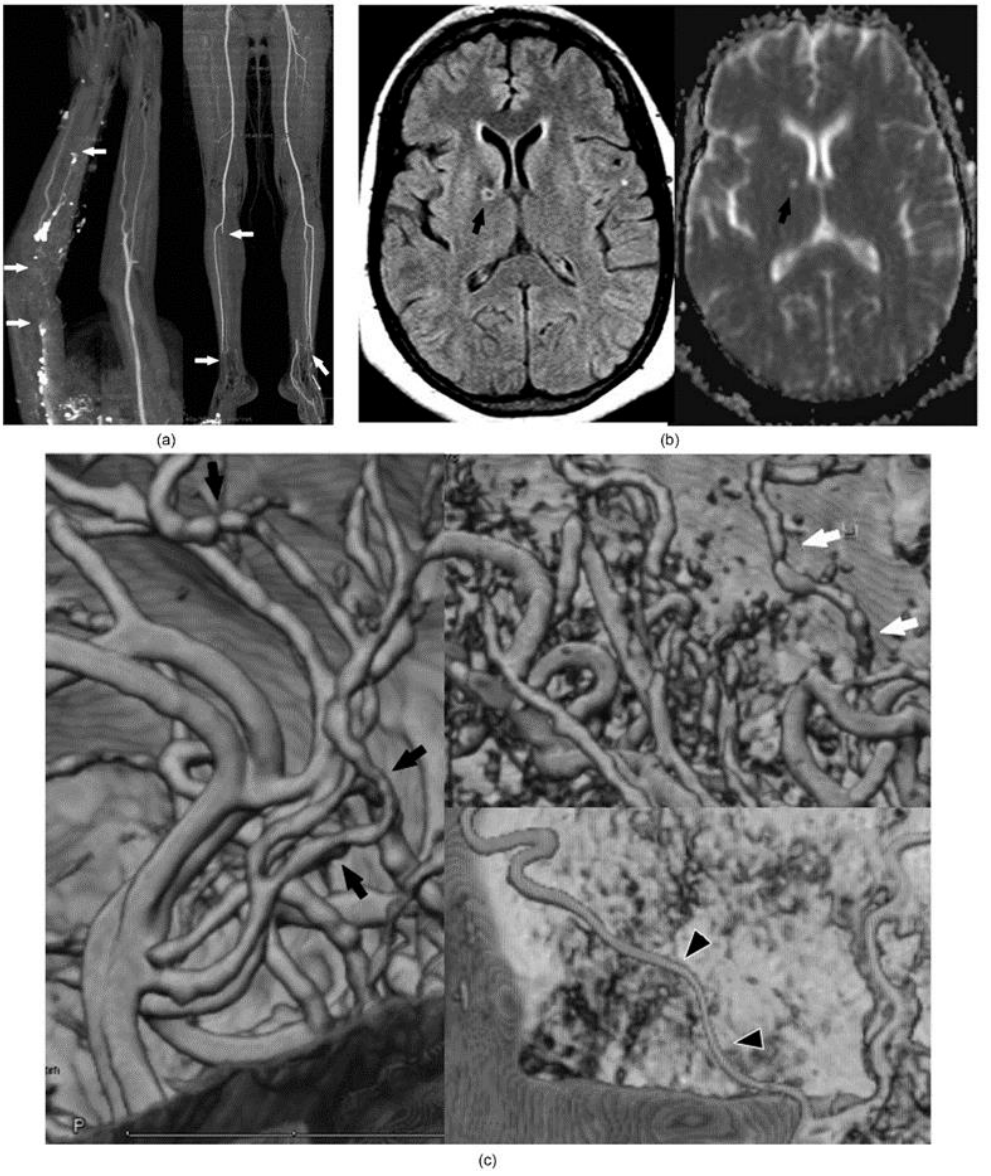


Figure 5 (a-c). Eosinophilic granulomatosis with polyangiitis. (a) MRA of the limbs demonstrates multifocal brachial, radial, posterior tibial and dorsalis pedis artery stenoses and occlusions. (b) MRI of the brain (FLAIR left, ADC right) reveals a punctate right basal ganglia chronic lacunar infarct (black arrows). (c) CTA of the brain demonstrates multifocal short and long segment luminal narrowing within the anterior cerebral artery (black arrows), middle cerebral artery (white arrows) and superficial temporal artery (black arrowheads). Intracranial vessels demonstrate marked luminal contour irregularity while the extracranial arteries demonstrate a more long segment smooth and concentric narrowing, reflecting the variability of the radiographic findings of these diseases even in the same individual. Abbreviations: MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; ADC, apparent diffusion coefficient; CTA, computed tomographic angiography. Courtesy of Adam Davis, MD.

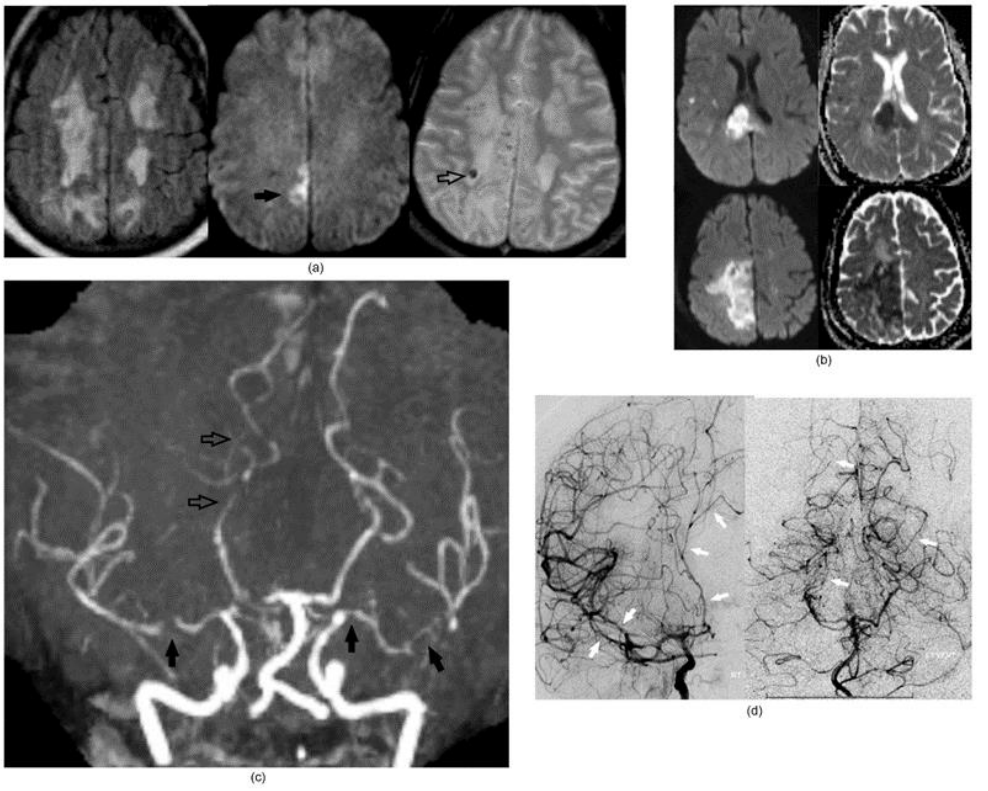


Figure 6 (a-d). Systemic lupus erythematosus. (a) MRI FLAIR sequence at presentation (left) reveals bilateral hemispheric white matter signal abnormality with involvement of the parietal and occipital grey matter. Right medial parietal cortical hyperintensity on diffusion weighted imaging (Figure 6a, middle, black arrow) with ADC low signal intensity (not shown) is consistent with acute ischemia in the right posterior cerebral artery parieto-occipital division. Gradient echo imaging (right, black outlined arrow) demonstrates focal susceptibility effect, indicating hemosiderin deposition from microhemorrhage. (b) Diffusion MRI of the brain at a later date reveals restricted diffusion characterized by increased T2 diffusion and decreased ADC signal intensity within a large confluent region of the medial right parietal lobe and occipital lobes, extending to the splenium of the corpus callosum, consistent with extension of acute infarction in the right posterior cerebral artery territory. (c) MRA demonstrates multifocal luminal narrowing, mostly short segment and occasionally severe, as well as long segment stenoses within the bilateral middle cerebral artery M1 segments (black arrows). Similar changes are present within the distal internal carotid artery (not marked). The right posterior cerebral artery demonstrates multifocal luminal narrowing and abrupt occlusion of the parieto-occipital branch (black outlined arrows). The extensive large and medium vessel multi-segmental, tandem, luminal irregularity and narrowing is more indicative of a vasculitic process than a thromboembolic process. (d) CA confirms the long segment irregular luminal narrowing with interspersed segments of normal luminal caliber and contour within all vascular territories. Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography; CA, catheter angiography. Courtesy of Adam Davis, MD.

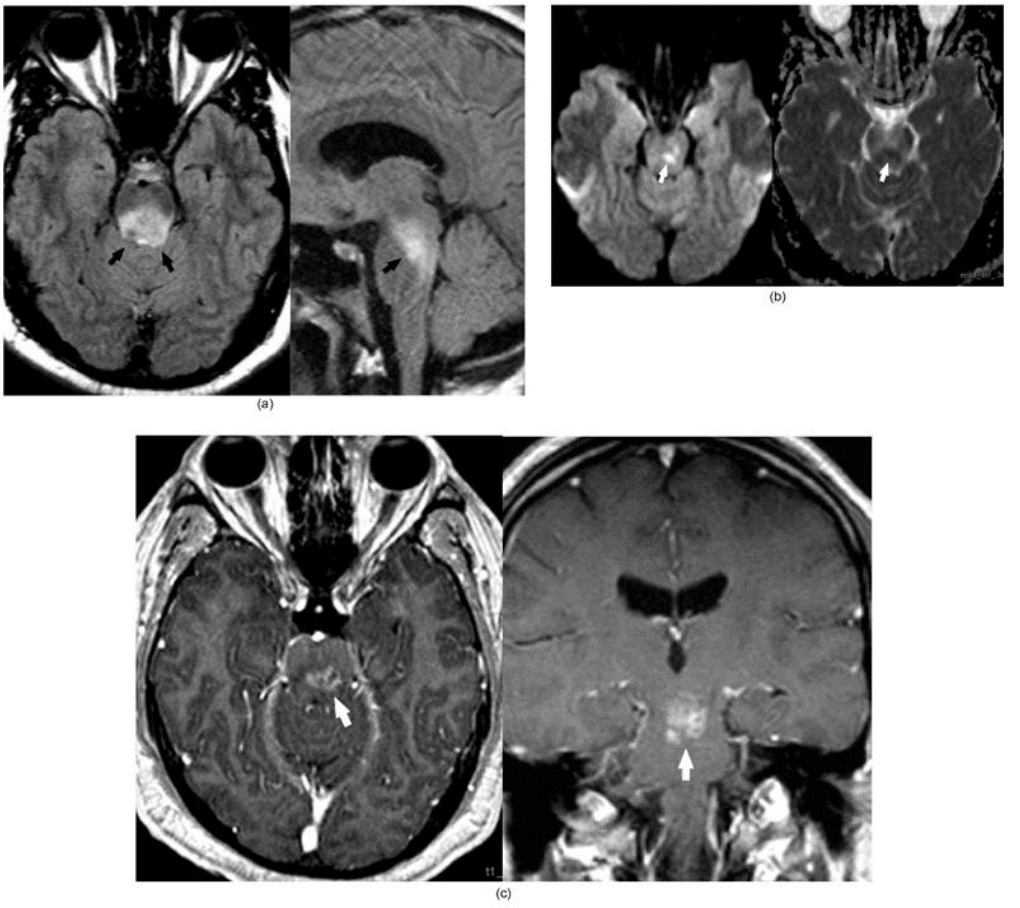


Figure 7 (a-c). Behçet disease. (a) Axial and sagittal FLAIR imaging (left and right respectively) demonstrates strikingly geographic abnormal hyperintense signal intensity in the midbrain and pontine tegmentum with little mass effect. (b) Areas of diffusion restriction characterized by T2 diffusion hyperintense and ADC hypointense signal (left and right respectively, white arrows) in the left paramedical caudal midbrain reflective of acute or early subacute infarction. (c) Axial and coronal post gadolinium T1-weighted images (left and right respectively) demonstrate peripheral curvilinear and punctate nodular enhancement. Abbreviations: FLAIR, fluid attenuation inversion recovery; ADC, apparent diffusion coefficient. Courtesy of Adam Davis, MD.

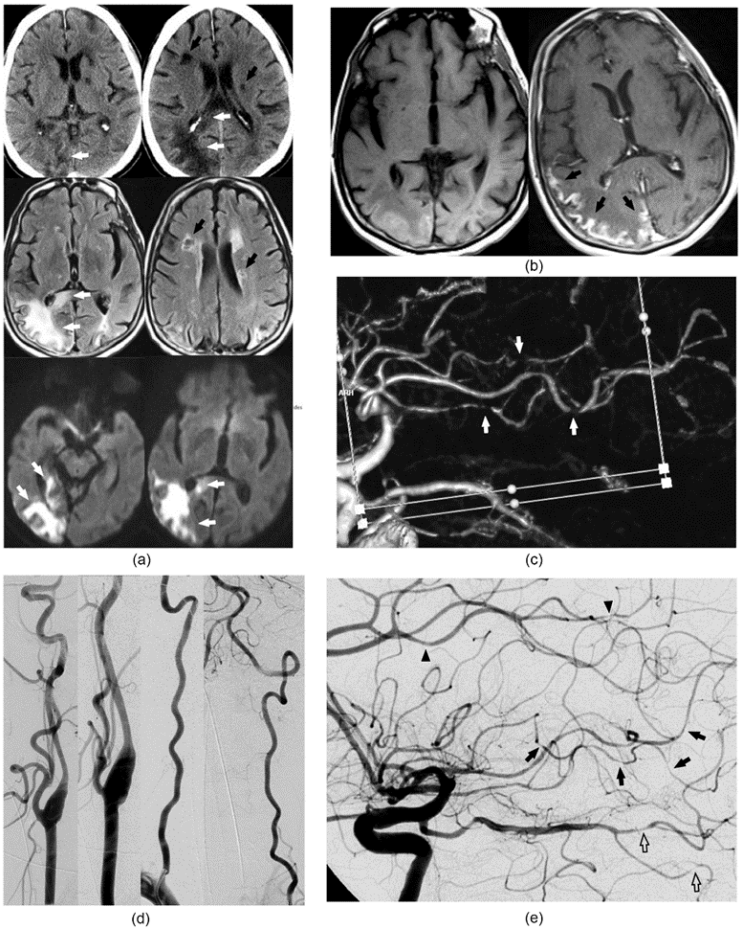


Figure 8 (a-e). Primary angiitis of the central nervous system. (a) Non-contrast CT (top) demonstrates multifocal regions of low attenuation. Those in the right frontal subcortical white matter and left basal ganglia (black arrows) are sharply defined, without mass effect and likely reflect old infarctions. Both the cortex and underlying white matter of the right occipital lobe are involved as is the right splenium of the corpus callosum (white arrows). In these locations the margins are more ill-defined and there is subtle mass effect characterized by sulcal and ventricular effacement, suggesting acute ischemia in the right posterior cerebral artery territory. MRI FLAIR imaging (middle) demonstrates central low and peripheral high signal intensity within the frontal and periventricular white matter lesions (black arrows) consistent with chronic encephalomalacia from old infarctions. The FLAIR hyperintense signal within the right occipital lobe is more confluent and extends to the posterior temporal lobe and splenium, involving both cortex and white matter (white arrows) and better delineates the extent of the acute infarct. DWI (bottom) demonstrates restricted diffusion consistent with acute ischemia. (b) T1-weighted imaging pre and post-gadolinium demonstrates extensive leptomeningeal enhancement along the cortical surface of the posterior temporal and occipital lobes. (c) CTA demonstrates multifocal vascular narrowing within several branches of the MCA (white arrows) with intervening regions of normal appearing vasculature. At the bottom of the image vascular narrowing within the posterior cerebral artery (not marked) is present. (d and e) CA reveals completely normal extra-cranial vasculature. The anterior cerebral (black arrowheads), middle cerebral (black arrows) and posterior cerebral artery (black outlined arrows) demonstrate mild to severe short segment stenoses. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; CTA, computed tomographic angiography; DWI, diffusion-weighted imaging; MCA, middle cerebral artery. Courtesy of Adam Davis, MD and Tibor Bescke, MD.

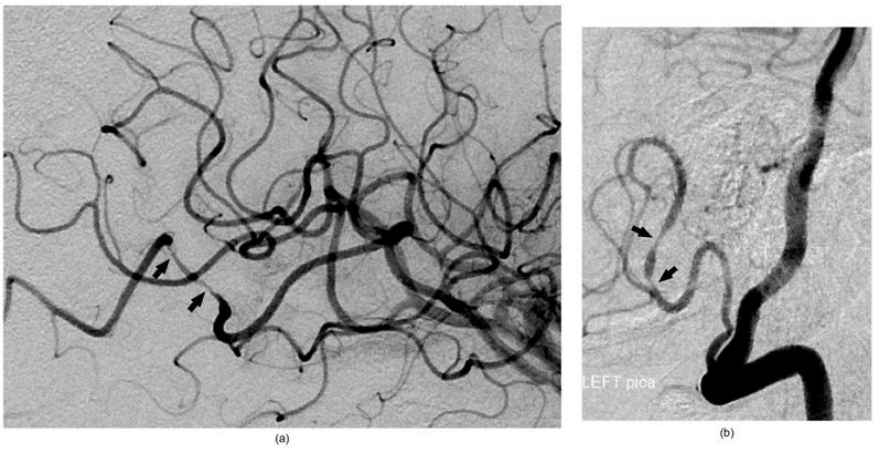


Figure 9 (a, b). Primary angiitis of the central nervous system. (a and b) CA reveals multifocal long and short segment stenosis. Abbreviation: CA, catheter angiography. Courtesy of Adam Davis, MD and Tibor Bescke, MD.

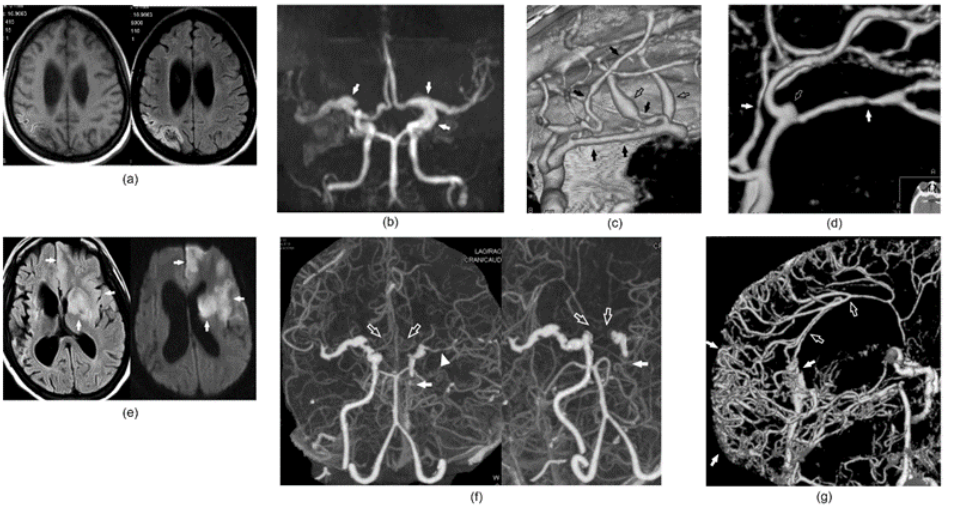


Figure 10 (a-g). HIV vasculitis. (a) MRI FLAIR imaging (right) demonstrates abnormal hyperintense signal and volume loss within the cortex and underlying white matter of the right parietal and far lateral occipital lobes consistent with remote right middle cerebral artery territory infarction. T1-weighted imaging (left) demonstrates gyrifrom increased signal intensity. (b) MRA demonstrates bilateral long segment, irregular, fusiform dilatation of the internal carotid artery and proximal anterior and middle cerebral artery segments (white arrows). Areas of luminal stenosis are seen (right). CTA reveals a more detailed and diagnostic view of the intracranial vasculature. (c) The right middle cerebral artery demonstrates regions of short and long segment concentric vascular stenoses (black arrows) with intervening luminal dilatation (black outlined arrows). The ACA demonstrates short and long segment concentric stenoses (white arrows) and a small pericallosal saccular aneurysm (white outlined arrow). In followup imaging (d) MRI now demonstrates extensive abnormal FLAIR hyperintensity within the left basal ganglia and left frontal lobe cortex and underlying white matter, with restricted diffusion (left and right respectively). (e) CTA (maximum intensity projection, AP on the left and oblique on the right) demonstrates occlusion of the skull base left petrous internal carotid artery and cervical internal carotid artery segments (white arrows). (f) Bilateral anterior cerebral arteries are occluded (open white arrows) and the left middle cerebral artery is markedly stenotic (white arrowhead). Findings are consistent with disease progression and luminal thrombosis. (g) CTA volume rendered imaging demonstrates extensive collateral circulation to the anterior cerebral artery (open white arrows) from the right posterior cerebral artery via cortical leptomeningeal branches and posterior choroidal branches (white arrows). Abbreviations: HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; ACA, anterior cerebral artery; AP, anteroposterior. Courtesy of Adam Davis, MD and Tibor Bescke, MD.

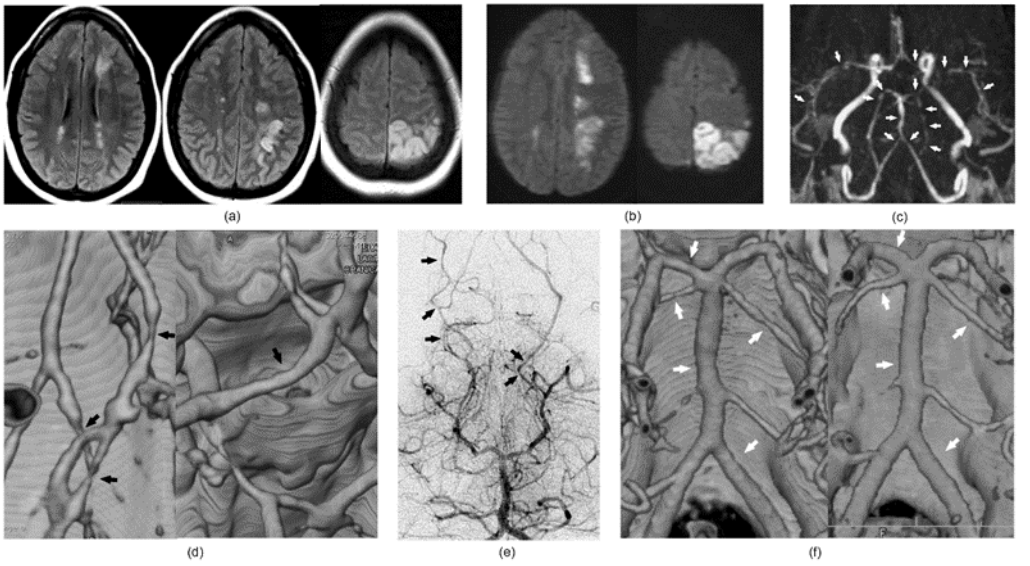


Figure 11(a-f). Reversible cerebral vasoconstrictive syndrome. (a) MRI FLAIR imaging on presentation demonstrates multifocal abnormal hyperintense signal within the bilateral hemispheric white matter, more prominent in the parietal and occipital lobes where it extends to the cortex. (b) T2-diffusion imaging demonstrates restricted diffusion consistent with acute ischemia. The white matter distribution within the left hemisphere straddles the anterior, middle and posterior cerebral vascular territories, a 'watershed' distribution. (c) MRA at admission demonstrates short segment multifocal narrowing within the distal bilateral vertebral arteries, the basilar artery, and bilateral middle and posterior cerebral vasculature (white arrows). (d) CTA demonstrates moderate narrowing within the right PCA P2 segment and a more severe narrowing distally within the P3 parieto-occipital segment (left, black arrows). Mild narrowing is present within the ACA A1 segment (right, black arrow). (e) CA confirms multifocal narrowing within the bilateral posterior cerebral arteries (black arrows). (f) Follow up CTA (at presentation on the left, 5 months follow-up on the right) reveals complete resolution of the original findings. Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; PCA, posterior cerebral artery; CA, catheter angiography; ACA, anterior cerebral artery. Courtesy of Adam Davis, MD.

REFERENCES

[1] Giannini C, Salvarani C, Hunder G, et al. Primary central nervous system vasculitis: pathology and mechanisms. *Acta Neuropathol.* 2012; 123:759–772.

[2] Wynne PJ, Younger DS, Khandji A, et al. Radiographic features of central nervous system vasculitis. *Neurol. Clin.* 1997; 15:779-804.

[3] Marsh EB, MD, Zeiler SR, Levy M, et al. Diagnosing CNS Vasculitis: The Case Against Empiric Treatment. *Neurologist* 2012; 18:233–238.

[4] Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. *Ann. Intern Med.* 2003; 139:505-515.

[5] Adams HP, Kapelle J, Biller J, et al. Ischemic Stroke in Young Adults. Iowa Registry of Stroke in Young Adults. *Arch. Neurol.* 1995; 52:491-495.

[6] Gemmete JJ, Davagnanam I, Toma AK, et al. Arterial Ischemic Stroke in Children. *Neuroimaging Clinics of North America* 2013; 23:781-798.

[7] Younger DS. Adult and childhood vasculitis of the nervous system. Chapter 14. *Motor Disorders*, 3rd Ed. DS Younger, Ed, David S. Younger MD PC: New York, 2013; 235-280.
[8] Younger DS, Kass RM. Vasculitis and the nervous system. *Neurol. Clin.* 1997; 15:737-758.
[9] Cupps TR, Fauci AS. The Vasculitides. *Major Problems in Internal Medicine* 1981; 21:1-5.
[10] Citron BP, Halpern M, McCarron M, et al. Necrotizing angiitis associated with drug abuse. *N. Engl. J. Med.* 1970; 283:1003-1011.
[11] Citron B, Peters R. Angiitis in drug abusers [Letter]. *N. Engl. J. Med.* 1971; 284:111-113.
[12] Baden M. Angiitis in drug abusers [Letter]. *N. Engl. J. Med.* 1971; 284:111.
[13] Hinck V, Carter C, Rippey C. Giant cell (cranial) arteritis. A case with angiographic abnormalities. *AJR* 1964; 92:769-775.
[14] Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospective diagnostic and therapeutic experience. *Am. J. Med.* 1983; 74:97-105.
[15] Moore PM, Cupps TR. Neurological complications of vasculitis. *Ann Neurol* 1983; 14:155-167.
[16] Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1988; 67:20-39.
[17] Hajj-Ali RA, Calabrese LH. Central nervous system vasculitis. *Curr. Opin Rheumatol.* 2009; 21:10-18.
[18] Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis Rheum.* 1990; 33:1065–1067.
[19] Lie JT. Illustrated histopathologic classification criteria for selected vasculitis syndrome. *Arthritis Rheum.* 1990; 33:1074-1087.
[20] Lightfoot RW Jr., Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Polyarteritis Nodosa. *Arthritis Rheum.* 1990; 33:1088-1093.
[21] Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Takayasu Arteritis. *Arthritis Rheum.* 1990; 33:1129-1134.
[22] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 Criteria for the Classification of Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis. *Arthritis Rheum.* 1990; 33:1094-1100.
[23] Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Wegener's Granulomatosis. *Arthritis Rheum.* 1990; 33:1101-1107.
[24] Calabrese LH, Michel BEA, Bloch DA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Hypersensitivity Vasculitis. *Arthritis Rheum.* 1990; 33:1108-1113.
[25] Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Henoch-Schönlein Purpura. *Arthritis Rheum.* 1990; 33:1114-1121.

[26] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 Criteria for the Classification of Giant Cell Arteritis. *Arthritis Rheum.* 1990; 33:1122-1128.

[27] Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. *Arthritis Rheum.* 1994; 37:187-192.

[28] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1-11.

[29] Kuker, W. Cerebral Vasculitis: Imaging Signs Revisited. *Neuroradiology* 2007; 49:471–479.

[30] Kaufman TJ, Kallmes DF. Diagnostic Cerebral Angiography: Archaic and Complication-Prone or Here to Stay for Another 80 Years? *AJR* 2008; 190:1435–1437.

[31] Hajj-Ali RA, Calabrese LH. PACNS. *Autoimmunity Reviews* 2013; 12:463–466.

[32] Gomes LJ. The role of imaging in the diagnosis of central nervous system vasculitis. *Curr. Allergy Asthma Rep.* 2010; 10:163–170.

[33] Lie JT. Vasculitis associated with infectious agents. *Current Opinions in Rheumatology* 1996; 8:26–29.

[34] Zuccoli G, Pipitone N, Haldipur A, et al. Imaging findings in primary central nervous system vasculitis. *Clin. Exp. Rheumatol.* 2007; 29 (Suppl 64): S104-S109.

[35] Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62:442-451.

[36] Kuker W. Imaging of cerebral vasculitis. *International Journal of Stroke* 2007; 2:184–190.

[37] Wasserman BA, Stone JH, Hellman, et al. Reliability of Normal Findings on MR Imaging for Excluding the Diagnosis of Vasculitis of the Central Nervous System. *AJR* 2001; 177:455–459.

[38] Pomper M, Miller T, Stone J, et al. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. *AJNR* 1999; 20:75–85.

[39] Rossi CM, Comite G. The clinical spectrum of the neurological involvement in vasculitides. *Journal of the Neurological Sciences* 2009; 285:13–21.

[40] Neel A, Pangnoux C. Primary angiitis of the central nervous system. *Clin. Exp. Rheumatol.* 2009; 27: S95-S107.

[41] Spitzer C, Mull M, Rohde V, et al. Non-traumatic cortical subarachnoid haemorrhage: diagnostic work-up and etiological background. *Neuroradiology* 2005; 47:525–531.

[42] Ay H, Sahin G, Saatci I, et al. PACNS and silent cortical hemorrhages. *AJNR* 2002; 23:1561-1563.

[43] Miller DV, Salvarani C, Hunder GG, et al. Biopsy findings in PACNS. *Am. J. Surg. Pathol.* 2009; 33:35-43.

[44] Salvarani C, Brown RD Jr, Gene G. Adult primary central nervous system vasculitis. *Lancet* 2012; 380:767–777.

[45] Küker W, Gaertner S, Nägele T, et al. Vessel Wall Contrast Enhancement: A Diagnostic Sign of Cerebral Vasculitis. *Cerebrovasc Dis* 2008; 26:23–29.

[46] Muccio CF, DiBlasi A, Espositio G, et al. Perfusion and spectroscopy magnetic resonance imaging in a case of lymphocytic vasculitis mimicking brain tumor. *Pol. J. Radiol.* 2013; 78:66-69.

[47] Park MS, Marlin AE, Gaskill SJ. Angiography-negative primary angiitis of the central nervous system in childhood. *J. Neurosurg. Pediatr* 2014; 13:62-67.

[48] Mandell DM, Mossa-Basha M, Qiao Y, Vessel Wall Imaging Study Group of the American Society of Neuroradiology. Intracranial Vessel Wall MRI: Principles and Expert Consensus Recommendations of the American Society of Neuroradiology. *Am J Neuroradiol*. 38:218-229.

[49] Choe YH, Han BK, Koh EM, et al. Takayasu's arteritis: assessment of disease activity with contrast-enhanced MR imaging. *AJR* 2000; 175:505–551.

[50a] Bley TA, Uhl M, Carew J, et al. Diagnostic value of high-resolution MR imaging in giant cell arteritis. *AJNR* 2007; 28:1722–1727.

[50b] Kuker W, Gaertner S, Nagele T, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. *Cerebrovasc Dis 2008*; 26:23-29.

[50c] Obusez EC, Hui F, Hajj-Ali RA, et al. High-resolution MRI vessel wall imaging: spatial and temporal patterns of reversible cerebral vasoconstriction syndrome and central nervous system vasculitis. AJNR *Am J Neuroradiol* 2014; 35:1527-1532.

[51] Brouwer PA, Bosman T, van Walderveen MA, et al. Dynamic 320-section CT angiography in cranial arteriovenous shunting lesions. *AJNR* 2010; 31:767–770.

[52] Demaerel P, De Ruyter N, Maes F, et al. Magnetic resonance angiography in suspected cerebral vasculitis. *Eur. Radiol.* 2004; 14:1005–1012.

[53] Khandelwal N, Kalra N, Garg MK, et al. Multidetector CT angiography in Takayasu's Arteritis. *Eur. J. Radiol.* 2011; 77:369–374.

[54] Yamada I, Nakagawa T, Himeno Y, et al. Takayasu's arteritis: evaluation of the thoracic aorta with CT angiography. *Radiology* 1998; 209:103–109.

[55] Kermani TA, Warrington KJ, Crowson CS, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann. Rheum. Dis.* 2013; 72:1989-1994.

[56] Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *New Engl. J. Med.* 2014; 4:371:50-57.

[57] Zhu FP, Luo S, Wang ZJ, et al. Takayasu arteritis: imaging spectrum at multidetector CT angiography. *British Journal of Radiology* 2012; 85:e1282-e1292.

[58] Mnif N, Chaker M, Oueslati S, et al. Abdominal polyarteritis nodosa: angiographic features. *J. Radiol.* 2004; 85:635-638.

[59] Lecler A, Obadia M, Savatovsky J, et al. TIPIC Syndrome: Beyond the Myth of Carotidynia, a New Distinct Unclassified Entity. *AJNR Am J Neuroradiol* 2017; 38:1391-1398.

[60] Cloft HJ, Phillips CD, Dix JE, et al. Correlation of Angiography and MR Imaging in Cerebral Vasculitis. *Acta Radiol.* 1999; 40:83-87.

[61] Alrawi A, Trobe JD, Blaivas M, et al. Brain biopsy in primary angiitis of the central nervous system. *Neurology* 1999; 53:858–860.

[62] Harris KG, Tran DD, Sickels WJ, et al. Diagnosing intracranial vasculitis: the roles of MR and angiography. *AJNR* 1994; 15:317–330.

[63] Duna GF, Calabrese LH. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. *J. Rheumatol.* 1995; 22: 662–667.

[64] Chu CT, Gray L, Goldstein LB, et al. Diagnosis of intracranial vasculitis: a multi-disciplinary approach. *J. Neuropathol. Exp. Neurol.* 1998; 57:30–38.

[65] Benseler SM, et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. *Arthritis Rheum*. 2005; 52: 2159-2167.

[66] Hellmann DB, Roubenoff R, Healy RA et al. Central nervous system angiography: Safety and predictors of a positive result in 125 consecutive patients evaluated for possible vasculitis. *J. Rheumatol.* 1992; 19:568–572.

[67] Cheng Y, Lu N, Wang Z, et al. 18F-FDG-PET in assessing disease activity in Takayasu's arteritis: a meta-analysis. *Clin. Exp. Rheumatol.* 2013; 31:S22-S27.

[68] Besson FL, Arienti JJ, Bienvenu B et al. Diagnostic performance of ^{18}Fuorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. *Eur. J. Nucl. Med. Mol. Imaging* 2011; 38:1764-1772.

[69] Amezcua-Guerra LM, Pineda C. Imaging studies in the diagnosis and management of vasculitis. *Curr. Rheumatol. Rep.* 2007; 9:320–327.

[70] Direskeneli H, Aydın SZ, Merkel PA. Assessment of disease activity and progression in Takayasu's arteritis. *Clin. Exp. Rheumatol.* 2011; 29:S86-S91.

[71] Blockmans D, de Ceuninck L, Vander-Schueren S, et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006; 55:131-137.

[72] Karapolat I, Kalfa M, Keser G, et al. Comparison of 18F-FDG PET/CT findings with current clinical disease status in patients with Takayasu's arteritis. *Clin. Exp. Rheumatol.* 2013; 31:S15-S21.

[73] Yuh WTC, Ueda T, Maley JE, et al. Diagnosis of microvasculopathy in CNS vasculitis: value of perfusion and diffusion imaging. *J. Magn Reson Imaging* 1999; 10:310-313.

[74] Masdeu JC, Brass LM, Holman BL, et al. Brain single-photon emission computed tomography. *Neurology* 1994; 44:1970-1977.

[75] Meusser S, Rubbert A, Manger B, et al. 99m-Tc-HMPAO-SPECT in diagnosis of early cerebral vasculitis. *Rheumatol. Int.* 1996; 16:37-42.

[76] Zhang X, Zhu A, Zhang F, et al. Diagnostic value of single-photon-emission computed tomography in severe central nervous system involvement of systemic lupus erythematosus: A case-control study. *Arthritis Rheum.* 2005; 53:845-849.

[77] Sato T, Ushiroda Y, Oyama T, et al. Kawasaki disease-associated MERS: Pathological insights from SPECT findings. *Brain Dev.* 2012; 34:34:605-608.

[78] Suh J-S, Hahn W-H, Cho R-S, et al. A rare case of cerebral vasculitis in Henoch-Schönlein purpura with emphasis on the diagnostic value of magnetic resonance angiography (MRA) and single-photon emission computed tomography (SPECT) given normal magnetic resonance imaging (MRI). *Int. J. Dermatol.* 2010; 49:803-805.

[79] Sener RN. Neuro-Behcet's disease: Diffusion MR imaging and proton MR spectroscopy. *AJNR* 2003; 24:1612-1614.

[80] Marienhagen J, Geissler A, Lang B. High resolution single photon emission computed tomography of the brain in Wegener's granulomatosis. *J. Rheumatol.* 1996; 23:1828-1830.

[81] Groothuis DR, Mikhael MA. Focal cerebral vasculitis associated with circulating immune complexes and brain irradiation. *Ann. Neurol.* 1986; 19:590-592.

[82] Rottenberg DA, Chernik NL, Deck MEF, et al. Cerebral necrosis following radiotherapy of extracranial neoplasms. *Ann. Neurol.* 1977; 1:339-357.

[83] Faust TW, Chang EH, Kowal C, et al. Neurotoxic lupus antibodies alter brain function through two distinct mechanisms. *Proc. Natl. Acad. Sci.* USA 2010 107:18569-18574.

[84] Shih W-J, Wilson D, Stipp V, et al. Heterogeneous uptake on brain SPECT. *Semin. Nucl. Med.* 1999; 29:85-88.

[85] Gotway M, Araoz PA, Macedo TA, et al. Imaging findings in Takayasu's arteritis. *AJR* 2004; 184:1945–1950.
[86] Kissin EY, Merkel PA. Diagnostic imaging in Takayasu's arteritis. *Curr. Opin. Rheumatol.* 2004; 16:31–37.
[87] Schmidt WA, Nerenheim A, Seipelt E, et al. Diagnosis of early Takayasu's arteritis with sonography. *Rheumatology (Oxford)* 2002; 41:496–502.
[88] Seth S, Goyal NK, Jagia P, et al. Carotid intima–medial thickness as a marker of disease activity in Takayasu's arteritis. *Int. J. Cardiol.* 2006; 108:385-390.
[89] Schmidt WA, Kraft HE, Vorpahl K, et al. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N. Engl. J. Med.* 1997; 337:1336-1342.
[90] Pfadenhauer K, Weber H. Giant cell arteritis of the occipital arteries: A prospective color coded duplex sonography study in 78 patients. *J. Neurol.* 2003; 250:844-849.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 7

ADULT PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM AND RELATED SYNDROMES

Rula A. Hajj-Ali, MD and Leonard H. Calabrese*, DO
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University,
Center for Vasculitis Care and Research, Cleveland Clinic Foundation,
Cleveland, OH, US

ABSTRACT

Primary angiitis of the central nervous system is one of the most complex and serious forms of central nervous system vasculitis. Adding to the challenge of diagnosis and recognition in the absence of predictive non-invasive laboratory tests, research into this disorder is limited by the scarcity of human pathological material and absence of an animal model. Nonetheless, there have been significant advances in the recognition of the clinical heterogeneity of the disorder and the differentiation from those that may mimic it. This chapter reviews the epidemiological, clinicopathologic, diagnostic laboratory and therapeutic aspects of primary angiitis of the central nervous system.

INTRODUCTION

Primary angiitis of the central nervous system (PACNS) is a vasculitic disorder confined to the brain, spinal cord, and its coverings. It is differentiated from secondary forms of CNS vasculitis most often due to concomitant or undying infection, connective tissue disease, or primary systemic vasculitis, and other disorders that may mimic it. Adult [1] and childhood PACNS (cPACNS) [2], primary CNS vasculitis (PCNSV) [3], granulomatous angiitis of the brain (GAB) [4], CNS (GACNS) or nervous system (GANS) [5], and isolated angiitis of the CNS (IACNS) [6], are roughly equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS of diverse cause and clinicopathologic expression.

* Corresponding Author's E-mail: calabrl@ccf.org.

The past decade has witnessed renewed interest in PACNS since the first description of PACNS by Calabrese and Mallek [7] of eight patients from the Cleveland Clinic Foundation patients, two of which included children age 10 and 12 years. Selection criteria for the definite diagnosis of PACNS [7] included a history of clinical findings of an acquired neurological deficit that remained unexplained after a thorough initial basic evaluation, and demonstration of classic angiographic or histopathologic features of CNS angiitis without evidence of systemic vasculitis or another disorder to explain the observed laboratory findings. These criteria were expanded by Benseler and colleagues [8] to include children age 18 years or less with neurological or psychiatric involvement, emphasizing their unique neuropsychiatric and cognitive presentations. At least three reasons account for the renewed interest in PACNS. First, the recognition that cPACNS fit into the larger designation of inflammatory brain disease (IBD) [8, 9]; moreover, PACNS was the most frequently diagnosed IBD at the Hospital for Sick Children in Toronto between 1990 and 2012. Second, the inclusion of PACNS as a prototypical single organ vasculitis (SOV) in the 2012 Revised Chapel Hill Consensus Conference [10] so defined as vasculitic involvement of arteries or veins of a single organ without features to indicate the limited expression of a systemic vasculitis. Third, the formation of the French COVAC' Cohort, a collaboration of the French Vasculitis Study Group and French NeuroVascular and Internal Medicine Societies [11] of antemortem diagnosed PACNS cases available for prospective analysis.

This chapter reviews the epidemiological, clinicopathologic, diagnostic laboratory and therapeutic aspects of adult PACNS. This topic has been recently reviewed by the present authors [12].

BACKGROUND

Primary CNS vasculitis was first described by Harbitz in 1922 [13] in two patients, one with worsening headaches, mental change, and ataxia culminating in stupor, spastic paraparesis, coma and death in 2 years; and a second patient with hallucinations and confusion progressing to gait difficulty, stupor, coma and death in nine months. Granulomatous vasculitis of the meninges comprised of lymphocytes, multinucleated giant cells and epithelioid cells with vessel necrosis and extension into the brain along involved veins and arteries of varying caliber. Over the ensuing quarter century, additional patients were reported under the rubric of allergic angiitis and granulomatosis [14], giant cell arteritis [15] and even sarcoidosis [16]. Cravioto and Fegin [17] delineated the clinicopathologic syndrome of non-infectious granulomatous angiitis of the CNS, and for two more decades, rare affected patients were identified in life. The identification of angiographic beading of cerebral vessels at sites of presumed arteritis was first noted by Hinck and coworkers [18] in cases of giant cell arteritis (GCA), and later by Cupps and Fauci in IACNS [6]. In the same year, 1988, that Calabrese and Mallek [7] proposed unifying criteria for the antemortem diagnosis of PACNS, Younger and colleagues [4] described clinicopathologic heterogeneity of postmortem proven cases.

Calabrese and colleagues [19] and later Singhal [20] separated PACNS from the most common mimickers of PACNS, the angiographically-defined variants of reversible cerebral angiopathy including benign angiopathy of the CNS. By 2007, these reversible syndromes were combined into a separate nosology termed the reversible cerebral vasoconstriction syndromes

(RCVS) [21], the diagnosis of which was clinically suggested by sudden, severe thunderclap-like headache with or without associated neurological deficits, and reversible angiographic findings not due to true vasculitis. In the same year, Salvarani and colleagues [3] reported a large cohort of more than 100 patients with primary CNS vasculitis (PCNSV) from a single center based upon the criteria of Calabrese and Mallek for PACNS [7], delineating clinicopathological subsets of heterogeneous disease. The importance of the accurate definition of disease employing the criteria of Calabrese and Mallek [7] was apparent in two forms of cPACNS, one with a prediction for small meningeal and penetrating cerebral vessels and unobvious cerebral angiographic features [9, 22], and another that affected medium-to-large named cerebral vessels in which angiographic features were readily apparent [8, 22, 23].

CLINICAL FEATURES

PACNS

PACNS affects patients of all ages with a peak at about 50 years of age and a more frequent occurrence among men than women. A retrospective analysis of 101 cases [3] revealed an average annual incidence of 2.4 cases per 1,000,000 million person-years. Although underdiagnosed in the setting of an evaluation for dementia, CNS vasculitis was found to be one of the common misdiagnoses of patients with presumed sporadic Jakob-Creutzfeldt disease [24]. The clinical signs and symptoms of PACNS are non-specific reflecting the diffuse and often patchy nature of the pathological process with a clinical course that varies from hyperacute to chronic and insidious. The most common presenting symptoms are headache followed by progressive focal neurologic deficits. The headache may vary in description, intensity and pattern, but is most often chronic and insidious. Thunderclap headache virtually never occurs in true PACNS and its presence should lead to a suspicion of RCVS [21]. Other symptoms including cognitive impairment, stroke and transient ischemic attacks, occurred in 30% to 50% of patients [3, 25]. Strokes are frequently multiple and vary in age and anatomic distribution, affecting both grey and white matter. Cranial nerve palsies occur rarely as may myelopathy, seizures, and ataxia. Constitutional symptoms and signs such as weight loss and specific organ-related disease are atypical in PACNS and when present suggests a systemic inflammatory process. PACNS should be strongly considered when there are multiple areas of cerebral ischemia affecting different vascular territories in association with an inflammatory cerebrospinal fluid (CSF) profile; and subacute or chronic headache with cognitive impairment or chronic aseptic meningitis, especially after exclusion of infectious and neoplastic disorders.

GACNS

With less than a handful of such patients seen at our center per year, the epidemiology of the disease is poorly understood, but appears to be a male-predominant disorder that occurs at virtually any age with a median of 50 years [25, 26]. Four patients with GACNS [4] were defined by the presence of granulomatous giant cell and epithelioid cell infiltration in the walls of arteries of various calibers from named cerebral vessels to small arteries and veins at

postmortem examination. Whereas the typical patient with PACNS might present with headache of gradual onset accompanied by focal signs and symptoms, or rapidly progressive neurological deficits evolving over days, weeks, or months with seemingly prolonged periods of stabilization, those with GACNS present with headache, mental change, and elevated CSF protein content with or without pleocytosis. Headache was noted at onset in all four patients of one series of GACNS [4] and in 57% of literature patients, as well as, in the course of the disease in 78% of patients overall. Neuroimaging employing magnetic resonance imaging (MRI) typically shows multiple bilateral ischemic foci. The combination of a normal MRI and normal CSF examination carries a high negative predictive value for the diagnosis of GACNS whereas hemiparesis, quadriparesis, progressive lethargy and impending coma were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis with certainty.

Salvarani and colleagues [3] diagnosed primary PCNSV in 31 patients by histopathology and 70 patients by angiography, in whom 18 had a granulomatous inflammatory pattern, 8 a lymphocytic pattern, and 5 an acute necrotizing pattern. Headache was the most common symptoms noted overall in 63% of patients, followed by abnormal cognition, hemiparesis and persistent neurological deficit. A granulomatous pattern of inflammation was seen most often in those with altered cognition and at an older age.

The diagnosis of GACNS is generally established by pathologic examination of the brain and leptomeninges that shows granulomatous giant cell and epithelioid cell vasculitis of the walls of arteries of various calibers from named cerebral vessels to small arteries and veins. Examination of antemortem leptomeningeal and brain tissue is vital to the exclusion of infectious, malignant, and other etiologies that may lead to a similar neuropathology. Although false-negative biopsy can occur in 25% to 50% of cases [27], the yield is enhanced when a radiographically abnormal area is targeted, and the specimen includes leptomeningeal tissue in addition to the brain parenchyma. The size of the vessels affected in GACNS is beyond the spatial resolution of cerebral angiography, which is typically normal in these patients.

Younger and colleagues [4] noted one patient each with non-Hodgkin lymphoma, sarcoidosis, Varicella-zoster virus (VZV) infection, and no associated disorder in their four cases. In a subsequent review of the cumulative literature up to 1997, the same authors [5] reported a new case of GACNS and described the clinicopathologic features of 136 published cases, 51 of which had concomitant lymphoproliferative diseases, VZV infection, amyloidosis, sarcoidosis, systemic lupus erythematosus, GCA, and human immunodeficiency virus type 1(HIV1) without the acquired immunodeficiency syndrome (AIDS). Whether such cases are equivalent to GACNS occurring *de novo* is unknown, but this analysis remains the basis of much of the clinical appreciation for this relatively rare disorder.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PACNS and hence GACNS (Table 1) comprises primary and secondary arteriopathies that mimic the clinical and angiographic presentation of PACNS. One category includes primary systemic vasculitis notably polyarteritis nodosa, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Behçet disease, Cogan syndrome; and diverse connective tissue disorders such as systemic lupus erythematosus, Sjogren syndrome,

and lymphomatoid granulomatosis, that can mimic PACNS, as may viral, bacterial, fungal and *Rickettsia* infections.

Malignant disorders such as primary CNS lymphoma, malignant angioimmunoproliferative, carcinomatous and gliomatous brain tumors; and coagulopathies resulting from thrombotic thrombocytopenic purpura, subacute bacterial endocarditis, cardiac myxoma and embolism, can lead to confusion with PACNS, as may atherosclerotic diabetic, dyslipidemic and hypertensive cerebral arteriopathy, moyamoya disease, intracranial dissection, and fibromuscular dysplasia. Genetically inherited disorders including Susac syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and the autosomal recessive variant CARASIL, retinal vasculopathy with cerebral leukoencephatlopathy (RVCL), may also have a clinical presentation similar to PACNS.

Table 1. Differential Diagnosis pf PACNS

Primary Systemic Disorders *Vasculitis*: PAN, MPA, GPA, EGPA, BD, CS *Connective Tissue Disease*: SLE, Sjogren syndrome, sarcoidosis, lymphomatoid granulomatosis
Infection Viral, bacterial, fungal, *Rickettsia*
Malignancy Angioimmunoproliferative disorders, carcinomatous meningitis, infiltrating glioma, malignant angioendotheliomatosis, PCNSL
Arterial Vasospasm Primary: RCVS Secondary: Pheochromocytoma, aneurysmal subarachnoid hemorrhage
Hypercoagulation Thrombotic thrombocytopenic purpura, embolism, subacute bacterial endocarditis, cardiac myxoma, paradoxical emboli; APL
Other Cerebral Arteriopathies Moyamoya disease, cerebrovascular atherosclerosis, arterial dissection, fibromuscular dysplasia
Demyelination Demyelinating disease
Radiation Radiation vasculopathy
Genetically Inherited RVCL, Susac syndrome, NF, MELAS, CADASIL, CARASIL

Abbreviations: PAN, Polyarteritis nodosa; MPA, Microscopic polyangiitis; GPA, Granulomatosis with polyangiitis; EGPA, Eosinophilic granulomatosis with polyangiitis; BD, Behçet disease; CS, Cogan syndrome; SLE, Systemic lupus erythematosus; PCNSL, Primary CNS lymphoma; RCVS, Reversible cerebral vasoconstriction syndrome; APL, Antiphospholipid syndrome; RVCL, retinal vasculopathy with cerebral leukodystrophy; Susac syndrome, Encephalopathy, branch retinal artery occlusions and sensorineural hearing loss; NF, neurofibromatosis; APMPPE, Acute posterior placoid pigment epitheliopathy and cerebral vasculitis; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

Table 2. Essential Elements for RCVS

1. Thunderclap headache with or without other neurological signs and symptoms
2. No evidence of aneurismal subarachnoid hemorrhage
3. Normal or near normal cerebrospinal fluid analysis
4. Reversible cerebral segmental vasoconstriction involving arteries of Circle of Willis documented by serial angiography, CTA, MRA or a flow-related vascular study such as TCD within 12 weeks of onset

Abbreviations: RCVS, Reversible cerebral vasoconstriction syndrome; CTA, Computed tomography angiography; MRA, Magnetic resonance angiography; TCD, Transcranial Doppler.

However, RCVS [21, 28-31], and related disorders sharing a similar clinical phenotype of reversible cerebral artery vasoconstriction, may be indistinguishable from PACNS arteritis. The diagnostic criteria of RCVS (Table 2) include: 1) thunderclap headache with or without other neurological signs and symptoms, 2) absence of aneurysmal subarachnoid hemorrhage, normal or near-normal CSF profile, 3) reversible segmental vasoconstriction involving arteries of Circle of Willis documented by serial angiography, CTA, MRA or a flow-related vascular study within twelve weeks of onset of the presentation, and 4) resolution in 60 days. Subarachnoid and intracerebral hemorrhages were usually encountered in the first week of onset respectively in 34% and 20% of cases, and typically along the cerebral convexity. Ischemic infarction ensues in 39 % of patients with RCVS during the second week from onset of symptoms along watershed areas between the anterior and posterior circulations, so noted as multiple, bilateral and symmetrical lesions with or without associated cerebral edema [29, 30]. Clues to the differentiation of RCVS and PACNS include a history of vasoconstrictive drug exposure or recent childbirth and thunderclap rather than insidious or chronic headache in the former, with normal or near-normal CSF however both may demonstrate seizure, strokes, and abnormal cerebrovascular imaging. Neuroimaging is rarely normal in PACNS and infarcts tend to be ischemic, infrequently hemorrhagic, while RCVS manifests severe vasoconstriction without parenchymal lesions, alternatively lobar and cortical surface subarachnoid hemorrhages or reversible edematous lesions characteristic of the 'posterior reversible leukoencephalopathy syndrome.' The angiographic abnormalities in RCVS are typically more dynamic, severe, and resolve over weeks to 3 months. High-resolution MRI holds promise in differentiating RCVS from CNS vasculitis based upon the presence and the pattern of concentric and eccentric vessel wall contrast enhancement [32]. Nonetheless, differentiation of the two disorders may remain uncertain when other studies supporting PACNS including brain biopsy are falsely negative.

LABORATORY EVALUATION

Blood Studies

The diagnostic workup in PACNS, which may be extensive, covers a wide range of modalities reflective of the intrinsic lack of test specificity for this diagnosis. Peripheral blood counts, chemistries, acute phase reactants and inflammatory markers such as the C- reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are expectedly normal but useful to obtain to exclude an underlying or concomitant systemic inflammatory process. Although there are no specific serologic markers for PACNS it is useful to obtain antinuclear antibody (ANA),

ANCA, serum complement levels, antiphospholipid (APL), baseline coagulation studies, as well as acute and convalescent infectious antibody titers as may be suggested by epidemiological, host immune factors and exposure history.

Cerebrospinal Fluid

It is imperative to perform a lumbar puncture to analyze the CSF unless otherwise contraindicated especially to exclude infection and malignancy; and in GACNS, the majority of affected patients will demonstrate elevation of the protein level and lymphocytic pleocytosis, however in either disorder, neither the white blood cell count nor protein level will respectively exceed 250 cells/mm^3 or 500 mg/dL [25, 33, 34]. Emerging molecular techniques with next generation sequence applied to CSF provide an unbiased approach to identify infectious etiologies in patients with possible CNS vasculitis [35].

Magnetic Resonance Imaging

The reported sensitivity of MRI in PACNS, which has been 75% and approaching 100% [1] in the detection of cauative lesions, may not be reliable due to the erroneous inclusion of patients with RCVS. Cerebral infarction, the most common lesion seen on MRI, was noted overall in 53% of patients with PACNS [1], and often multiple, affecting the cortical and subcortical parenchyma; with nonspecific high-intensity T_2-weighted white matter FLAIR lesions [1]. Mass lesions occur in up to 5% of affected patients as do intracranial hemorrhage in 8% of patients. Collectively, abnormalities of CSF and MRI are noted in close to 100% of those with GACNS which then when normal, generates a high negative predictive probability for the diagnosis of GACNS [36].

Cerebral Angiography

The expected cerebral angiographic findings of PACNS are alternating areas of stenosis and dilatation that resemble beads on a string, which may be smooth or irregular in appearance, bilateral or involve single named vessels [37]. Other angiographic findings include tapering of the vessel lumen of a single vessel or multiple vessels. However, these angiographic findings are non-specific and can be observed in nonvasculitic atherosclerosis, radiation vasculopathy, fibromuscular dysplasia, infection, and especially RCVS. Moreover, the reported specificity of 30% of cerebral angiography in the diagnosis of PACNS suggests the need for further work-up to rule out other mimicking conditions when the typical angiographic features for vasculitis are not observed [37]. The sensitivity of direct cerebral angiography exceeds that of brain MRA, however the spatial resolution falls in vessels <500 mm in diameter. Accordingly, higher false negative results should be expected in the setting of known small vessel vasculitic pathology such as GACNS and angiography-negative small vessel cPACNS. High-resolution vessel wall MRI, which provides detail of vessel lumina and wall structure, has the capacity to increase the test specificity of non-invasive vascular neuroimaging in CNS vasculopathy [32].

Brain Biopsy

Pathologic examination of the brain is still the gold standard for the diagnosis of PACNS because of its ability to confirm the diagnosis of PACNS and more importantly exclude PACNS mimics [38]. Special stains are useful to examine for malignancy and as are tissues culture for infectious etiologies of secondary CNS vasculitis. A non-diagnostic or negative biopsy does not rule out PACNS, and false-negative biopsy results, that can be as high as 25% of autopsy-documented cases [38] are due to patchy vasculitic involvement and potential inaccuracy of a non-lesional biopsy sample. The microscopic appearance of GACNS includes segmental necrotizing multinucleated giant cell and epithelioid granulomatous vasculitic involvement of small to medium-sized arteries in the leptomeninges and cortex, with involvement of veins in about one-half of cases. Not all of these features are present in all patients, and the distribution of lesions may be patchy in the CNS. Although loosely formed granulomatous giant cell lesions may be encountered, well-formed granulomas are more commonly observed, with up to 20% of cases demonstrating lymphocytic inflammation of vessel walls without prominent granulomas [38]. Tissue biopsy should ideally be performed through open craniotomy with sampling of both leptomeningeal and parenchymal brain tissue at abnormal sites suggested by neuroimaging, and if inaccessible, along the temporal tip of the non-dominant hemisphere [38].

TREATMENT AND PROGNOSIS

Rheumatologists and neurologists treating adult patients with PACNS must choose their treatment from among available immunosuppressant and biological agents without the benefit of randomized-controlled clinical trials however the literature does provide some guidance. The historical basis for the use of aggressive immunosuppressant therapy for CNS vasculitis commenced with the reports of the efficacy of combination immunosuppressant therapy employing oral corticosteroids and intravenous cyclophosphamide by Cupps and coworkers [6, 27], and later Moore [40] who ascertained the diagnosis of CNS vasculitis based upon the clinical criteria of a clinical pattern of headache, multifocal neurological deficits and cerebral angiography demonstrating segmental arterial narrowing, with exclusion of systemic inflammation and infection and proof of vascular inflammation in a leptomeningeal or parenchymal biopsy tissue. Empiric therapy with corticosteroids and cyclophosphamide was advocated at doses similar to that employed for granulomatosis with polyangiitis [41] in all five patients in the series by Moore [40] even though brain or leptomeningeal biopsy showed unequivocal evidence of cerebral vasculitis in only two patients, and non-diagnostic perivascular inflammation in three others. The author's explanation was that while useful in diagnosis and management, antemortem biopsy could be less striking and inconsistent. Prednisone alone appeared to have either a transient or no effect on the course of the disease process.

It has been suggested that historical surveys of PACNS might be misleading because of the bias of ascertainment, favoring the larger number of postmortem cases that proved fatal without treatment [5]. A meta-analysis of 54 literature patients comprising 30 patients diagnosed antemortem and 24 patients treated before postmortem confirmation [5] found equally satisfactory outcomes in those treated with corticosteroids alone or with oral

cyclophosphamide, with overall improvement in 24 of 34 (70%) so treated. Three patients treated with corticosteroids and oral cyclophosphamide died due to serious sequela of the latter treatment. Although the findings appeared to challenge the imperative of aggressive empiric treatment, there is still agreement among experts [5] that cyclophosphamide can be safely employed in histologically-confirmed patients, especially those who continued to progress while on corticosteroids and can be closely monitored for medication related side effects.

Hutchinson and colleagues [42] described the treatment of small vessel PACNS in a single-center open-label childhood cohort. They employed cyclophosphamide at doses of 500 to 750 mg/m^2 monthly infusions for six months, followed by maintenance therapy of azathioprine 1 mg/kg/day and a target dose of 2 to 3 mg/kg/day, with mycophenolate mofetil titrated at dosages of 800 to 1200 mg/m2/day for up to 24 months. Outcome was rated using a pediatric stroke outcome measures (PSOM). Among 13 who completed the treatment regimen, nine had a good neurological outcome by PSOM scoring and four achieved remission of disease. Therapeutic guidelines remain informal, based upon expert opinions and historical bias suggesting that PACNS is progressive and uniformly fatal if left untreated [25].

In our experience, the majority of patients with documented GACNS should be treated with combination corticosteroid and cyclophosphamide therapy similar to systemic small vessel vasculitis algorithms [42, 43] to control the disease, implementing maintenance therapy with mycophenolate mofetil or azathioprine [1], and monitoring the activity of disease clinically and with serial MRI. All patients should receive prophylaxis for *Pneumocystis jirovecii* infection and followed for infections, osteoporosis, and other treatment-related complications [1], and followed by a team of health care professionals in rheumatology, neurology, neuroradiology, and physical therapy to ensure optimal care.

CONCLUSION

Adult PACNS is one of the most challenging and complex vasculitic disorders to diagnose and treat. Moreover, research into this disorder has been limited by the scarcity of human pathological material and absence of an animal model. There have been significant advances in the recognition of the clinical heterogeneity of the disorder and the differentiation from less fatal disorders that may mimic it.

REFERENCES

[1] Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. *Lancet Neurol.* 2011; 10:561-572.

[2] Twilt M, Benseler SM. The spectrum of CNS vasculitis in pediatrics and adults. *Nat. Rev. Rheumatol.* 2012; 8:97-107304.

[3] Salvarani C, Brown RD Jr., Calamia KT et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann. Neurol*. 2007; 62:442-451.

[4] Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain. An inflammatory reaction of diverse etiology. *Arch. Neurol.* 1988; 45:514-518.

[5] Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. *Neurol. Clin.* 1997; 15:821-834.

[6] Cupps T, Fauci A. Central nervous system vasculitis. *Major Problems in Internal Medicine* 1981; 21:123-132.

[7] Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1988; 67:20-39.

[8] Benseler SM, Silverman E, Aviv RI et al. Primary central nervous system vasculitis in children. *Arthritis Rheum* 2006; 54: 1291-1297.

[9] Benseler SM, deVeber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. *Arthritis Rheum* 2005; 52: 2159-2167.

[10] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1-11.

[11] de Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first 52 adult patients enrolled in the French COVAC' Cohort. *Arthritis Rheum* 2012; 64(Suppl):S663.

[12] Hajj-Ai RA, Calabrese LH. Primary angiitis of the central nervous system. *Autoimmunity Reviews* 2013; 12:463-466.

[13] Harbitz F. Unknown forms of arteritis with special reference to their relation to syphilitic arteritis and periarteritis nodosa. *Am. J. Med. Sci.* 1922; 163:250-272.

[14] Neuman W, Wolf A. Noninfectious granulomatous angiitis involving the central nervous system. *Trans Am. Neurol. Assoc.* 1952; 77:114-117.

[15] McCormack H, Neuberger K. Giant cell arteritis involving small meningeal and intracerebral vessels. *J. Neuropathol. Exp. Neurol.* 1958; 17:471-478.

[16] Meyer J, Foley J, Campagna-Pinto D. Granulomatous angiitis of the meninges in sarcoidosis. *Arch. Neurol.* 1953; 69:587-600.

[17] Cravioto H, Fegin I. Noninfectious granulomatous angiitis with a predilection for the nervous system. *Neurology* 1959; 9:599-607.

[18] Hinck V, Carter C, Rippey C. Giant cell (cranial) arteritis. A case with angiographic abnormalities. *AJR* 1964; 92:769-775.

[19] Calabrese LH, Gragg LA, Furlan AJ. Benign angiopathy: a distinct subset of angiographically defined primary angiitis of the central nervous system. *J. Rheumatol.* 1993; 20:2046-50.

[20] Singhal AB. Postpartum angiopathy with reversible posterior leukoencephalopathy. *Arch. Neurol.* 2004; 61:411-416.

[21] Calabrese LH, Dodick DW, Schwedt TJ et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann. Intern Med.* 2007; 146:34-44.

[22] Lanthier S, Lortie A, Michaud MD, et al. Isolated angiitis of the CNS in children. *Neurology* 2001; 56:837-842.

[23] Elbers J, Benseler SM. Central nervous system vasculitis in children. *Curr. Opin. Rheumatol.* 2008; 20:47-54.

[24] Paterson RW, Torres-Chae CC, Kuo AL, et al. Differential diagnosis of Jakob-Creutzfeldt disease. *Arch. Neurol.* 2012; 69(12):1578-1582.

[25] Calabrese LH, Duna GF, Lie JT. Vasculitis in the central nervous system. *Arthritis Rheum.* 1997; 40:1189-1201.

[26] Calabrese LH, Duna GF. Evaluation and treatment of central nervous system vasculitis. *Curr. Opin. Rheumatol.* 1995; 7:37-44.

[27] Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospective diagnostic and therapeutic experience. *Am. J. Med.* 1983; 74:97-105.

[28] Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol.* 2012; 11:906-917.

[29] Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible Cerebral Vasoconstriction Syndromes: Analysis of 139 Cases. *Arch. Neurol.* 2011; 68:1005-1012.

[30] Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007; 130:3091-3101.

[31] Chen S-P, Fuh J-L, Wang S-J, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. *Ann. Neurol.* 2010; 67:648-656.

[32] Mandell DM, Matouk CC, Farb RI, et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and central nervous system vasculitis: preliminary results. *Stroke* 2012; 43:860-862.

[33] Younger DS. Vasculitis of the nervous system. *Curr. Opin. Neurol.* 2004; 17:317-336.

[34] Younger DS, Kass RM. Vasculitis and the nervous system. Historical perspective and overview. *Neurol. Clin.* 1997; 15:737-758.

[35] Wilson MR, O'Donovan BD, Gelfand JM, et al. Chronic Meningitis Investigated via Metagenomic Next-Generation Sequencing JAMA Neurol. 2018 Aug 1;75(8):947-955

[36] Stone JH, Pomper MG, Roubenoff R, et al. Sensitivities of noninvasive tests for central nervous system vasculitis: a comparison of lumbar puncture, computed tomography, and magnetic resonance imaging. *J. Rheumatol.* 1994; 21:1277-1282.

[37] Pomper MG, Miller TJ, Stone JH, et al. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. *AJNR Am. J. Neuroradiol.* 1999; 20:75-85.

[38] Parisi JE, Moore PM. The role of biopsy in vasculitis of the central nervous system. *Semin. Neurol.* 1994; 14:341-348.

[39] Lie JT. Primary (granulomatous) angiitis of the central nervous system: a clinicopathologic analysis of 15 new cases and a review of the literature. *Hum. Pathol.* 1992; 23:164-171.

[40] Moore PM. Diagnosis and managements of isolated angiitis of the central nervous system. *Neurology* 1989; 39:167-173.

[41] Fauci AS, Haynes BF, Katz P, et al. Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients over 21 years. *Ann. Intern. Med.* 1983; 98:76-85.

[42] Hutchinson C, Elbers J, Halliday W et al. Treatment of small vessel primary CNS vasculitis in children: an open-label cohort study. *Lancet Neurol.* 2010; 9:1078-1084.

[43] Langford CA. Small-vessel vasculitis: therapeutic management. *Current Rheumatol. Rep.* 2007; 9:328-335.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 8

PRIMARY CNS VASCULITIS: PATHOPHYSIOLOGICAL DIVERSITY*

Nicolò Pipitone[1], MD, PhD, Gene G. Hunder[2], MD and Carlo Salvarani[1,†], MD
[1]Department of Rheumatology,
Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
[2]Emeritus Staff Center, Mayo Clinic, Rochester, MN, US

Keywords: primary CNS vasculitis, primary angiitis of the nervous system, clinical presentation, cerebrospinal fluid pathological diversity, treatment, brain and meningeal biopsy, granulomatous angiitis of the brain

INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is a rare vasculitis that affects the brain and occasionally the spinal cord of adults and children [1]. Extensive progress has been achieved in the recognition of clinicopathological subsets that has translated into useful nosology reflective of the natural history and response to immunosuppresant treatment.

HISTORICAL BACKGROUND OF PRIMARY CNS VASCULITIS

The first case of PCNSV was described in 1952 by Newman and Wolf [2] and subsequently by Cravioto and Feigin [3] in 1959. The latter authors designated the disease as granulomatous angiitis of the nervous system (GANS) or granulomatous angiitis of the central nervous system (GACNS), because of the histologic granulomatous vasculitic changes they observed. Cupps

* The authors have nothing to disclose.

† Corresponding Author's Email: Salvarani.carlo@asmn.re.it.

and Fauci [4], influenced by their advances in the classifcation, diagnosis, and treatment of systemic vasculitides at the National Institute of Health (NIH) [5], named the disorder isolated angiitis of the central nervous system (IACNS). Over the ensuing decades, PCNSV was relegated to the penumbra of vasculitis [6]. In 1988, Younger and colleagues [7] recognized the diversity in etiology due to association of some cases with neurosarcoidosis, non-Hodgkin lymphoma, or varicella zoster virus infection as well as the varied pathological expression which included arteries and veins of variable caliber both intracerebral and more distal leptomeningeal vessels. In the same year of 1988, Mallek and Calabrese [8] described the clinicopathogical aspects, findings in diagnostic studies, and response to therapy in 8 Cleveland Clinic Foundation cases and a review of 40 patients in the literature. Headache was noted in 58% of entire group followed by hemiparesis in 35% of patients, mental impairment in 27%, dysphasia in 15%, seizures in 13% and ocular signs in 13%. Cerebrospinal fluid (CSF) was abnormal in 81% of patients. Two-thirds of patients who underwent conventional cerebral angiography manifested vascular changes consistent with cerebral vasculitis. Histopathologic confirmation of CNS vasculitis was available in 26 of 37 (74%) patients examined at postmortem examination, and in 10 of 14 (71%) of patients by antemortem brain biopsy with or without leptomeninges. Of the four patients with negative antemortem brain biopsy, one specifically did not include leptomeninges, and three others had demonstrable vasculitis of meningeal vessels at postmortem examination emphasizing the importance of obtaining combined brain and leptomeningeal tissue. Mortality was noted in 28 of 46 (61%) patients, however among the Cleveland Clinic Foundation patients, full resolution was achieved in six treated with combination corticosteroid and cyclophosphamide therapy, as well as in one patient each treated with high dose prednisone and another patient with only angiographic validation of vasculitis, who was untreated. These observations suggested an improved prognosis with an aggressive therapeutic approach as was previously proposed by Cupps and colleagues [4] and Fauci and colleagues [5]. Although not so stated, there was an obvious admixture of benign angiopathy in the patient who fully resolved without treatment. Calabrese and Mallek [8] proposed formal diagnostic criteria requiring fulfillment of three conditions: a history or presence of an acquired neurological deficit, histological or angiographic evidence of vasculitis, and lack of evidence of a systemic vasculitis or other conditions to which the angiographic or pathologic features could be attributed. The interchangeable term primary CNS angiitis (PACNS) like PCNSV, underscored the restricted nature of the illness, and like IACNS, emphasized the primary and often idiopathic nature of the disorder [9, 10] rather than the granulomatous pathology. The rationale was that giant cells and epithelioid cells, usually found at postmortem examination were inconstant findings in meningeal and brain biopsy tissue and therefore not necessary for antemortem diagnosis [11].

Later observations by Salvarani and colleagues in adults [12] would begin the unravel the clinicopathological dichotomy of granulomatous and non-granulomatous histology in adults beyond the simplistic assumption that granulomatous pathology was simply more lethal and found most often at postmortem examination than less fatal non-granulomatous changes so seen antemortem. Contemporaneously, PCNSV was described in two children with acute presentation of headache and focal neurological signs diagnosed by combined leptomeningeal and brain biopsy demonstrating non-granulomatous, non-necrotizing lymphocytic vasculitis predominantly affecting leptomeningeal arterioles, capillaries and venules [13]; and three others with acute headache and focal neurological deficits who died. In the latter three, postmortem examination showed involvement of large named vessels by necrotizing

granulomatous vasculitis including the distal vertebral [14], basilar [15], and middle cerebral artery [16] arteries. The clinicopathologic dichotomy of PCNSV in children was later summarized by Benseler and colleagues [17]. Angiographic large CNS vessel stenoses or occlusions in affected children caused strokes with manifestations of hemiparesis, hemifacial weakness, and hemisensory loss due to decreased perfusion in the area of the stenotic vessel and ischemia of the dependent brain territory. In contrast, distal CNS vasculitic and adjacent parenchymal inflammation led to diffuse neurologic deficits including headache, seizures, and subtle or overt cognitive, behavioral and personality changes. Those with both small- and large-vessel inflammatory vasculitic involvement might present with overlapping clinical deficits. Yet, in contrast to fatal adult PCNSV and the few fatal childhood cases [14-16], brain and meningeal biopsy performed in children at one center [18] with suspected vasculitis but negative angiograms revealed non-granulomatous, lymphocytic vasculitis of small vessels. This subset in children appears to be the fastest growing group of children with primary vasculitis at most centers [17].

SPECTRUM OF PRIMARY CNS VASCULITIS

The achievements of the 1980s proved to be the lessons for the 1990s. Although the acceptance and application of diagnostic criteria for PCNSV facilitated research and clinical studies alike, as the number of recognized patients increased, it became clear that PCNSV was more heterogeneous than previously thought. Moreover, enthusiasm for the empiric treatment of cerebral vasculitis waned as it became evident that cerebral angiography alone was insufficient for the diagnosis of PCNSV. This was noted in Case 3 of Calabrese and Mallek's 1987 paper [8] with angiographically diagnosed CNS vasculitis and full resolution without treatment. In later publications, Calabrese and colleagues [19-21] displayed the increasing awareness that patients who they earlier called "benign angiopathy of the CNS" (BACNS), represented a reversible cerebral vasoconstriction syndrome (RCVS) [21] and might be intermixed with angiographically-proven PCNSV due to common clinical and angiographic findings as shown in Table 1. By 1997, with 136 published cases of histologically-defined granulomatous CNS vasculitis alone [22] and the recognition that the criteria were performing poorly in discriminating PCNSV from RCVS, Calabrese and coworkers [21] proposed formal criteria for RCVS, the five critical elements of which included, transfemoral cerebral angiography or indirect computerized tomography angiography (CTA) or magnetic resonance angiography (MRA) documenting multifocal segmental cerebral artery vasoconstriction; lack of evidence for aneurysmal subarachnoid hemorrhage; normal or near-normal CSF with protein content <80 mg%, normal glucose content, and <10 mm^3 leukocytes; development of acute severe headache with or without additional neurologic signs or symptoms; and reversibility of angiographic abnormalities within 12 weeks of onset. If death occurred before the followup studies were completed, postmortem examination should exclude vasculitis, intracranial atherosclerosis and aneurysmal subarachnoid hemorrhage, which might also manifest with headache and stroke similar to RCVS. The accuracy of cerebral angiography alone for detecting vasculitis was estimated to be 50% to 90%, citing Salvarani and colleagues [12], when beading and interposed regions of ectasia of normal luminal architecture were present.

Magnetic resonance imaging (MRI) is also helpful in the evaluation of CNS vasculitis. MRI abnormalities were observed in 90% or more of affected cases, the most common of which were subcortical white matter lesions followed by deep gray matter, deep white matter, and cerebral cortical lesions [23]. Cerebrospinal fluid studies have demonstrated one or more abnormal findings in 88% of confirmed cases, most often elevated protein concentration (median, 98mg/dL) and leukocyte pleocytosis (median, 17 cells/ml) or both citing Salvarani and colleagues [12].

Birnbaum and Hellmann [24] proposed changes to the criteria of Calabrese and Mallek [8]. The proposed criterion for "definite" CNS vasculitis was a positive CNS biopsy. Patients classified as "probable" CNS vasculitis should have CNS angiograms showing changes suggesting vasculitis, concordant MRI abnormalities, and CSF findings consistent with CNS vasculitis but without biopsy confirmation.

Further, discriminatory clinical features of PCNSV and RVCS which might help suggest RVCS in patients with high-probability findings on cerebral angiography and a normal CSF, were female sex, acuteness and severity of the headache, focality of neurological deficits at onset, history of provocative vasospastic syndromes, dynamic improvement after three months, and amelioration with non-cytotoxic therapy [24].

Table 1. Characteristics of PCNSV and RCVS[1]

	PCNSV	RCVS
Precipitating factor	None	Post-partum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leucocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 6–12 weeks
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

PCNSV=primary CNS vasculitis. RCVS=reversible cerebral vasoconstriction syndrome. CSF=cerebrospinal fluid.

[1]Reproduced from Salvarani C, Brown RD, Jr., Hunder GG Adult primary central nervous system vasculitis. *Lancet* 2012; 380:767-777, with permission.

SUBSETS OF PRIMARY CNS VASCULITIS

Further evidence of the heterogeneous nature of PCNSV was appreciated in a review of 101 patients seen at the Mayo Clinic over a 21-year period from 1983 to 2003 [12]. Diagnostic criteria similar to those of Calabrese and Mallek [8] were used. Diagnostic histopathological features were transmural vascular inflammation involving leptomeningeal or parenchymal vessels. Angiographic changes indicating a high probability of vasculitis included areas of smooth-wall segmental narrowing or dilatation and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other causes. Those with single vessel abnormalities in multiple arterieis or multiple abnormalities in a single artery were excluded from the analysis. Cases with other conditions that might mimic PCNSV, such as

hypercoagulability, varicella zoster virus and other infectious vasculitides, were excluded. There were 58 women and 43 men with a median age at diagnosis of 47 years. The diagnosis of PCNSV was ascertained by cerebral angiography in 70 patients and by CNS tissue in 31 patients. The clinical features of the patients are detailed in Table 2. Patients with large-artery involvement, characterized by multiple, large brain lesions on MRI and diffuse stenoses on angiograms, had more severe neurological disease and worse outcomes. Conversely, those with PCNSV that predominantly affected small leptomeningeal and cerebral arteries, characterized by prominent enhancement of lesions or meninges on MRI after intravenous administration of gadolinium, had less disability and a lower risk of mortality. Moreover, three histological patterns were observed, granulomatous (in 58%), lymphocytic (in 28%), and necrotizing (in 14%) of histologically-proven cases. β-amyloid vascular deposits were noted in 8 specimens, all of which showed granulomatous inflammation. Granulomatous changes were also more frequently encountered in older-onset patients, and in those with altered cognition. These histological patterns appeared to identify subsets of disease rather than different stages of the same process since no individual patient had histological evidence of more than one pattern. Underscoring this hypothesis, were findings in seven patients in whom two biopsy specimens were obtained at different times. In four such patients both specimens were positive for vasculitis and each pair of specimens showed the same inflammatory pattern.

In 2011, Salvarani and colleagues [25] extended the previous cohort of PCNSV [12] to include the period 2004 to 2007, yielding a total of 131 cases, to assess the clinical characteristics of similarly defined patients with PCNSV. Several subgroups were identified. Using a modified Rankin scale [26] to assess outcomes, a subgroup with rapidly progressive PCNSV was distinguished. Among 131 consecutive patients in the updated cohort, 11 (8.4%) had a rapidly progressive course resulting in severe disability or death, (Rankin 5 and 6). Such patients had more frequent paraparesis or quadriparesis at presentation, cerebral angiographic evidence of bilateral, large vessel vasculitis, and MRI evidence of cerebral infarctions. The latter lesions were usually multiple and bilateral, involving both cortex and subcortical regions on initial MRI. Of three open CNS tissue biopsies, one each showed granulomatous changes, necrotizing vasculitis, or both. All 11 patients failed to respond to aggressive immunosuppressant therapy, culminating in stroke as the cause of death in eight and fatal aspiration pneumonia in two patients. One patient who was alive at followup had fixed major neurological impairment.

Eight patients (8%) with biopsy positive-cerebral angiography-negative PCNSV were identified from 101 consecutive patients in the original cohort of Salvarani and colleagues [12, 27]. In comparison to 76 patients with cerebral angiography-positive PCNSV, the former more commonly manifested a cognitive disorder, elevated CSF protein level and leukocyte pleocytosis, and enhancement of meningeal or parenchymal lesions on MRI after administration of intravenous gadolinium. All patients responded to treatment and none died. A similar favorable outcome was reported in children with cerebral angiography-negative PCNSV [18].

Eight (26%) of the 101 patients in the same cohort [12, 28] with positive biopsies also had cerebrovascular amyloid deposits (cerebrovascular amyloid angiopathy or CAA). Compared to PCNSV without CAA, such patients (Figure 1) were comparatively older at diagnosis, predominantly male, had a more acute onset of PCNSV, with greater frequency of cognitive

dysfunction, and prominent enhancement of leptomeningeal lesions by brain MRI after intravenous administration of gadolinium. The presence of vascular amyloid in this group raised the suggestion that the deposits may somehow be an inciting factor in the vascular inflammation. Six of the eight patients responded promptly to therapy, similar to the others in the cohort.

Table 2. Clinical features at Presentation in PCNSV[1]

Characteristics	All Patients (N = 101), n (%)	Patients Diagnosed by Biopsy (n = 31), n (%)	Patients Diagnosed by Angiography (n = 70), n (%)
Headache	64 (63)	16 (52)	48 (69)
Altered cognition	50 (50)	22 (71)	28 (40)
Hemiparesis	44 (44)	6 (19)	38 (54)
Persistent neurological deficit or stroke	40 (40)	8 (26)	32 (46)
Aphasia	28 (28)	11 (36)	17 (24)
Transient ischemic attack	28 (28)	5 (16)	23 (33)
Ataxia	19 (19)	5 (16)	14 (20)
Seizure	16 (16)	2 (7)	14 (20)
Visual symptom (any kind)	42 (42)	9 (29)	33 (47)
Visual field defect	21 (21)	5 (16)	16 (23)
Diplopia (persistent or transient)	16 (16)	5 (16)	11 (16)
Blurred vision or decreased visual acuity	11 (11)	0 (0)	11 (16)
Monocular visual symptoms or amaurosis fugax	1 (1)	0 (0)	1 (1)
Papilledema	5 (5)	2 (7)	3 (4)
Intracranial hemorrhage	8 (8)	2 (7)	6 (9)
Amnestic syndrome	9 (9)	4 (13)	5 (7)
Paraparesis or quadriparesis	7 (7)	4 (13)	3 (4)
Parkinsonism or extrapyramidal sign	1 (1)	0 (0)	1 (1)
Prominent constitutional symptom	9 (9)	4 (13)	5 (7)
Fever	9 (9)	4 (13)	5 (7)
Nausea or vomiting	25 (25)	6 (19)	19 (27)
Vertigo or dizziness	9 (9)	3 (10)	6 (9)
Dysarthria	15 (15)	2 (7)	13 (19)
Unilateral numbness	13 (13)	0 (0)	13 (19)

[1]Reproduced from Salvarani C, Brown RD, Jr., Calamia KT et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62:442-51 with permission.

The clinical findings, response to therapy, and outcomes of patients with cerebral vascular β-amyloid deposition with and without inflammatory vascular infiltration were evaluated in 2013 by Salvarani and coworkers in 78 consecutive patients with cerebral vascular β-amyloid deposition [29]. Compared to 118 consecutive patients with PCNSV without β-amyloid deposition, the 28 patients with granulomatous vasculitis (A β –related angiitis or ABRA) had similar results of treatment and outcomes, confirming that ABRA represents a distinct subset of PCNSV.

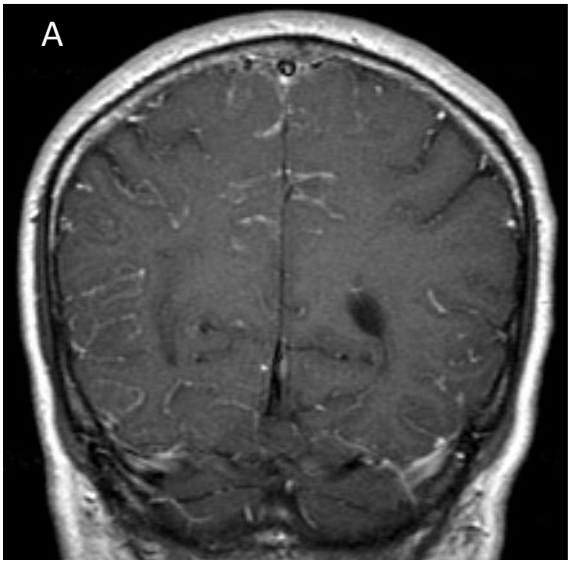


Figure 1. Brain MRI and histopathological features of a PCNSV patient with leptomeningeal vasculitis and amyloid angiopathy. A. MRI at onset of symptoms shows prominent leptomeningeal enhancement after intravenous administration of gadolinium. B. Histopathological findings shows destructive vasculitis with well-formed granulomata in leptomeningeal vessels and wall thickening with eosinophilic material (*) (Hematoxylin and eosin stain X100). The right-hand image shows amyloid-β deposits in all vessels (Iimmunoperoxidase stain for βA4 amyloid X100).

Sixteen patients (12%) with evidence of intracranial hemorrhage at or near the time of diagnosis of PCNSV were identified from 131 consecutive patient with PCNSV [25], and reanalyzed further by Salvarani and colleagues [30]. Twelve patients had intracerebral hemorrhages, and four were subarachnoid in location. Twelve were diagnosed by findings on cerebral angiography and four by findings on CNS tissue biopsy. Compared to the 115 patients without intracranial hemorrhage, the 16 affected patients were more frequently women, altogether had less alteration of cognition, persistence of the neurological deficit, stroke at presentation, MRI evidence of cerebral infarction, or needed therapy at last followup visit. Among the four patients with evidence of hemorrhage on CNS tissue biopsy, three showed necrotizing histopatholgic pattern of vasculitis. None of the patients with intracranial hemorrhage had evidence of lymphoproliferative disorders, in contrast to one-third in the series described by Calabrese and colleagues [20]. These findings indicate that while intracranial hemorrhage does not occur in the majority of patients with early PCNSV, it nonetheless needs to be considered in the differential diagnosis.

Five patients (5%) with spinal cord involvement were identified from 101 consecutive patients with PCNSV [12, 31]. Five others in the cohort had spinal symptoms but no objective findings and were therefore not included in the spinal group [31]. In the five so studied, the median time from onset of symptoms was 26 days that included leg weakness or paralysis, numbness, and urinary incontinence in all patients, in addition to cerebral symptoms. Symptoms of spinal cord involvement developed before cerebral symptoms in one patient, simultaneously in two patients, and after cerebral disease in two others. Spinal cord vasculitis was the only manifestation in one patient preceding symptomatic brain involvement by 10 months. Spinal cord MRI showed enhancement of thoracic lesions after administration of

intravenous gadolinium in all five patients. Cerebral angiography performed in four of the patients were normal. CNS tissue biopsy showed necrotizing vasculitis in three patients and granulomatous histology in two specimens. Although the small number of patients with spinal cord involvement precluded statistical comparison, there were no significant differences in the clinical and laboratory studies other than symptoms of myelopathy, which occurred exclusively in those with thoracic lesions. Notwithstanding, cerebral angiography showed evidence of vasculitis more frequently in those without spinal cord involvement, while the patients with spinal cord involvement had CNS tissue biopsy findings more often consistent with vasculitis perhaps indicating more widespread disease. Overall, four of the five patients responded to therapy that included corticosteroids alone in one, and combined in the others with cytotoxic agents including cyclophosphamide, azathioprine or mycophenolate mofetil for a median duration of 19 months. Four patients recovered with slight or moderate deficits and disability; however, all sustained at least one relapse or recurrence.

Molloy and colleagues [32] described tumor-like mass lesions (ML) in 38 patients with PCNSV including seven patients from the case records of the Cleveland Clinic, and 31 patients of 535 (5.6%) with PCNSV from the English language medical literature . Patients were included only if they presented with a solitary cerebral ML and histological proof of vasculitis; 13 of 45 (29%) cases of amyloid-b related angiitis (ABRA) reported in the literature were included. The commonest symptoms of PCNSV with a ML were headache (74%), focal neurological deficit (64%), diffuse neurological deficit (50%), and seizures (47%), prompted affected patients to present typically one month after onset compared to patients with PCNSV without a ML who typically presented on average 6 months afterward. Neuroimaging, which detected the ML employing MRI in all 24 patients so studied, and by computed tomography (CT) in 29 of 30 patients, showed edema, contrast enhancement, and hemorrhage in association with the ML respectively in 17, 15, and five patients. Cerebrospinal fluid showed an elevation of the protein content and pleocytosis in two-thirds of patients so studied; and cerebral angiography performed in 14 patients, showed mass effect but no suggestion of vasculitis in in eight patients, and angiographic evidence of small vessel vasculitis in the other six. The diagnosis of PCNSV was confirmed by CNS tissue in all 38 patients with granulomatous changes in 20 (53%) and lymphocytic vasculitis in 18 (47%); positive staining for amyloid was found in 13 of 38 CNS tissue biopsies (34%), accompanied by granulomatous vasculitis in 10 of 13 (77%). Overall, 26 of 38 (68%) entered remission status defined as regression of the lesion and resolution or stabilization of neurological symptoms. Six patients died during followup, five of whom were ABRA-positive. Moderate or severe residual deficits were noted in three-quarters of patients, occurred more often in those treated with corticosteroids alone as compared with those administered combination therapy with corticosteroids and cyclophosphamide.

A recent study from Mayo Clinic evaluated the clinical findings, response to therapy, and course of patients with PCNSV associated with lymphoma [33]. Ten patients were identified (6 with Hodgkin lymphoma – HL – and 4 with non-HL) and their findings compared with those from 158 patients with PCNSV without lymphoma seen at Mayo Clinic over 29 years. In 7 patients, lymphoma and PCNSV were diagnosed simultaneously, suggesting an immunologic paraneoplastic mechanism. A granulomatous vasculitis was found in all 8 patients with cerebral biopsies, associated with CAA in 2.

Patients with lymphoma had more neurologic disability at last follow-up and their survival was reduced compared to patients without lymphoma, appearing to have a more severe form of vasculitis.

CONCLUSION

Primary CNS vasculitis is a multifaceted disease with diverse clinicopathological subsets. Affected patients with small-artery vasculitis characterized by positive histology, negative cerebral angiography and prominent leptomeningeal enhancement on MRI after intravenous gadolinium administration have a milder disease course and more favorable outcome compared to those with large-artery PCNSV with multiple large-artery stenoses on cerebral angiography and extensive lesions on MRI. Subsets of patients presenting with rapidly progressive PCNSV, solitary ML, association with lymphoma and vascular amyloid deposits have the worst prognosis.

REFERENCES

[1] Salvarani C, Brown RD, Jr., Hunder GG Adult primary central nervous system vasculitis: an update. *Curr Opin Rheumatol* 2012;24:46-52.

[2] Newman W, Wolf A Non-infectious granulomatous angiitis involving the central nervous system. *Trans Am Neurol Assoc* 1952;56:114-117.

[3] Cravioto H, Feigin I Noninfectious granulomatous angiitis with a predilection for the nervous system. *Neurology* 1959;9:599-609.

[4] Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospsective diagnostic and therapeutic experience. *Am J Med* 1983; 74:97-105.

[5] Fauci AS, Haynes BF, Katz P. The spectrum of vasculitides. Clinical, pathologic, immunologic, and therapeutic considerations. *Ann Intern Med* 1978; 89:660-676.

[6] Calabrese L Primary angiitis of the central nervous system: the penumbra of vasculitis. *J Rheumatol* 2001;28:465-466.

[7] Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain: an inflammatory reaction of diverse etiology. *Arch Neurol* 1988; 45:514-518.

[8] Calabrese LH, Mallek JA Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1988;67:20-39.

[9] West SG Central nervous system vasculitis. *Curr Rheumatol Rep* 2003;5:116-127.

[10] Neel A, Pagnoux C Primary angiitis of the central nervous system. *Clin Exp Rheumatol* 2009;27:S95-107.

[11] Moore PM. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology* 1989; 39:167-173.

[12] Salvarani C, Brown RD, Calamia KT et al. Primary central nervous system vasculitides: analysis of 101 patients. *Ann Neurol* 2007; 62:442-451.

[13] Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. *Neurology* 2001; 56:837-842.

[14] Kumar R, Wijdicks EFM, Brown RD, et al. Isolated angitis of the CNS presenting as subarachnoid hemorrhage. *J Neurol Neurosurg Psychiatry*1997; 62:649-651.

[15] Marsden HB. Basilar artery thrombosis and giant cell arteritis [Abstract]. *Arch Dis Child* 1974; 49:75.

[16] Nagaratnam N, James WE. Isolated angiitis of the brain in a young female on the contraceptive pill. *Postgraduate Medical Journal* 1987; 63:1085-1086.

[17] Benseler SM. Central nervous system vasculitis in children. *Curr Rheumatol* 2006; 8:442-449.

[18] Benseler SM, deVerber G, Hawkins C, et al. Angiography-negative primary central nervous system vasculitis in children: a newly diagnosed inflammatory central nervous system disease. *Arthritis Rheum* 2005; 52:2159-2167.

[19] Calabrese LH, Gragg LA, Furlan AJ Benign angiopathy: a distinct subset of angiographically defined primary angiitis of the central nervous system. *J Rheumatol* 1993;20:2046-50.

[20] Calabrese LH, Duna GF, Lie JT Vasculitis in the central nervous system. *Arthritis Rheum* 1997;40:1189-201.

[21] Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007; 146:34-44.

[22] Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. *Neurol Clin* 1997; 15:821-834.

[23] Pomper MG, Miller TJ, Stone JH, et al. CNS vasculitis in autoimmune diseases: MR imaging findings and correlation with angiography. *AJNR* 1999; 20:75-85.

[24] Birnbaum J, Hellmann DB Primary angiitis of the central nervous system. *Arch Neurol* 2009;66:704-709.

[25] Salvarani C, Brown RD, Jr., Calamia KT et al. Rapidly progressive primary central nervous system vasculitis. *Rheumatology* 2011;50:349-58.

[26] Sulter G, Steen C, De Keyser J. use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke* 1999; 30:1538-1531.

[27] Salvarani C, Brown RD, Jr., Calamia KT et al. Angiography-negative primary central nervous system vasculitis: a syndrome involving small cerebral vessels. *Medicine* 2008;87:264-71.

[28] Salvarani C, Brown RD, Jr., Calamia KT et al. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. *Rheumatology* 2008;47:1671-1677.

[29] Salvarani C, Hunder GG, Morris JM, et al. Ab-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology 2013*; 81:1596–1603.

[30] Salvarani C, Brown RD, Jr., Calamia KT et al. Primary central nervous system vasculitis presenting with intracranial hemorrhage. *Arthritis Rheum* 2011;63:3598-606.

[31] Salvarani C, Brown RD, Jr., Calamia KT et al. Primary CNS vasculitis with spinal cord involvement. *Neurology* 2008;70:2394-2400.

[32] Molloy ES, Singhal AB, Calabrese LH Tumour-like mass lesion: an under-recognised presentation of primary angiitis of the central nervous system. *Ann Rheum Dis* 2008;67:1732-1735.

[33] Salvarani C, Brown RD, Christianson TJH, et al. Primary central nervous system vasculitis associated with lymphoma. *Neurology* 2018; 90:e847-e855.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 9

STROKE DUE TO VASCULITIS IN ADULTS

David S. Younger**, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health, City University of New York, New York, NY, US

ABSTRACT

The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in vessel walls. There is an increased propensity for ischemic stroke due to the compromise in vessel lumina and distal tissue ischemia, with hemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity.

INTRODUCTION

The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in their walls. There is an increased propensity for ischemic stroke due to the loss of vascular integrity with stenosis of vessel lumina and distal tissue ischemia; and hemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity. The 2012 Revised Chapel Hill Consensus Conference (CHCC) [1] nomenclature provides systemic nosology and a categorization of primary and secondary vasculitides. Central nervous system (CNS) involvement and stroke both occur in the single-organ vasculitic (SOV) syndrome primary CNS vasculitis (PCNSV) [2], as well as, due to limited or multiorgan manifestations of primary systemic vasculitides [1].

* Corresponding Author's Email: youngd01@nyu.edu

PRIMARY CNS VASCULITIS

With several proposed diagnostic schemes for PCNSV over the years [3-5], the combination of clinical and histopathological findings derived from cerebral angiography and leptomeningeal and brain biopsy remains the recommended method of definite diagnosis [6]. This approach facilitates the identification of clinicopathologic subtypes with persistent focal deficits and stroke [2] or intracranial hemorrhage [7] from those with reversible cerebral vasoconstriction syndrome (RCVS) [8] that may mimic true vasculitis, but do not require cytotoxic therapy.

Torres and colleagues [9] did not find a significant correlation between brain and leptomeningeal tissue, and the results of cerebrospinal fluid (CSF), neuroimaging, surgical technique, biopsy characteristics, or preoperative immunosuppressive therapy in 9/79 (11%) patients with suspected CNS vasculitis studied between 2005 and 2013. Yet in nearly three-fold (30%) of patients undergoing biopsy, the investigators noted alternative diagnoses of cerebral amyloid angiopathy, encephalitis, demyelination, and lymphoma. Postoperative complications occurred in 16%, 4% of which were serious. The authors concluded that while brain biopsy remains an important diagnostic tool, however further studies are needed to establish the clinical variables associated with a positive yield, as well as the surgical techniques that are most likely to provide diagnostic results with the lowest complication risk.

Historically, Younger and colleagues [3] described four patients with granulomatous angiitis of the brain histopathologically manifesting necrotizing vasculitis of arteries and veins of varying caliber in conjunction with giant cells and epithelioid cells. These authors [3] noted non-focal symptoms of headache and mental change, followed by focal weakness, seizures, and fatal coma in all four patients. Focal weakness with a stroke onset was noted in two (Patient 1 and 3) of the four patients, Patient 1 had onset of lethargy, focal ptosis and hemiparesis had predominant anterior (ACA), middle (MCA), posterior cerebral artery (PCA) and basilar artery involvement at postmortem examination. Patient 3, who presented with hemiparesis, ataxia, and dysarthria, and found to have predominant small leptomeningeal artery and vein involvement. Altogether, 15% of 78 patients overall had focal weakness with stroke onset compared to 42% who presented with focal deficits during the course of the illness.

In the same year, 1988, Calabrese and Mallek [4] described eight patients with classic angiographic or histopathologic features of PCNSV or so called primary angiitis of the CNS (PACNS), and reviewed the literature of 40 literature cases. Patient 2 [9] who presented with the clinical diagnosis of isolated angiitis of the CNS (IACNS) defined by classical angiographic features, had a clinical onset of transient weakness that progressed to fixed hemiparesis, nonfluent aphasia, alexia, and agraphia with later stabilization after combination prednisone and cyclophosphamide therapy.

Birnbaum and colleagues [5] proposed changes to the criteria of Calabrese and Mallek [4] to include a definite diagnosis of PCNSV only after tissue biopsy confirmation, noting strokes or persistent deficits in less than 20% of patients at onset, and with only about 28% of symptoms overall related to large cerebral vessel involvement. Salvarani and co-workers [2] noted that persistent neurological deficit or stroke and headache were the commonest initial symptoms affecting 68% of 101 patients so studied with PCNSV defined by diagnostic criteria similar to

those suggested earlier [4]. Cerebral infarction noted on magnetic resonance imaging (MRI) of the brain in 53% of patients, were multiple in appearances in 85%, bilateral in 83%, and involved the cortex and subcortex in 63%. Overall, their appearance suggested large-artery, branch-artery or small-artery distributions. Intracranial hemorrhage was noted in 8% of patients, and gadolinium enhancement was found in a third of patients, a quarter of whom demonstrated gadolinium enhancement of the meninges.

Montefort and co-workers [10] described a 57-year-old man with brain-biopsy confirmed PCNSV and a 2-month history of right arm weakness and numbness superimposed on a history of left-sided headache and intermittent visual field loss. Brain MRI showed evidence of cortical infarction across more than one vascular territory with signal changes consistent with hemorrhage in the left basal ganglia and parieto-occipital lobe. There was angiographic evidence of irregular narrowing and aneurysmal dilatation of the left terminal carotid artery that stabilized without new areas of new infarction after treatment with intravenous pulsed cyclophosphamide and corticosteroids followed by azathioprine. The neuroimaging features of this patient are shown in Figures 1 to 4, as well as, in a similarly affected patient in Figures 5 and 6.

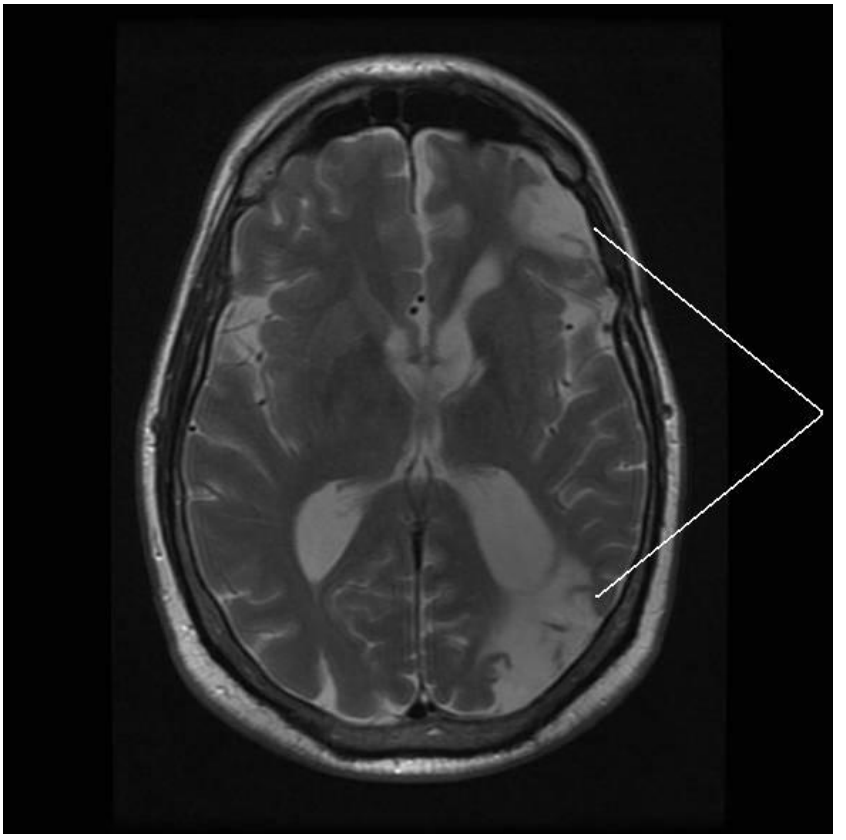


Figure 1. Primary CNS vasculitis. T_2-weighted MRI of the brain demonstrates left frontal and parieto-occipital lobe areas of infarction. Reproduced with permission from [10].

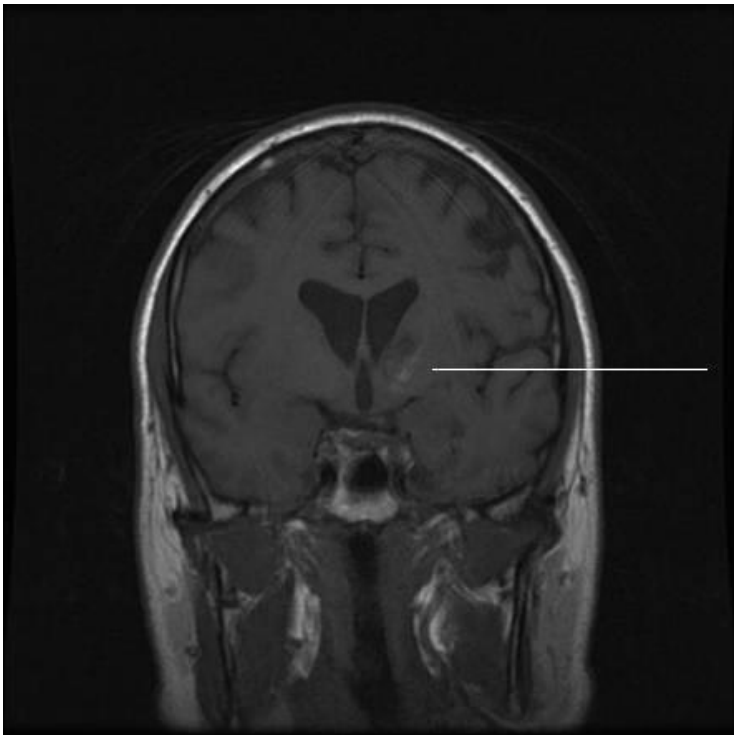


Figure 2. Primary CNS vasculitis. T_1-weighted MRI of the brain showed left basal ganglia hemorrhage. Reproduced with permission from [10].

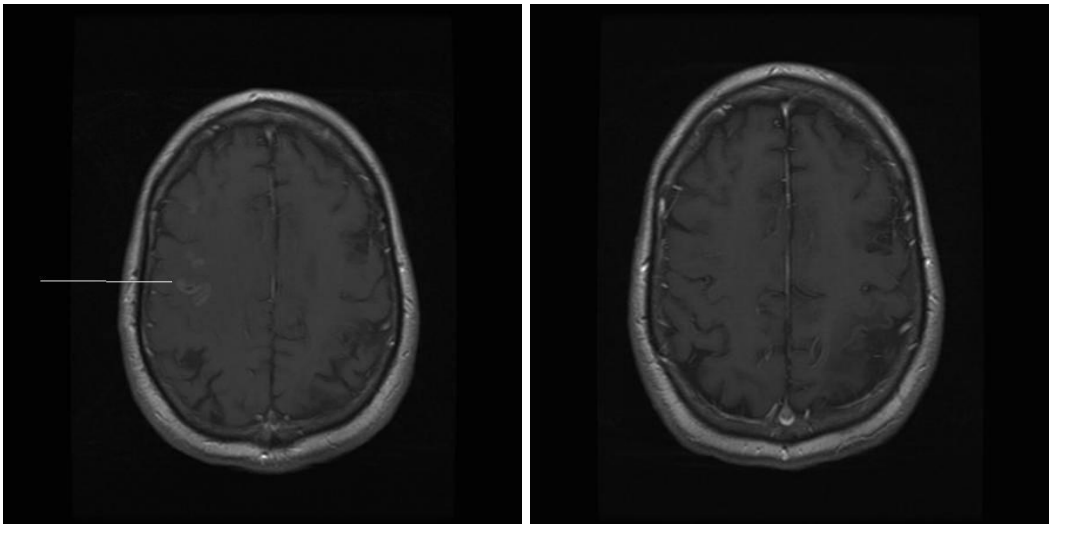


Figure 3. Primary CNS vasculitis. T_1-weighted MRI of the brain demonstrates gyral enhancement after intravenous administration of gadolinium before treatment (A), that resolves after immunosuppressant therapy (B). Reproduced with permission from [10].

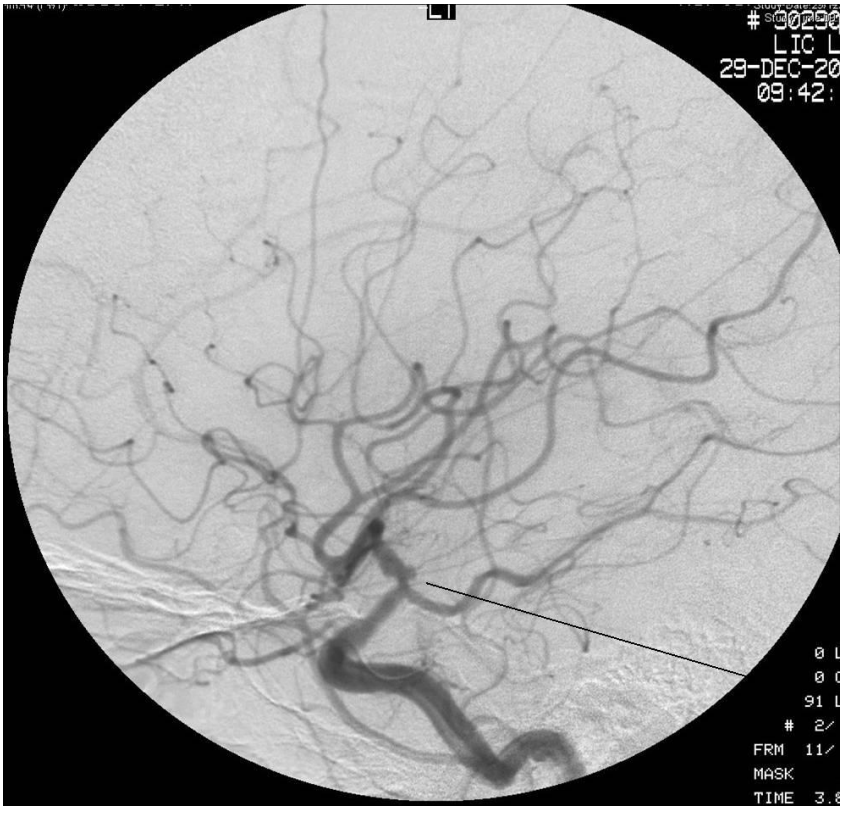


Figure 4. Primary CNS vasculitis. Cerebral angiography shows a sessile internal carotid artery aneurysm. Reproduced with permission from reference 10.

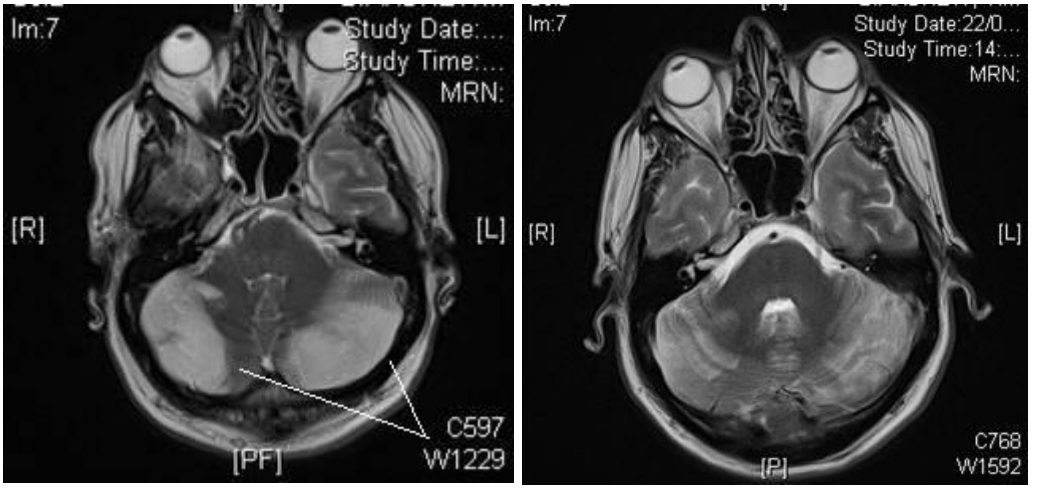


Figure 5. Primary CNS vasculitis. T_2-weighted MRI of the brain shows bilateral cerebellar hemispheric infarcts and abnormal signal hyperintensities before treatment (A) that resolve after immunosuppressant.

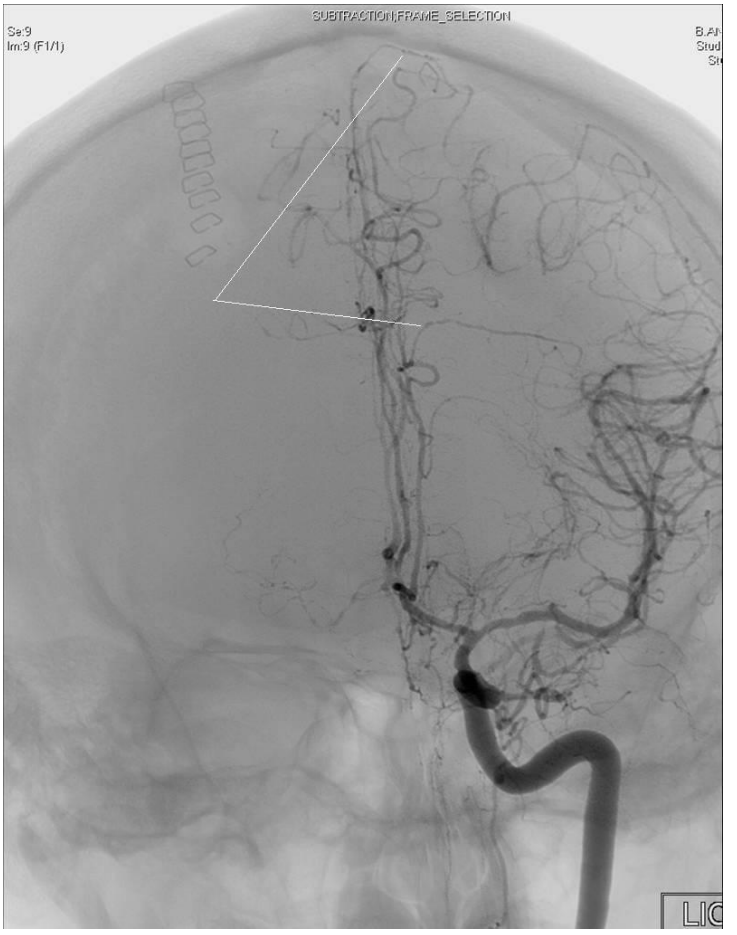


Figure 6. Primary CNS vasculitis. Cerebral angiography shows widespread vessel irregularity and beading.

PRIMARY LARGE VESSEL VASCULITIS

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are prototypical large vessel granulomatous vasculitides (LVV). They involve the aorta and its major branches however any size artery can be affected [1]. Imaging studies and fluorescein angiography studies have shown that ocular involvement in GCA can affect not only ophthalmic, but also medium caliber retinal arteries and multiple ciliary arteries and their smaller branches; blindness may result from not only LVV but also injury to smaller ophthalmic branches [1]. Whereas GCA has a predilection for branches of the carotid and vertebral arteries and an age of onset older than 50 years, there is often polymyalgia rheumatic. TAK involves proximal subclavian and carotid arteries with an onset of 40 years or less. Neuroimaging studies employing ultrasonography, high-resolution MRI, and ^{18}flurodeoxyglucose-positron emission tomography (FDG-PET) imaging are useful modalities to depict superficial cranial and extracranial vessels, and large vessel subclavian and aortic involvement in GCA and TAK [11].

CNS involvement in GCA, which results from thrombosis of the carotid and vertebral arteries rather intracranial arteritis, affects vessels that contain elastin, more specifically the internal elastic lamina that is absent from intracranial vessels more than 5 millimeters beyond the point of dural perforation. Reich, colleagues [12], Gonzalez-Gay, and co-workers [13] summarized the literature pertaining to stroke and GCA. Reports of CNS involvement have erroneously attributed to intracranial GCA rather than PCNSV [14-16]. Hellenhorset and colleagues [17] noted CNS events including stroke in 7.4% of 175 patients with confirmed GCA, as well as, and one patient with massive cerebral hemorrhage, two with stroke, and six with occlusive disease of the aortic arch. Caselli and colleagues [18] noted transient ischemic attacks or stroke in 7% of 166 patients with biopsy-proven GCA, among whom four had events in the vertebrobasilar systemic, and eight affected the carotid arterial system. With approximately 30% of patients manifesting neurological findings, the commonest of which were neuropathies of the arms and legs according to Caselli and colleagues [18], Salvarani and colleagues [19] observed that transient ischemic attacks or stroke in the territory of the carotid or vertebrobasilar arteries were less common neurological findings.

Gonzalez-Gay and co-workers [13] ascertained the frequency of cerebrovascular accidents (CVA) in association with GCA among 239 patients in a multicenter retrospective analysis to assess the features, therapeutic response, and predictors of visual loss and CVA. Eight patients (3%) developed CVA, equally divided between the vertebrobasilar and carotid territories. Symptoms of vascular ischemia preceded onset of arteritis by a median of 1.5 months, and were more frequent in those with visual involvement, especially permanent visual loss. Two patients with vertebrobasilar stroke died within one month despite aggressive corticosteroid therapy. Stepwise logistical regression analysis revealed visual loss and jaw claudication as the predictors of CVA.

Kerr and colleagues [20] summarized the clinical, laboratory and treatment responses of 60 patients with TAK based upon the presence of symptoms and signs of ischemic, inflammatory large-vessel disease as well as supportive arteriographic findings, noting ten (17%) patients with either transient ischemic attacks or CVA, and carotid or vertebral artery disease, eight of whom corresponded to the neurological deficit. One of the remaining two had hypertension, whereas the other patient had isolated stenosis of the innominate artery. Riehl [21], and Riehl and Brown [22] reported the clinical and pathological features of six patients with TAK noting widespread arteritis that not only involved the aortic arch and its tributaries by clinical and angiographic studies, but many other medium-, and large-sizes vessels. One patient with TAK manifested clinical and histopathological evidence of CNS involvement. That patient, a 43-year-old woman who presented with rapidly disappearing blood pressure and complained of spells of progressively worsening dizziness and dimness of vision, died of severe congestive heart failure. At postmortem examination, there was severe stenosis of the distal aorta, thrombosis of an aortic arch graft with nearly complete obstruction of all the great vessels by granulomatous panarteritis, as well as vasculitic involvement of the proximal portion of the left MCA, both PCA arteries, and anterior third of the basilar artery. There was massive infarction of the left temporoparietal region, the left half of the midbrain, brain stem, and cerebellum.

PRIMARY MEDIUM VESSEL VASCULITIS

Polyarteritis nodosa (PAN) and Kawasaki disease (KD) are prototypical medium vessel vasculitides (MVV). Although any size of artery is affected in this category, PAN is associated with necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules; however, it is not associated with anti-neutrophilic cytoplasmic antibodies (ANCA) [1]. By contrast, KD is an infantile or childhood disorder that is associated with the mucocutaneous lymph node syndrome, predominantly affecting medium and small arteries, occasionally coronary, the aorta, and other large arteries [1].

Among early postmortem series of PAN, Middleton and McCarter [23] noted CNS involvement due to arteritic lesions in one (Patient 1) that consisted of an occasional small artery. Brain tissue was not examined in one patient (Patient 2) and was not mentioned in another (Patient 3). Kernohan and Woltman [24] summarized the clinicopathological aspects of adult PAN in six patients studied at postmortem examination, estimating CNS involvement associated with stroke in about 8% of cases, and a combination of acute and chronic lesions that correlated with known exacerbations. In three patients, the peripheral nervous system (PNS) was widely involved at onset and at postmortem examination in addition to systemic involvement typically sparing the CNS, while in one patient, the PNS and CNS was involved alone. That patient was a 32-year-old man with onset of left arm and leg hemisensory loss and headache that progressed to paralysis. At postmortem examination, there was marked thickening and near complete obliteration of the right MCA, less so on the left side, and obstruction of the right PCA by a recent thrombus, with a normal PCA on the left. Microscopic analysis showed subacute and chronic lesions of PAN.

According to Guillevin and co-workers [25], CNS involvement is rare but motor deficiencies, stroke and brain hemorrhages can occur as well as cognitive disturbances associated with abrupt memory loss and scattered T_2-weighted hyperintensities on brain MRI suggestive of cerebral vasculitis. CNS involvement including stroke was noted in 9.6% of 115 patients in the FVSG [26] with hepatitis B virus (HBV)-PAN between 1972 and 2002. The FVSG treatment protocol for HBV-PAN generally included cyclophosphamide, corticosteroids and plasma exchange (PE), alone or together, followed by vidarabine, interferon-alpha (INF-α), or lamivudine, depending upon the time of diagnosis and different treatment protocols available [27-29]. So treated, nine patients (9.7%) who achieved remission subsequently relapsed, one of whom died of stroke, although the relationship between PAN and stroke was not clearly established. A retrospective study of 348 adult patients registered in the FVSG [30] who satisfied criteria for the diagnosis of PAN between 1963 and 2005 noted CNS involvement including stroke in 4.6% of patients overall, with a relatively equivalent frequency among patients with and without HBV-related illness.

PRIMARY SMALL VESSEL VASCULITIS

Small vessel vasculitis affects intraparenchymal arteries, arterioles, capillaries, and venules, however medium-sized vessels and veins are also be involved [1]. Two major categories of SVV include ANCA-associated vasculitis (AAV) characterized by necrotizing vasculitis with few or no immune complex (IC) deposits predominantly affecting small arteries,

arterioles, capillaries, and venules associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3). Marked vessel wall deposits of immunoglobulin (Ig) and complement characterize immune complex vasculitides. Granulomatosis with polyangiitis (GPA) (Wegener granulomatosis [WG] type], eosinophilic granulomatosis with polyangiitis (EGPA) [Churg-Strauss syndrome [CSS]), and microscopic polyangiitis (MPA) (microscopic polyarteritis) are prototypical AAV, while cryoglobulinemic vasculitis (CV), IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP), and hypocomplementemia urticarial vasculitis (HUV) associated with C1q antibodies comprise the IC vasculitides; HSP/IgAV is predominantly a disorder of childhood.

ANCA-ASSOCIATED VASCULITIS

Granulomatosis with Polyangiitis

GPA leads to necrotizing granulomatous inflammation of the upper and lower respiratory tracts associated with necrotizing vasculitis of small to medium arteries, arterioles, capillaries, veins, and venules together with glomerulonephritis [1]. Drachman [31] described a patient with one month of headache that awakened him from sleep followed by rhinitis, nasal obstruction, epistaxis, mononeuropathy multiplex, confusion and hypertension. Active arteritis and necrotizing granulomata were found in the brain but not in peripheral nerves. Based upon the observations in a single postmortem studied patient, cerebral involvement according to Drachman [31], depended upon a combination of four separate entities, 1) Frank vasculitis of larger arterial branches particularly over the surface of the brain as demonstrated in his patient report; 2) Ischemia in portions of the territory supplied by the affected vessels; 3) Subarachnoid hemorrhage and hypertensive encephalopathy evidenced by microscopic infarcts in close relation to arteries with fibrinoid impregnation of their walls; and 4) Meningeal infiltration by mononuclear cells. Nishino and colleagues [32] described neurological involvement in 34% of 324 consecutive patients with GPA at the Mayo Clinic between 1973 and 1991 classified according to the American College of Rheumatology (ACR) [33] that included peripheral neuropathy in 16% compared to cerebrovascular events in 4% at some time in the course of illness, however rarely if ever at presentation. Of five patients with presumed clinical vasculitis, cerebral angiography was negative in two. Of twelve patients studied at postmortem examination, findings of vasculitis were found in only two. Fauci and colleagues [34] noted nervous system involvement in 22% of 85 patients, 10 patients (12%) of whom had CNS involvement including strokes at some point in the illness although not specifically mentioned at presentation. Moore and co-workers [35] estimated the frequency of neurological abnormalities of GPA at 23% to 50%, citing possible mechanisms of neural dysfunction due to inflammation from primary sites, remote granuloma formation, and vasculitis. Drachman [31] opinioned that contiguous extension of necrotizing granulomas might account for 24% of all neurological complications including those of the CNS.

Extensive cerebral infarction in the territory of the bilateral ACA was ascertained in a 67-year-old man with frontal headache that preceded detection of a large midline frontal mass lesion on computed tomography (CT), and known biopsy-proven GPA and granulomatous vasculitis of the nasal cavity, liver and kidney. Postmortem examination showed cerebral

infarction in the areas supplied by A2 branches of both ACA, with occlusion of large sized ACA vessels by organized mural thrombi, and fibrinoid necrosis in the arterial branches. There was similar vasculitis with multinucleated giant cells involving small arteries and veins diffusely in the frontal region of the brain suggesting contiguous spread from granulomatous nasal cavity lesions. Hoffman and colleagues [36] retrospectively assessed 180 patients with GPA for 6 months to 24 years noting nervous system involvement in 23% of patients, including CNS involvement and stroke in 8% of patients. A prospective analysis of clinical, electrophysiologic, radiologic, and serologic data of 128 GPA patients over 19 months [37] noted CNS involvement in 7%, the latter including granulomatous infiltration of frontobasal cortex arising from adjacent paranasal sinus granulomas, cerebral vasculitis, stroke, vascular myelopathy, and meningeal granulomatosis.

Microscopic Polyangiiits

Microscopic polyangiitis is a necrotizing AAV vasculitis with few or no IC deposits and commonly associated glomerulonephritis without granulomatous inflammation [1]. Davson and colleagues [38] separated fourteen postmortem studied patients from 1934 to 1947 with MPA into two groups based upon the presence of severe widespread glomerular damage. Wainwright and Davson [39] described MPA among six post-mortem studied patients from 1947 to 1948, mentioned CNS involvement. However, neither paper [38, 39] recorded stroke or histopathologic evidence of brain involvement. Nor was there mention of patients with CNS involvement by Adu and co-workers [40] among 43 patients with renal histologic evidence of MPA. Savage and co-workers [41], who studied 34 patients with MPA, all of whom presented with clinical evidence of a systemic SVV predominantly affecting the skin and musculoskeletal systemic associated with focal necrotizing glomerulonephritis, cited CNS involvement at presentation in 18% of patients without specific mention of stroke. Serra and colleagues [42], who reported the presentation, histopathology and long-term outcome of 53 patients with MPO from 1965 to 1981, cited CNS involvement at presentation in 15% of patients, the findings of which included stroke, convulsions, headache, confusion and drowsiness. Guillevin and co-workers [43] who reported the clinical and laboratory findings in 85 patients from the FVSG with MPA from 1969 to 1995, noted CNS involvement in 11.8% of patients at presentation and in 3% of 29 patients who experienced a relapse; however, there was no specific mention of stroke. Gayraud and co-workers [44] analyzed four prospective trials that included 278 patients with PAN, MPA and EGPA from 1980 to 1993, that reported stroke occurrence that accounted for 85 deaths. Villiger and Guillevin [45], who reviewed several retrospective European patient cohorts [40-43, 46], cited CNS involvement that included subarachnoid hemorrhage, cerebrovascular disease, meningitis and diffuse brain injury. Ben Sassi and colleagues [47] described intracerebral hemorrhage secondary to necrotizing vasculitis that similarly involved the nerves and muscles, citing three additional patients with hemorrhagic stroke due to MPA [48-50]. Ahn and colleagues [51] studied 55 patients with MPA, 69% of whom demonstrated perinuclear ANCA by immunofluorescence (IF) or MPO ANCA-seropositivity, noting CNS involvement in 5 (9.1%), none of whom developed end-stage renal disease. and one of whom died at follow-up without known autopsy.

Eosinophilic Granulomatosis with Polyangiitis

EGPA is a necrotizing vasculitis involving small to medium vessels that differs from GPA by the presence of eosinophil-rich necrotizing granulomatous inflammation of the respiratory tract in association with asthma and eosinophilia, and ANCA seropositivity when glomerulonephritis is present [1]. Churg and Strauss [52] described the clinical and postmortem findings of thirteen patients with asthma, fever, and hypereosinophilia. This was accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation that constituted the so called allergic granuloma. The latter were found within vessels walls and extravascular connective tissue of major organ systems. CNS organ manifestations were described in 8 (61.5%) of patients, and the cause of death in 3 patients who sustained cerebral hemorrhage or subarachnoid hemorrhage. Chumbley and co-workers [53] described 30 asthmatic patients from the Mayo Clinic over the period from 1950 to 1974 with necrotizing vasculitis of small arteries and veins, extravascular granulomas and infiltration of vessels and perivascular tissue eosinophilia. Lanham and colleagues [54], who emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas suggested by Churg and Strauss [52] occurred contemporaneously in only a minority of patients, and that such histological findings could be encountered in other granulomatous, vasculitic and eosinophilic disorders in the absence of clinical asthma, allergic rhinitis, sinusitis, pulmonary infiltrates, and cardiac involvement pathognomonic of EGPA, noted CNS involvement in 25% of cases. Cerebral hemorrhage and infarction as a consequence of vasculitis or hypertension was a major cause of morbidity and mortality, accounting for 16% of deaths.

Sehgal and colleagues [55] noted neurological involvement among 14 patients with the clinical diagnosis of EGPA, three of whom had cerebral infarction two to fifteen years after initial diagnosis. The first patient was a 68-year-old woman with a stroke involving the territory of the MCA manifested as hemiparesis and aphasia. The second patient was a 34-year-old man with a right parietal lobe infarction pursuant to embolization of a left ventricular thrombus, manifested incoordination and hemisensory loss of the arm. The third patient was a 62-year-old woman with a thalamic infarction who manifested hemibody sensory loss. Guillevin and co-workers [56] studied 96 patients with EGPA between 1963 and 1995, noting ischemic stroke onset in 6 (6%) by brain computed tomography (CT). Mouthon and colleagues [57], reported 38 patients with EGPA from 1978 to 1998, citing CNS involvement in 3 elderly patients (7.9%) in whom CNS vasculitis was suggested by MRI of the brain in only one patient. Among 383 patients with EGPA enrolled in the FVSG Cohort [58] employing the definition of the ACR [59], CNS involvement was noted in 20 (5.2%) of patients at onset, with two-fold greater frequency of ANCA-seropositive serology than those ANCA-seronegative, but no specific mention of stroke frequency.

IMMUNE COMPLEX VASCULITIS

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) or CryoVas is typified by cryoglobulinemic IC deposited along small vessels predominantly arterioles, capillaries, veins, and venules in

association with serum cryoglobulins. In mixed cryoglobulinemia (MC), the immune complex is composed of IgM and polyclonal IgG with rheumatoid factor activity often in association with hepatitis C virus (HCV) infection. Disease manifestations of cryloglobulinemia was noted in 206 of 443 (47%) patients [60] that included palpable purpura, 12 (6%) of whom had CNS involvement; HCV Infection was the main etiologic factor noted overall in 75% of the 443 patients. A concomitant autoimmune disorder was noted in 24%, hematologic disease in 7%, and essential cryoglobulinemia in 11% of the patients overall. The original patient described by Lerner [61], a 56-year-old man who presented with chest pain, purpuric rash and a cold precipitating serum protein, did not have symptoms or postmortem findings referable to the nervous system. Marshall [62] noted widespread cerebral purpura with hemorrhage ascribed to occlusion of small blood vessels by eosinophilic protein precipitates that correlated with the clinical presentation of progressively fatal coma.

Abramsky and Slavin [63] described three patients with MC and CNS involvement. The first was a 55-year-old woman with anarthria, hyperreflexia, bilateral Babinski signs and progressively fatal coma, who was later found at postmortem to have multiple thrombotic occlusions of small intracerebral blood vessels with adjacent foci of ischemia and marked demyelination. The second patient was a 50-year-old woman, who presented with a Wallenberg syndrome and was found to have MC with occlusion of the left posterior inferior artery at angiography. The third patient, a 50-year-old woman who presented with right hemiparesis and pyramidal signs, was found to have a cryoprecipitate and occlusion of the left MCA.

Gorevic and colleagues [64] summarized the clinical aspects of long-term followup of 40 patients with MC noting incidental CNS involvement at postmortem examination and a fatal stroke in another patient. Petty and co-workers [65] described a 35-year-old woman with type II cryoglobulinemia, headache, purpura, and seizures who was found to have multiple areas of T_2 and proton density signal abnormalities in the cerebral and cerebellar hemispheres, with a gyral pattern of enhancement in the cerebral cortex, a nodular pattern of enhancement in the cerebellum, and early cortical infarction on right frontal brain biopsy without vasculitis; cerebral angiography was normal. HCV RNA was detected by polymerase chain reaction (PCR). Ince and colleagues [66] described a patient with paranoid psychosis and MC who was found to have right basal ganglia hemorrhage and multifocal small vessel occlusions by amorphous bland protein plugs and abundant Russell bodies present in arterioles and venules with relative sparing of capillaries.

Stroke was the presenting feature of CNS involvement in MC among two patients with lacunar infarcts and associated subcortical white matter changes on brain MRI [67, 68], and in one patient with a temporal arteritis-like syndrome with associated ischemic cerebral infarction [69]. Cacoub and co-workers [70] compared the features of patients with HCV examined for systemic vasculitis manifestations of PAN or MC noting two patients with cerebral vasculitis in the former versus none in the latter. Cacoub and colleagues [68] described CNS involvement in three patients with HCV infection and MC, one of whom was found to have a hemorrhagic lesion of the external capsule in association with pontine T_2 hyperintensities and parietal lobe infarcts. A second patient had a hemorrhagic occipital lobe lesion in association with cerebellar infarction and abnormal periventricular hyperintensities. A third patient had abnormal white matter hyperintensities.

Ferri and colleagues [71] studied the demographic, clinical, serologic features and survival of 231 patients with MC seen between 1972 and 2001, noting widespread vasculitis involving small- to medium-sized arteries, capillaries and venules with two or more visceral organs

including the kidney, gut, and lung, noting no CNS manifestations of MC with exception of focal dystonia during interferon treatment in in one patient [71]. Filipini and colleagues [72] reported a 63-year-old woman with acute severe encephalopathy HCV-related MC, dysarthria and hemiplegia. Fragoso and co-workers [73] reported a 35-year-old woman with dysarthria, left facial and left limb hemiparesis and hemisensory loss with MC in whom MRI showed ischemic lesions in the tail of the right caudate nucleus, corona radiate and posteromedial putamen. Casato and co-workers [74] reported the CNS findings in 40 patients with HCV-related CV in a multicenter, case-control study using MRI and neuropsychological testing. Although none evidenced cerebral infarction, small white matter lesions were found in all HCV-related MC subjects, a higher mean number of white matter intensities compared to HCV and healthy controls.

Terrier and co-workers [75] analyzed the data of 242 patients registered in the CryoVas survey ascertaining CNS involvement in 5 (2%) patients without specifying whether stroke was encountered. Terrier and Cacoub [76] reviewed CNS findings in HCV-seronegative and seropositive MC in CryoVas noting 2 (0.7%) patients among the former with CNS involvement, compared to 9 (5%) patients in the latter group evidencing CNS involvement but without further mention as to presence of stroke in any of the patients.

Hypocomplementemic Urticarial Vasculitis/C1q

Hypocomplementemic urticarial vasculitis/C1q presents with recurrent attacks of erythematous, urticarial and hemorrhagic skin lesions lasting up to 24 hours at a time, associated with recurrent attacks of fever, join swelling, and variable abdominal distress. Circulating hypocomplementemia and C1q antibodies are associated with necrotizing SVV in skin biopsy tissue affecting arterioles, capillaries, and venules [1]. Apart from orbital pseudotumor with ptosis, diplopia, and headache in one patient with HUV syndrome, there was no mention of CNS involvement or stroke in a review of 18 patients with HUV/C1q [77]. Nor was stroke mentioned in a review of four patients studied at postmortem examination with HUV/C1q [78]. Buck and colleagues [79] cited rare CNS manifestations in HUV/C1q including aseptic meningitis, pseudotumor cerebri, transverse myelitis but no mention of stroke or cerebral vasculitis. Grotz and colleagues [80] did not mention stroke or CNS vasculitis in a case report and review of the literature of HUV/C1q. In a review of HUV/C1q, Davies and Brewer [81] cited CNS involvement as “very rare”, attributing development of pseudotumor cerebri to vasculitis of the venous sinus system. Ludivico and colleagues [82] suggested that chronic pseudotumor cerebri in their patients was a diagnosis of exclusion and possibly related to chronic corticosteroid use, but did not cite patients with cerebral vasculitis or stroke.

REFERENCES

[1] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1-11.

[2] Salvarani C, Brown RD, Calamia KT et al. Primary central nervous system Vasculitides: analysis of 101 patients. *Ann. Neurol.* 2007; 62:442-451.

[3] Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain: An inflammatory reaction of diverse etiology. *Arch. Neurol.* 1988; 45:514-518.
[4] Calabrese LH, Mallek JA Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1988; 67:20-39.
[5] Birnbaum J, Hellmann DB Primary angiitis of the central nervous system. *Arch. Neurol.* 2009; 66:704-709.
[6] Younger DS. Vasculitis of the nervous system. *Curr. Opin. Neurol.* 2004; 17:317-336.
[7] Salvaranni C, Brown RD Jr., Calamia KT, et al. Primary central nervous system vasculitis presenting with intracranial haemorrhage. *Arthritis Rheum* 2011; 63:3598-3606.
[8] Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann. Intern Med.* 2007; 146:34-44.
[9] Torres J, Loomis C, Cucchiara B, et al. Diagnostic yield and safety of brain biopsy for suspected primary central nervous system angiitis. *Stroke* 2016; 47:2127-2129.
[10] Montefort M, Dashora U, Chowdhury M. Cerebral vasculitis presenting as a stroke. *BMJ Case Reports* 2012 Nov 27; 2012. Bcr2012007194. doi: 10.1136/bcr-2012-007194.
[11] Blockman D, Bley T, Schmidt W. Imaging for large-vessel vasculitis. *Curr Opin Rheumatol.* 2009; 21:19-28.
[12] Reich KA, Giansiracusa DF, Strongwater SL. Neurologic manifestations of giant cell arteritis. *Am. J. Med.* 1990; 89:67-72.
[13] Gonzalez-Gay MA, Blanco R, Rodriguez-Valverde V, et al. Permanent visual loss and cerebrovascular attacks in giant cell arteritis. Predictors and response to treatment. *Arthritis Rheum. 1998*; 41:1497-1504.
[14] McCormick HM, Neubuerger KT. Giant-cell arteritis involving small meningeal and intracerebral vessels. *J. Neuropathol. Exp. Neurol.* 1958; 17:471-478.
[15] Kjeldson MH, Reske-Nielsen E. Pathological changes of the central nervous system in giant-cell arteritis: report of a case. *Acta Ophthalmol.* 1968; 46:49-56.
[16] Enzman D, Scott WR. Intracranial involvement of giant-cell arteritis. *Neurology* 1977; 27:794-797.
[17] Hollenhorst RW, Brown JR, Wagener HP, et al. Neurologic aspects of temporal arteritis. *Neurology* 1960; 10:490-498.
[18] Caselli RJ, Hudner GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. *Neurology* 1988; 38:352-359.
[19] Salvarani C, Cantini F, Boiardi L, et al. Polymyalgia rheumatica and giant cell arteritis. *N. Engl. J. Med.* 2002; 347:261-271.
[20] Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann. Intern Med.* 1994; 120:919-929.
[21] Riehl J-L. Idiopathic arteritis of Takayasu. *Neurology* 1963; 13:873-884.
[22] Riehl J-L, Brown WJ. Takayasu's arteritis. *Arch. Neurol.* 1965; 12:92-97.
[23] Middleton WS, McCarter JC. *Am. J. Med. Sci.* 1935; 291-308.
[24] Kernohan JW, Woltman HW. Periarteritis nodosa: a clinicopathologic study with special reference to the nervous system. *Arch. Neurol.* 1938; 39:655-686.
[25] Guillevin L, Lhote F, Gherardi R. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: clinical aspects, neurologic manifestations, and treatment. *Neurol. Clin.* 1997; 15:865-886.

[26] Guilllevin L, Mahr A, Callard P, et al, for the French Vasculitis Study Group. *Medicine* 2005; 84:313-322.
[27] Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. *Medicine* 1995; 74:238-253.
[28] Guillevin L, Lhote F, Leon A, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. *J. Rheumatol.* 1993; 20:289-298.
[29] Guillevin L, Mahr A, Cohen P, et al. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum.* 2004; 51:482-487.
[30] Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa. *Arthritis Rheum.* 2010; 62:616-626.
[31] Drachman DA. Neurological complications of Wegener's granulomatosis. *Arch. Neurol.* 1963; 8:45-55.
[32] Nishino H, Rubino FA, DeRemee RA, et al. Neurological involvement in Wegener's granulomatosis: An analysis of 324 consecutive patients at the Mayo Clinic. *Ann. Neurol.* 1993; 33:4-9.
[33] Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegner's granulomatosis. *Arthritis Rheum* 1990; 33:1101-1107.
[34] Fauci AS, Haynes BF, Katz P, et al. Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients over 21 years. *Ann. Intern Med.* 1983; 98:76-85.
[35] Moore PM, Cupps TR. Neurological complications of vasculitis. *Ann. Neurol.* 1983; 14:155-167.
[36] Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann. Intern Med.* 1992; 116:488-498.
[37] De Groot K, Schmidt DK, Arlt AC, et al. Standardized neurologic evaluations of 128 patients with Wegener's granulomatosis. *Arch. Neurol.* 2001; 58:1215-1221.
[38] Davson J, Ball M, Platt R. The kidney in periarteritis nodosa. *QJM* 1948; 17:175-202.
[39] Wainwright and Davson J. The renal appearance in the microscopic form of periarteritis nodosa. *J. Pathol. Bact.* 1950; 62:189-196.
[40] Adu D, Howie AJ, Scotti GI, et al. Polyarteritis and the kidney. *QJM* 1987; 62:221-237.
[41] Savage COS, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. *QJM* 1985; 220:467-483.
[42] Serra A, Cameron JS, Turner DR, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *QJM* 1984; 201:181-207.
[43] Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis. *Arthritis Rheum.* 1999; 42:421-430.
[44] Gayraud M, Guillevin L, le Toumelin P, et al, and the French Vasculitis Study Group. *Arthritis Rheum* 2001; 44:666-675.
[45] Villigen PM, Guillevin L. Microscopic polyangiitis: clinical presentation. *Autoimmunity Reviews* 2010; 9:812-819.
[46] D'Agati V, Chander P, Nash M, et al. Idiopathic microscopic polyarteritis nodosa: ultrastructural observations on the renal vascular and glomerular lesions. *Am. J. Kidney Dis* 1986; 7:95-110.

[47] Ben Sassi S, Ben Ghorbel I, Mizouni H, et al. Microscopic polyangiitis presenting with peripheral and central neurological manifestations. *Neurol. Sci.* 2011; 32:727-729.
[48] Honda H, Hasegawa T, Morokawa N, et al. A case of MPO-ANCA related vasculitis with transient leukoencephalopathy and multiple cerebral haemorrhages. *Rinsho Shinkeigaku* 1996; 36:1089-1094.
[49] Han S, Rehman HU, Jayaratne PS, et al. Microscopic polyangiitis complicated by cerebral haemorrhage. *Rheumatol. Int.* 2006; 26:1057-1060.
[50] Ito Y, Suzuki K, Yamazaki T, et al. ANCA-associated vasculitis (AAV) causing bilateral cerebral infarction and subsequent intracerebral haemorrhage without renal and respiratory dysfunction. *J. Neurol. Sci.* 2006; 240:99-101.
[51] Ahn JK, Hwang J-W, Lee J, et al. Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea. *Rheumatol. Int.* 2012; 32:2979-2986.
[52] Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am. J. Pathol.* 1951; 27:277-301.
[53] Chumbley LC, Harrison EG, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin. Proc.* 1977; 52:477-484.
[54] Lanham. J.G, Elkon KB, Pussey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 63:65-81.
[55] Sehgal M, Swanson JW, DeRemee RA et al. Neurologic manifestations of Churg-Strauss syndrome. *Mayo Clin. Proc.* 1995; 70:337-341.
[56] Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome. *Medicine* 1999; 78:26-37.
[57] Mouthon L, Le Toumelin P, Andre MH, et al. Polyarteritis nodosa and Churg-Strauss angiitis. Characteristics and outcome in 38 patients over 65 years. *Medicine* 2002; 81:27-40.
[58] Comarmond C, Pagnoux C, Khellaf M, et al, for the French Vasculitis Study Group. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Arthritis Rheum* 2013; 65:270-281.
[59] Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990; 33:1094-1100.
[60] Trejo L, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia. Study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine* 2001; 80:252-262.219.
[61] Lerner AB, Watson CJ. Studies of cryoglobulins. II. The spontaneous precipitation of protein from serum at 5°C in various disease states. *Am. J. Med. Sci.* 1947; 214:416-421.
[62] Marshall RJ, Malone RGS. Cryoglobulinemia with cerebral purpura. *BMJ* 1954; 2:279-280.
[63] Abramsky O, Slavin S. Neurologic manifestations in patients with mixed cryoglobulinemia. *Neurology* 1974; 24:245-249.
[64] Gorevic PD, Kassab HJ, Levo Y, et al. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am. J. Med.* 1980; 69:287-308.
[65] Petty GW, Duffy J, Huston J. Cerebral ischemia in patients with hepatitis C virus infection and mixed cryogloblinemia. *Mayo Clin. Proc.* 1996; 71:671-678.

[66] Ince PG, Duffey P, Cochrane HR, et al. Relapsing ischemic encephalopathy and cryoglobulinemia. *Neurology* 2000; 55:1579-1581.
[67] Origgi L, Vanoli M, Carbone A, et al. Central nervous system involvement in patients with HCV-related cryoglobulin. *Am. J. Med. Sci.* 1998; 315:208-210.
[68] Cacoub P, Sbai A, Hausfater P, et al. Atteinte neurologique central et infection par le virus de l'hèpatite. *Gastroenterol Clin. Biol.* 1998; 22:631-633.
[69] Zancada Diaz de Entre-Sotos F, Pérez-Aloe Mejías MT, Pérez-Tovar JF. Z. Stroke and limb ischemia in hepatitis C virus-related cryoglobulinemia. *Irish J. Med. Sci.* 2004; 173:57.
[70] Cacoub P, Costedoat-Chalumeau N, Lidove O, et al. Cryoglobulinemia vasculitis. *Curr Opin. Rheumatol.* 2002; 14:29-35.
[71] Ferri G, Antonelli A, Puccini R, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Sem. Arthritis Rheum.* 2004; 33:355-374.
[72] Filipini D, Colombo F, Jann S, et al. [Central nervous system manifestations of HCV-related MC: review of the literature]. *Rheumatismo* 2002; 54:150-155.
[73] Fragoso M, Carneado J, Tuduri I, et al. [Essential mixed cryoglobulinemia as the cause of ischemic cerebrovascular accident. *Rev. Neurol.* 2000; 30:444-446.
[74] Casato M, Sasdoun D, Marchetti A, et al. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicentre case-control study using magnetic resonance imaging and neuropsychological tests. *J. Rheumatol.* 2005; 32:484-488.
[75] Terrier B, Krasinova E, Marie I, et al. Management of non-infectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood* 2012; 119:5996-6004.
[76] Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. *Curr. Opin Rheumatol.* 2013; 25:10-18.
[77] Wisnieski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. *Medicine* 1995; 74:24-41.
[78] McDuffie FC, Sams WM, Maldonado PH, et al. Hypocomplementemia with cutaneous vasculitis and arthritis. *Mayo Clin. Proc.* 1973; 48:340-348.
[79] Buck A, Christensen J, McCarty M. Hypocomplementemic urticarial vasculitis syndrome. A case report and literature review. *J. Clin. Aesthet Dermatol.* 2012; 5:36-46.
[80] Grotz W, Baba HA, Becker JU, et al. Hypocomplementemic urticarial vasculitis syndrome. *Dtsch Arztebl. Int.* 2009; 106:756-763.
[81] Davies MDP, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunol. Allergy Clin. N. Am.* 2004; 24:183-213.
[82] Ludivico CL, Myers AR, Maurer K. Hypocomplementemic urticarial vasculitis with glomerulonephritis and pseudotumor cerebri. *Arthritis Rheum* 1979; 22:1024-1028.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 10

CENTRAL NERVOUS SYSTEM VASCULITIS DUE TO INFECTION

David S. Younger[1]*, MD, MPH, MS and Patrica K. Coyle[2], MD
[1]Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University; Department of Health Policy and Management, School of Public Health, City University of New York, New York, NY
[2]Department of Neurology, Comprehensive Multiple Sclerosis Center, Stony Brook University Medical Center, and the School of Medicine, Stony Brook, New York, US

ABSTRACT

A number of pathogens have the propensity to involve blood vessels during central nervous system infection which can lead to cerebrovascular complications. Infection is a recognized cause of secondary central nervous system vasculitis. It is very important not to miss the diagnosis of infection-related central nervous system vasculitis since specific antimicrobial therapy may be necessary; this chapter reviews the major implicated organisms.

INTRODUCTION

Vasculitis or angiitis is defined as inflammation of blood vessels. Vasculitic involvement of large, medium and small caliber vessels respectively leads to arteritis, venulitis and capillaritis alone or in combination. Central nervous system (CNS) vasculitis typically affects blood vessels within the brain and rarely the spinal cord. It can also lead to a range of complications including ischemic infarction, intracerebral or subarachnoid hemorrhage, mycotic aneurysms, venous thrombosis, and transient ischemic attacks (TIA). Three suggestive clinical patterns are shown in Table 1 [1].

* Corresponding Author's Email: youngd01@nyu.edu

Table 1. Suggestive Clinical Presentations for CNS Vasculitis*

● Encephalopathy with headache
● Intracranial mass lesion with headache and other abnormalities
● Atypical relapsing multiple sclerosis picture (with headache, seizures, encephalopathy, stroke-like features)

*Adapted from reference [1].

Infection is a recognized cause of secondary CNS vasculitis. In a series of 16 patients with CNS vasculitis not due to primary CNS angiitis, 12.5% of cases were attributed to infection [2]. The 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature considered infectious vasculitis as vasculitis associated with a probable etiology [3]. Infection can injure blood vessels in different ways. The pathogen may bind to or actually infect endothelium, or may trigger an adjacent immune or toxic response that indirectly affects vasculature. Blood vessel injury may reflect the sequela of direct infection, compressive inflammatory exudate, septic emboli, or formation of mycotic aneurysms. The infectious agents associated with CNS blood vessel disease are shown in Table 2.

BACTERIAL PATHOGENS

Acute Septic Meningitis

Acute septic bacterial meningitis is associated with vascular complications in 15% to 20% of patients [4]. Vascular complications typically occur early including days to weeks following initiation of antibiotic therapy. Invasive pneumococcal disease (IPD) is defined as a proven isolation of *Streptococcus (S.) pneumoniae* bacteria from normally sterile sites such as blood or cerebrospinal fluid. It remains a major cause of morbidity and mortality worldwide despite the availability of antibiotic therapy and vaccines. Host as well as bacterial factors contribute to IPD pathogenicity. Ethnicity, extremes of age, comorbidities and alcoholism are well-known host risk factors associated with increased susceptibility and higher mortality. Pneumococcal meningitis remains a potentially devastating disease with high mortality rate and neurological damage among those who survive. Focal neurological findings may be present during the acute phase of bacterial meningitis, but more often occur after a few days as immunological complication of meningitis. Case death rates and risk of sequelae following meningitis are higher for *S. pneumoniae* than *Neisseria meningitidis* or *Haemophilus influenza* infection.

The ensuing proinflammatory cascade triggered by *S. pneumoniae* and self-perpetuated by a dysregulated host inflammatory response, triggers mediators with vascular toxicity resulting in seizures, diffuse brain swelling, hydrocephalus, hearing loss and ischemic or hemorrhagic stroke. Arteries are involved more often than veins, and show narrowing on ultrasonography [5]. Ischemic complications result from vasculitis, vasospasm, associated endocarditis, or intra-arterial thrombosis [5].

Among 87 consecutive adult patients with pneumococcal meningitis, mortality was 24.1% [6]. Cerebrovascular arterial complications were seen in 21.8%, and venous complications in 10.3% of cases. Bacterial meningitis produces a subarachnoid inflammatory exudate that worsens over time, encasing large vessels at the base of the brain. Invasion of blood vessel

walls by inflammatory cells leads to edema, focal stenosis and dilation, and intimal thickening. Large and medium vessels are typically involved in the Circle of Willis and along the terminal internal carotid artery (ICA), but the process can spread to involve smaller vessels as well. While vasculitis and vasospasm lead to cerebral ischemia and infarction however, disseminated intravascular coagulation may also supervene in the setting of septic meningitis and hypercoagulability, with activation of antifibrinolytic, proinflammatory, and procoagulant pathways. Pneumococcal meningitis was associated with cerebral venous thrombosis and carotid and vertebral artery dissection in one reported patient [7]. There are reports of late stroke with pneumococcal meningitis involving small penetrating arterioles [8].

Table 2. Infectious Agents Associated with CNS Blood Vessel Disease

Bacterial Pathogens: ● Agents of Acute Septic Meningitis: *S. pneumoniae*, *N. meningitidis*, etc. ● Infective Endocarditis ● *Mycobacterium tuberculosis* ● Spirochetal Infections: *T. pallidum*, *B. burgdorferi*, and Leptospirosis ● *Mycoplasma pneumonia* ● *Bartonella* ● *Tropheryma whippelii*
Viral Pathogens: ● Herpes Pathogens: VZV, CMV, HSV 1 and 2; EBV ● Retroviruses (HIV, HTLV-1) ● Hepatitis Agents: HBV, HCV ● Parvovirus B19 ● West Nile Virus ● Rare cases: Adenovirus, Echo/Coxsackie, Parainfluenza, Rubella
Fungal Pathogens: ● *Aspergillus* ● *Candida* ● *Coccidioides* ● *Cryptococcus* ● *Exserohilum rostratum* ● *Histoplasma capsulatum* ● Mucormycosis
Parasitic Pathogens: ● *Taenia solium* (Neurocysticercosis) ● *Plasmodium falciparum* (Malaria) ● *Schistosoma mansoni* ● *Toxoplasma gondii*
Rickettsial Pathogens: ● *Rickettsia rickettsiae* (RMSF) ● Scrub typhus

Abbreviations: VZV, Varicella zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; HTLV-1, human lymphotrophic virus type 1; HBV, hepatitis B virus; HCV, hepatitis C virus; RMSF, Rocky Mountain Spotted Fever.

There can be delayed or chronic vasculopathy and progressive arterial stenosis consistent with late immune-mediated mechanisms, the hypercoagulable state, or rebound inflammatory effects [4, 8, 9]. Such patients are exceptional but may respond to corticosteroid therapy.

Infective Endocarditis

Infection of the endocardial inner lining of the heart can involve heart valves, mural endocardium, and septal defects [10]; valvular heart disease is a predisposing factor for infective endocarditis. The commonest site of valvular infection is the mitral followed by the aortic valve; the pulmonic valve is the least frequently involved. Mitral valve carries the highest risk for CNS emboli as noted in Table 2. Both sterile and infected emboli may occur as a result of endocarditis. CNS vasculitis is a concern in the setting of subacute rather than acute endocarditis. Both isolated angiitis of the central nervous system (IAN) and bacterial endocarditis may present with similar clinical and auxiliary findings.

Endocarditis is generally due to bacterial infection, although fungi, *Rickettsiae* and viruses are occasional agents [11]. The microorganisms most commonly implicated are *Staphylococcus (S.) aureus*, followed by *Streptococcus viridans*, coagulase-negative *Staphlyococci*, other streptococci, and gram negative rod organisms [12]; *S. aureus* in particular infects endothelial cells. *Streptococcus bovis* is a rare cause of infective endocarditis in association with occult gastrointestinal tumors in up to 56% of cases [10]. Bacteremia associated with gingivitis due to *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella* (HACEK) organism with pneumonia or pyelonephritis, can infect sterile fibrin-platelet vegetation. Infection occurs with trivial everyday activities such as brushing of teeth, bowel movements, and invasive procedures such as dental extraction, prostate removal, endoscopy or colonoscopy, barium enema, and trans-esophageal echocardiography. Intravenous (IV) drug use is a risk factor for infectious-related endocarditis. Indwelling lines can be a source of bacteremia. Internal jugular lines are more likely to become infected than subclavian lines. Subacute endocarditis is not only associated with embolism, but it promotes the formation circulating immune complexes, cryoglobulins, agglutinating and complement-fixing bactericidal antibodies.

CNS complications occur in 20% to 40% of patients with infective endocarditis, the commonest of which is stroke due to septic embolism [11, 13, 14]. Clinically diagnosed intracranial mycotic aneurysms complicate 2% to 3% of infective endocarditis cases, although the postmortem rate is in the range of 5% to 10%. About 2% to 6% of all intracranial aneurysms are due to infection, tending to affect distal portions of secondary and tertiary branches of the middle cerebral artery (MCA).

The clinical features of neurologic involvement in endocarditis may initially be very subtle with nonspecific fever; headache, fatigue, and malaise are common. Abnormalities on physical examination suggestive of embolism include Janeway lesions, splinter hemorrhages, and Roth spots; multiple ischemic strokes may also be present. Rupture of resultant mycotic aneurysm can lead to acute catastrophic hemorrhage, the symptoms of which depend upon the location. Multiple microscopic emboli can lead to non-focal encephalopathy.

A recent analysis of neurologically asymptomatic patients with infective endocarditis [13] found that 71.5% of cases manifested occult brain magnetic resonance imaging (MRI) abnormalities consisting mainly of multiple small infarcts in a watershed distribution, and cerebral microscopic hemorrhages within cortical regions.

Most affected patients demonstrate leukocytosis, elevated acute phase reactants, and positive blood cultures. Diffusion-weighted and gradient-echo MRI sequences are recommended to image the commonest findings in affected patients that include ischemia and hemorrhage. While brain computed tomographic angiography (CTA) and MR angiography (MRA) detect mycotic aneurysms measuring 3 mm to 4 mm or larger in size, digital subtraction angiography (DSA) remains the gold standard, but can be associated with serious complications.

The differentiation of infective endocarditis and primary cerebral vasculitis is extremely important [15] Therapy of infective endocarditis includes both supportive care and medical interventions whereas cerebral vasculitis requires immunosuppression. Failure to accurately distinguish the two can result treatment failures and heightened morbidity and mortality. A comparison of the findings of six patients with biopsy-proven CNS vasculitis with the data of six patients with infective endocarditis showed that the former were generally younger (27-62 years) and presented with multiple strokes (n = 4), intracerebral hemorrhage (n = 1), epileptic seizures (n = 2), or encephalopathy (n = 1). All had pathologic cerebrospinal fluid (CSF) findings including pleocytosis (n = 5), protein elevation (n = 4), and angiography revealed multilocular stenoses in two cases while digital subtraction angiography was normal in four. Those with infective endocarditis were generally older (32-77 years) and presented with multiple (n = 3) or single ischemic strokes (n = 2) or encephalopathy and headache (n = 2). While all patients showed inflammatory serum findings (C-reactive protein n = 6, leukocytosis n = 4), CSF-pleocytosis was present in two cases only. Angiography revealed a vasculitic pattern in two patients. The diagnosis of BE was established based on transesophageal echocardiography and blood cultures. Leptomeningeal and brain biopsies performed in two cases were normal. Patients with either cerebral vasculitis or infective endocarditis may present with multiple strokes and encephalopathy. The frequency of a vasculitic pattern in angiography is similar in both conditions. While inflammatory serum findings are the rule in infective endocartidits, pathologic CSF findings were present in all of those with cerebral vasculitis. Transesophageal echocardiography and blood cultures should be performed in order to diagnose or exclude infective endocarditis in those at higher risk. Notwithstanding, immunosuppressive therapy may be dangerous in suspected cases of cerebal vasculitis without a confirmatory brain and leptomeningeal biopsy.

Mycobacteria

Mycobacterium (M.) tuberculosis (TB) meningitis was the first type of meningitis to be described clinically as *dropsy* of the brain in 1768, and subsequently shown to be inflammatory when meningeal tubercles and visceral tubercles were found to be identical in 1830. The tuberculoma, once the commonest intracranial tumor, is now exceptionally rare. The chief neurological signs and symptoms of tuberculous meningitis reflecting meningeal irritation are neck stiffness and positive Kernig sign; and raised intracranial pressure notably headache and vomiting with mental changes, seizures, and focal neurological signs. Arteritis is the rule in the vicinity of tuberculous lesions, wherein vessel walls are invaded by mononuclear cells, with the adventitia more heavily involved than the media [16]. The subintimal and intimal regions form a layer of homogenous fibrinoid material that later involves the media, and the vessel lumen is reduced by inflammatory cell exudation beneath the fibrinoid material, the end results

of which are reduction or complete obliteration of the lumen, proliferative endarteritis, and cerebral infarction. The vessels most heavily involved are those at the base of the brain and others in the Sylvian fissure. CNS involvement, which occurs in only 1% of TB infections, has the greatest mortality of any organ involvement], with fatality or severe residual mortality noted in up to one-half of cases of resultant TB meningitis [17]. Children and human immunodeficiency virus (HIV)-infected individuals are at special risk for developing CNS involvement. Polymorphisms in genes involved in the innate immune response such as the toll-like receptor 2 gene may influence dissemination and development of TB meningitis [17]. The pathogenesis of infection is usually due to rupture of a previously seeded meningeal, subpial, or subependymal focus. Chronic meningitis produces a thick, gelatinous inflammatory exudate that results in intimal thickening with obliterative vasculitis involving vessels at the base of the brain. Stroke occurs in 15% to 60% of affected patients and may be more common in HIV-infected individuals [4, 18]. Cerebral Infarction can be clinically silent, overshadowed by the meningeal features, or insidious in development. TB-related strokes show a prediction for the anterior rather than posterior circulation. The basilar exudates produce inflammatory vascular changes within the Circle of Willis. Distal ICA, proximal MCA and its perforating branches are particularly affected [17]. More severe meningitis carries a greater risk for vascular involvement. Vasospasm impacts strokes in the early period while proliferative intimal disease in a factor in later outcome. The immune reconstitution inflammatory syndrome (IRIS) can supervene during treatment for extraneural TB, unmasking latent TB meningitis and presenting with neurologic features including stroke. Hydrocephalus is a common sequela with often associated meningeal enhancement particularly along basal brain regions. Contrast-enhanced MRA is more sensitive in the detection of small vessel involvement. Pathologically-proven TB-associated CNS vasculitis has been described in five heterogeneous patients to date [16].

The diagnosis is confirmed by detection of TB bacilli in CSF using a Ziehl-Neelsen stain and culture, as well as a positive polymerase chain reaction (PCR). A positive yield is increased with large sample volumes, and ventricular CSF demonstrating an even higher yield than lumbar CSF. Interferon (INF)-γ releasing assays and TB antigen analysis can be studied in CSF [20]. Neuroimaging features of basilar exudate and hydrocephalus are suggestive.

Treatment involves induction therapy for two months with isoniazid, rifampin, pyrazinamide, and a fourth drug either streptomycin or ethambutol, followed by maintenance therapy with two drugs for an additional seven to ten months, typically isoniazid and rifampin. Fluoroquinolones are used in multidrug resistant cases. Adjunctive corticosteroids may be warranted in the first six to eight weeks. Aspirin is potentially useful in reducing stroke and mortality [20].

Spirochetal Agents

Spirochetes, which have a propensity to cause vasculopathy, can be associated with CNS vascular disease.

Syphilis

Syphilis is a spirochetal infection due to *Treponema (T.) pallidum*. Infection is acquired or congenital, with an estimated worldwide annual incidence of 12 million new adult cases [21].

About 4% to 10% of untreated patients develop CNS involvement. Symptomatic neurosyphilis presents with meningitis and meningovascular syndromes. Meningitis occurs in the first year of infection, producing basilar meningitis often culminating in stroke and vasculitis. Meningovascular syphilis comprises 39 to 61% of all symptomatic cases of neurosyphilis. It is characterized by obliterative endarteritis that affects blood vessels of the brain, spinal cord and leptomeninges, precipitating substantial ischemic injury. Often referred to as Heubner arteritis, it involves medium-sized to large arteries with lymphoplasmacytic intimal inflammation and fibrosis however there is a variant form termed Nissl-Alzheimer arteritis that characteristically affects small vessels and produces both adventitial and intimal thickening. Both types can lead to vascular thrombotic occlusions and cerebral infarction, with preferential involvement of the MCA

Meningovascular syphilis occurs months to years later associated with perivascular inflammatory endarteritis that leads to luminal narrowing and rarely dilatation. It typically involves large and medium-sized intracranial vessels, in particular the MCA, as may small intracranial vessels, altogether comprising 15% to 23% of cases [4].

Patients may experience prodromal symptoms of headache, vertigo, insomnia, and behavioral changes. Stroke symptoms developed in a subacute progressive pattern in one-quarter of patients. A recent Australian series [21] noted a prevalence of 4% for stroke or TIA among those with seropositive meningovascular syphilis.

The affected supraclinoid ICA and proximal vessels of the Circle of Willis show smooth or beaded segmental narrowing on neuroimaging, without common or cavernous ICA involvement atypical for atherosclerotic disease. Amorphous proteinacious firm masses with a necrotic center surrounded by inflammatory tissue termed gumma are noted in the brain of patients with tertiary syphilis and meningovascular disease.

The fluorescent *Treponemal* antibody (FTA-Abs), which detects specific *T. pallidum* antibodies later in the course of the disease, can be used to confirm the results of plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests which register reactivity to cardiolipin-lecithin-cholesterol antigen elaborated early in the course of syphilis exposure. The CSF in affected patients with neurosyphilis demonstrates pleocytosis, reactive VDRL, and increased intrathecal *T. pallidum* antibody index. All patients should be checked for HIV infection. Treatment of neurosyphilis is IV penicillin for 10 to 14 days with CSF monitoring in HIV-positive individuals to document normalization. Aspirin 81mg daily can be added for stroke prophylaxis.

The search for the cause of stroke in young adults should include meningovascular syphilis as a potential etiology. Sudden acute severe headache heralded onset of occlusion of bilateral vertebral and proximal basilar artery documented by MRA was noted in an African man who responded to thrombectomy with restoration of blood flow but succumbed to fatal pontine and subarachnoid hemorrhages [22]. Postmortem examination revealed RPR and a positive VDRL test in CSF with CNS vasculitis characterized by mural thrombi along the vertebrobasilar arteries with well-defined lines of Zahn of alternating layers of fibrin, platelet and red blood cell aggregates, and inflammatory cell infiltration of the arterial walls particularly in the adventitia. Another patient with abrupt onset of confusion, aphasia, and hemiparesis had carotid angiography that documented normal named cerebral vessels except for smaller than average caliber, with an abnormal complement fixation test of the blood and CSF, positive colloidal gold curve test, and leptomeningeal biopsy that showed lymphocytic infiltration, focal fibrosis, and chronic perivasculitis consistent with meningovascular syphilis [23].

Lyme Neuroborreliosis

The term Lyme neuroborreliosis was introduced by Veenendaal-Hilbers and colleagues [24] in 1988 to emphasize that CNS involvement due to Lyme disease. *Borrelia (B.) burgdorferi sensu lato* is the spirochete responsible for Lyme disease. *B. burgdorferi sensu stricto*, hereafter referred to a *B. burgdorferi*, is the species agent that causes Lyme disease and its neurological complications in North America; *B. garinii* and *afzelii* species predominante outside of North America. Virtually all cases result from an infected *Ixodes* tick bite. Lyme disease is a systemic infection with most patients manifesting the prototypical expanding skin lesion at the bite site termed erythema migrans. Both the CNS and peripheral nervous system (PNS) are targeted body organs. CNS vasculitis while exceedingly uncommon, probably accounted for less than 1% of all Lyme disease cases in endemic area. Patients with Lyme neuroborreliosis may present with cerebral infarction, intracerebral or subarachnoid hemorrhage, and TIA [25-30].

Only three patients reported in the literature with neurovascular clinical syndromes ascribed to CNS vasculitis in which detailed information was available including documentation of positive CSF Lyme serology, were ultimatey found to have verifiable vasculitis [28-30]. Two patients [28] presented with headache were ultimately noted to have histopathologically confirmed vasculitis on brain biopsy. Patient 3 of Oksi and colleagues [28] was an 11-year-old boy with headache and hyperactivity syndrome who developed gait difficulty concomitantly with a stroke visualized on brain MRI. Subsequent craniotomy and biopsy of the area of enhancement disclosed lymphocytic vasculitis of small vessels without fibrinoid necrosis, and CSF *B. burgdorferi* serology was positive. Headache and the MRI improved with intravenous antimicrobial therapy. Patient 2 of Topakian and coworkers [29] presented with headache, fatigue, malaise, nausea and vomiting first considered migrainous then psychosomatic until subsequent MRI disclosed ischemic brain infarctions, MRA was compatible with diffuse vasculitis, and CSF showed lymphocytic pleocytosis with positive oligoclonal bands, and diagnostic CSF and serum *B. burgdorferi* serology. Brain biopsy showed vasculitis involving leptomeningeal arteries comprised of lymphoplasmacytic vessel wall infiltration with focal necrosis. Epithelioid cells were beaded in multiple granuloma-like formations in the leptomeninges. There was symptomatic improved after a course of intravenous antimicrobial therapy. The third patient reported by Miklossy and colleagues [30], a 50-year-old man with leg spasticity and CSF pleocytosis for 15 months who progressed to hemiparesis and ventilatory support, was later found to have diagnostic *B. burgdorferi* serology in serum and CSF. Postmortem examination showed perivascular lymphocytic inflammation of leptomeningeal vessels, some of which displayed infiltration of the vessel walls, duplication of the elastic lamina, narrowing of lumina, and complete obstruction of some leptomeningeal vessels by organized thrombi.

There are rare instances of cerebral venous sinus thrombosis. *B. burgdorferi* infection in the CNS may be associated with lymphocytic cerebral vasculitis [31] preceding clues of which include, headache, arthralgia, myalgia, peripheral facial nerve palsy, and flu-like illness during the summer months. Laboratory evaluation may demonstrate meningeal enhancement on brain MRI although there appears to be a propensity of vasculitis to involve the posterior circulation. Lumbar CSF analysis typically reveals pleocytosis, increased protein, and intrathecal Lyme antibody production. CNS vasculitis due to Lyme neuroborreliosis should be treated with IV ceftriaxone 2 grams daily for four weeks via midline or permanent intravenous catheter (PIC) line with daily acidophilus to lower risk of *Clostridium difficile* colitis.

Leptospirosis

Leptospirosis is a worldwide zoonotic infection due to a spirochete from the genus *Leptospira*. It is transmitted by the urine of infected animals, and to people exposed to the pathogenic organism through contact with contaminated water, blood or soil. Infection is biphasic, with flu-like symptoms, followed by a second immune phase that can involve meningitis, jaundice with liver injury, and renal failure. Infection can be asymptomatic. About 90% of symptomatic infections manifest a benign biphasic febrile illness with 10% involving icteric Weil disease, and a fatality rate of 10%. Spirochetes are found in blood and CSF early in the course of the illness, and in the urine later in the disease. Leptospirosis more commonly causes meningitis or meningoencephalitis. Clinically apparent CNS vascular involvement is unusual but can result in stroke, hemorrhage and venous sinus thrombosis [32-34]. Diagnostic tests include screening serology via enzyme linked immunosorbant assay (ELISA), microscopic agglutination test, and polymerase chain reaction (PCR). Vasculitis is a recognized feature of this infection involving capillaries, with consequent edema, necrosis, and lymphocytic infiltration. Therapy involves primarily doxycycline however other effective antibiotics include cefotaxime, penicillin, ampicillin, and amoxicillin.

Relapsing Fever

Relapsing fever is spread by tick or lice bites. Louse-borne relapsing fever is due to *Borrelia recurrentis*. Tick-borne relapsing fever is due to at least 15 different *Borrelia* species. Clinical illness is characterized by febrile episodes accompanied by prominent headache and myalgia. Neurologic involvement is characterized by meningitis, facial palsy, myelitis, radiculitis, and focal or diffuse CNS dysfunction [35]. Neuropathologic changes involve edema, subarachnoid, and parenchymal hemorrhage, with perivascular mononuclear infiltrates. Spirochetes can be found in the cerebral microvasculature and interstitial spaces. Diagnosis is based on culture and stain. Treatment includes administration of doxycycline, oxytetracycline, or cephalosporin.

Other Bacterial Agents

Mycoplasma

Mycoplasmas are very small bacteria that have a plasma membrane boundary, but lack a cell wall. The nervous system is a major extrapulmonary target, and neurologic disease can occur after primary atypical pneumonia or *de novo* [36]. Mycoplasma encephalitis reflects direct brain invasion or an immune-mediated syndrome. There is evidence for vascular injury and microthrombi, with endothelial cell infection [36, 37]. Stroke occurs in both children and adults [38]. Diagnosis is based on serology and PCR when positive. Therapy involves a course of macrolide antibiotics, although neurologic involvement may be post-infectious and immune-mediated. Anticoagulation can be considered for thrombotic disease [].

Rosales and colleagues [38] described isolation of *Mycoplasma gallisepticum* and *synoviae* from the brains of poultry showing meningeal vasculitis and encephalitis, postulating a role for invasive mycoplasma species in human across the blood-brain barrier (BBB).

Bartonella

Bartonella are facultative gram negative intracellular bacteria that cause human and zoonotic disease. *Bartonella henselae* causes cat scratch disease. Several *Bartonella* species are associated with neuroretinitis, a retinal vasculitis. Immunocompromised hosts are vulnerable to more severe infections. *Bartonella* species can produce cutaneous and systemic vasoproliferative lesions [39]. *Bartonella henselae* is known to invade and colonize vascular endothelial cells, among others. Among a broad neurologic spectrum, there are rare cases of ischemic stroke and cerebral arteritis. Diagnosis is based on serology and PCR. Therapy involves doxycycline, or azithromycin.

Balakrishnan and colleagues [40] described isolation of Bartonella henselae DNA by PCR from a 12 year old's brain and blood with headaches, visual and auditory halluncations, anxiety, vision loss, bouts of paralysis, facial palsy, chronic insomnia, seizures, dizziness, cognitive dysfunction, and memory loss resulting in cerebal infaction so noted on brain biopsy tissue, postulating cerebral vasculitis, however frank vasculitic lesions were not observed.

Trophyrema whippelii

Tropheryma (T.) whippelii, a member of gram positive Actinobacteria family, is the etiologic agent of Whipple disease is the soil-borne gram positive bacillus. CNS involvement, which occurs in up to 43% of cases, may be the initial presentation of infection in 5% of cases [41]. CNS involvement occurs in the setting of active Whipple disease, as well as in those relapsing previously treated disease, and isolated CNS involvement [42]. Stroke presentation, while very rare, has been described [43] and should be in the differential diagnosis of CNS vasculitis. Stroke also occurs with leptomeningeal arterial fibrosis and thrombosis, or associated with endocarditis [41]. Clues to diagnosis are extraneural disease including weight loss, fever, polyarthritis, diarrhea, and uveitis. Oculomasticatory myorhythmia and supranuclear gaze palsy are characteristic neurologic features. The diagnosis can be confirmed with PCR and tissue biopsy that reveals macrophages that stain positive for glycogen with the Periodic Acid Schiff (PAS) assay, or the identification of the causative organism by immunoreactive antigen. Effective treatment includes administration third generation cephalosporins followed by long-term, on average two years of trimethoprim-suflamethoxazole (TMP-SMZ) and doxycycline.

Famularo and colleagues [44] identified arteral and arteriolar fibrosis, thrombosis, and thickening associated with inflammation of adjacent brain parenchyma and leptomeninges and cerebral vasculitis in a patient with cerebral Whipple's disease and stroke syndrome of without gastrointestinal involvement due to hematogenous spread of *Trophyrema whippelii*.

VIRAL PATHOGENS

Herpes Viruses

Herpes viruses are a large family of enveloped DNA viruses. Nine distinct agents affect humans, and all result in lifelong latent infection.

Varicella Zoster Virus

Varicella zoster virus (VZV) is the cause of childhood chickenpox and most children manifest only mild neurologic sequela, and an important infectious agent of associated blood vessel disease. After the infection resolves, the virus becomes latent in neurons of cranial and spinal ganglia of nearly all individuals, and has the propensity to reactivate in elderly adults and immunocompromised individuals to produce shingles. An uncommon but serious complication of virus reactivation is ischemic and hemorrhagic stroke. VZV vasculopathy affects both immunocompetent and immunocompromised individuals typically presenting with headache and mental status changes with or without focal neurological deficits and a spectrum of vascular damage from vasculopathy to vasculitis with stroke Both large and small vessels can be involved and MRI shows multifocal ischemic lesions, commonly at gray-white matter junctions. The diagnosis of VZV can be missed when symptoms and signs occur months after zoster, or in the absence of a typical zoster rash.

It is the only virus documented to replicate in human arteries, and is a recognized risk factor for ischemic stroke in children, and stroke and TIA in adults under age 40 [45, 46]. It is latent in cranial nerve, dorsal root, and autonomic nervous system ganglia. VZV but when re-activated, spreads to arteries of the brain and spinal cord to produce a large and small vessel vasculopathy. Cerebral blood vessels show multinucleated giant cells, Cowdry type A inclusion bodies with viral particles, and detectable VZV antigens and DNA, consistent with direct infection. In one series of 30 patients [7], 50% had both large and small vessel involvement; 37% showed small artery involvement and 13% manifested large artery invasion [47]. Clinical sequela includes infarction, aneurysm, hemorrhage, and ICA dissection [48]. Recently, VZV vasculopathy was recognized as an etiologic agent in patients presenting with giant cell arteritis (GCA) in spite of non-informative temporal artery biopsy. Vascular involvement can be unifocal or multifocal. Both immunocompetent and immunocompromised hosts are affected, although more commonly it is the immunocompromised patient. Infarctions can be superficial or deep. Gray-white matter junction lesions are suggestive. With regard to primary infection, there are unusual cases of cerebral infarction or hemorrhage in children. With regard to reactivated infection, vasculopathy can occur up to 6 months after a zoster outbreak. Herpes zoster ophthalmicus (HZO) can be followed weeks later by delayed contralateral hemiparesis, with segmental carotid siphon arteritis, typically in immunocompetent individuals.

Small vessel involvement may lead to central retinal or posterior ciliary artery involvement, with monocular vision loss. Neuroimaging in these VZV cases is typically abnormal. CSF is often abnormal with an increase in WBC and RBC, raised CSF protein content and present oligoclonal bands. The CSF VZV IgG antibody should be measured along with a sample for PCR analysis however the former is more likely to be informative in true cases. CNS VZV vasculopathy often presents with headache and progressive neurologic deficits without a history of zoster rash; rarely is VZV associated with spinal cord infarction. Treatment involves antiviral therapy with IV acyclovir however oral valcyclovir can be employed to extend the length of treatment in more profoundly affected or refractory cases due to concomitant HIV-infection.

Thirteen patients with VZV-related vasculopathy with detailed clinicopathologic data including histological findings of vasculitis have been described in the literature. VZV DNA and VZV-specific antigen were found in three of five cerebral arteries examined with histologically-confirmed CNS vasculitis involving the circle of Willis. Patient 1 of Eidelberg and colleagues [49] who presented with headache and herpes zoster ophthalmicus (HZO) rash

was deemed to have CNS vasculitis based upon complete occlusion of the MCA and so treated, however postmortem examination showed no evidence of vasculitis. One patient with contralateral hemiplegia one month after HZO was found at postmortem examination to have endarteritis of unilateral ACA, MCA and PCA [50] with VZV DNA from the involved vessels.

Cytomegalovirus

Cytomegalovirus (CMV) replicates in leukocytes and vascular endothelial cells during primary infection with single patient reports of CMV associated with vasculitis. Venous involvement can be found in addition to occlusive arteritis. Affected individuals are usually HIV-positive or an immunocompromised host [51]. Diagnosis involves serological studies, PCR, culture, and histopathological tissue analysis for the causative organism. Therapy includes IV ganciclovir, foscarnet, or a combination of both. One recently described elderly woman with CMV encephalitis [52] later developed a post-infectious primary CNS vasculitis .

Koeppen and coworkers [53] described rapidly progressive CNS and peripheral nervous system (PNS) deterioration two years after chemotherapy for small cell undifferentiated lymphoma in whom postmortem examination demonstrated occlusive arteritis in gray and white matter with involvement of veins indicative of vasculitis, in addition to Cowdry A inclusions and chorioretinitis.

Herpes Simplex and Epstein-Barr Virus

Herpes simplex virus (HSV), types 1 and 2, and *Epstein Barr virus* (EBV) have been associated with CNS vasculitis [54, 55], however vessel wall contrast enhancement may be a clue in suspected patients [55] and a positive findings in CSF PCR is adequate to justify antiviral therapy. However, in contrast to VZV where reactivation is the mechanism of causation, CNS vasculitis may be problematic due to latency of infection. Kano and colleagues [56] described EBV-associated CNS vasculitis in brain biopsy tissue of a patient with rapid CNS deterioration and positive EBV DNA in CSF.

Retroviruses

Human Immunodeficiency Virus

Approximately 1% to 5% of individuals infected with human immunodeficiency virus (HIV) are at risk of developing a stroke due to opportunistic infections, coagulopathy, cardioembolism, HIV-associated vasculopathy and frank vasculitis [57]. Moreover, HIV-associated arterial vasculitis is believed to account for 13% to 28% of ischemic strokes. CNS vasculitis which is estimated to occur in less than 1% of cases of HIV infection is a diagnosis of exclusion. Typically patients are in an advanced stage of the infection. HIV can be associated with a granulomatous inflammation involving small arteries and veins within the brain and leptomeninges. HIV patients with vasculitis should be assessed for cryoglobulins and accompanying infection especially TB, syphilis, CMV, VZV, hepatitis B and C virus (HBV and HCV), or a drug induced vasculitis. Therapy typically involves highly active antiretroviral therapy (HAART), with corticosteroids reserved for refractory cases due to vasculitis.

Early in the HIV and the acquired immune deficiency syndrome (AIDS) epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their

associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections. The two postulated periods in the neurobiology of HIV when autoimmune disease manifestations and cerebral vasculitis can occur are shortly after seroconversion and before the spread of productive infection, and after initiation of HAART in association with the immune reconstitution inflammatory syndrome (IRIS). The timing of early HIV invasion has been difficult to ascertain based on the presence of one or well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis, HIV-associated dementia and AIDS-dementia complex, all of which are indicative of symptomatic infection. Six presymptomatic HIV-seropositive drug abusers by Gray and colleagues [58] had non-necrotizing cerebral vasculitis at postmortem examination.

HTLV-1

Human T-cell lymphotropic virus-type 1 (HTLV-1) was the first described human retrovirus. It causes adult T-cell leukemia and lymphoma, as well as a progressive myelopathy referred to as tropical spastic paraparesis-HTLV-1 associated myelopathy in less than 1% of infections. Neurological syndromes associated with HTLV-1 infection appear to be due to active and selective expansion of retrovirus infected T-cells that harbor provirus that selectively express HTLV-1 proteins such as Tax. In particular, activated cytotoxic CD8+ T-cells are increased. Perivascular inflammation is a frequent histopathological feature. The laboratory diagnosis of HTLV-1 infection is based on serological and PCR studies. There is no proven antiviral therapy. Ma and coworkers [59] reported vasculitis in brain biopsy tissue of a patient with HTLV-1 infection.

Hepatitis Agents

Hepatitis C is estimated to affect 170 million people worldwide with extrahepatic involvement that occurs in 38% to 74% of cases. Hepatitis C is associated with cryoglobulinemia, arthritis, and palpable purpura. There is an immune response to the Fc portion of immunoglobulin, characterized by the Wa idiotype. The resulting immune complex which contains virus, idiotypic antibody, and antibody precipitates in the cold and produces a small vessel vasculitis. HCV can cause CNS vasculitis independent of cryoglobulinemia, and CNS vasculitis may be the first clinical manifestation of hepatitis C infection.

Affected patients present with progressive headache, multiple strokes, and typical angiographic patterns. Therapy includes the antiviral agents interferon (IFN), ribavirin, sofosbuvir, protease inhibitors, and corticosteroids. Both HBV and HCV have been associated with polyarteritis nodosa (PAN) [60] that typically involves the peripheral nervous system (PNS), but unusual cases may involve the CNS. In such cases antiviral therapy is added to corticosteroids, and cyclophosphamide in more severe cases. This might involve the virostatic agent lamivudine or INF-alpha for HBV and ribavirin for HCV [61]. Plasma exchange and rituximab can be added in specific cases as needed.

Parvovirus B19

Parvovirus B19 is a small non-enveloped DNA virus that only infects humans. It causes erythema infectiosum also known as fifth disease, a benign childhood condition characterized by a classic slapped-cheek appearance. It can cause anemia with pre-existing disease as well as arthritis. The cellular receptor for parvovirus B19 is an antigen of the P blood group present on endothelial cells and erythroid progenitor cells. Rare patients with CNS vasculitis have been reported in association with Parvovirus B19 infection [62]. The diagnosis is based on serological studies and PCR testing. There is no specific antiviral therapy for Parvovirus B19 infection; however both intravenous immune globulin (IVIG) and corticosteroids have been used therapeutically.

West Nile Virus

West Nile virus is a flavivirus typically transmitted by the bite of infected culex mosquitos. Less than 1% of patients develop invasive neurological disease that includes meningitis, encephalitis, and resultant flaccid paralysis, with rarely reported cases of ischemic infarction and CNS vasculitis [63-65] and occlusive retinal artery vasculitis. Patients with a history of diabetes and alcohol abuse, and older individuals are at increased risk for ischemic complications. Diagnosis is based on IgM antibody and viral RNA detection, as well as virus isolation. There is no antiviral therapy, but IVIG has been beneficial in individual patients.

Zika Virus

Zika virus is an arbovirus belonging to the *Flaviviridae* family. Younger has reviewed the epidemiology of Zika virus [66]. Originally isolated in Uganda, known to cause mild clinical symptoms similar to those of dengue and chikungunya, Zika is transmitted by different species of *Aedes* mosquitoes. Non-human primates and possibly rodents play a role as reservoir. Direct interhuman transmission has been reported to occur perinatal, through blood transfusion and sexually. The first human cases were reported in Africa and, but recent outbreaks in several regions of the world including including Brazil, highlighted the needs of the scientific and public health community to consider it as an emerging global threat.

Its clinical profile is that of a dengue-like febrile illness but recently associated Guillain-Barre syndrome and microcephaly have appeared. There is neither a vaccine nor prophylactic medications available to prevent Zika virus infection so current public health recommendation advise pregnant women to postpone travel to areas with Zika viral infection is epidemic, and if not, to follow steps to avoid mosquito bites to avert fetal brain injury associated with intrauterine infection. Viral RNA indicating Zika virus, Chikungunya virus, and Dengue infection can be pathogenically isolated from the CSF of adults with neurological symptoms with meningitis or encephalitis, Guillain-Barré Syndrome, and CNS vasculitis.

FUNGAL PATHOGENS

Aspergillus

Aspergillosis is the most common invasive mold infection worldwide. It typically causes disease in immunocompromised hosts, although CNS vasculitis and stroke occur in immunocompetent patients [67, 68]. The major human pathogens are from the *Aspergillus fumigatus*, *niger* and *flavus* species. Patients with hematologic malignancies and a history of bone marrow transplantation can have fulminant CNS courses with mortality rates of 85% to 99% [4].

The *Aspergillus* organisms invade blood vessels with resultant production of proteases that weaken the vessel wall leading to aneurysm formation [69]. The course can be more chronic and insidious in those with lesser degrees of immune compromise, such as due to diabetes mellitus. Spread to the CNS occurs via hematogenous routes from the lung, or by direct extension through the paranasal sinuses and orbits. CNS involvement which occurs in 10% to 50% of systemic infections includes meningoencephalitis and intracerebral hemorrhage, as well as, vasculopathy, and mycotic aneurysm formation leading respectively to stroke and potentially fatal subarachnoid hemorrhage with greater involvement of penetrating than larger named vessels.

Aspergillus infection should be considered in immunocompromised hosts with pulmonary disease and either ischemic or hemorrhagic stroke. The diagnosis can be difficult since CSF cultures are positive in less than 50% of cases, and PCR is investigational. Two antigen assays, each for biomarkers including galactomannan and beta-D-glucan, have not been standardized in the CSF. Tissue biopsy can be confirmatory. Brain neuroimaging may demonstrate ring-enhancing lesions, meningeal enhancement, and ischemic or hemorrhagic stroke. Therapy involves oral voriconazole and surgical resection of focal cerebral and extraneural sites of involvement.

Candida

Candida species are part of normal human flora and thus typically are not pathogenic unless there is mitigating systemic immune compromise. Neutropenia is a major risk factor for invasive disease. *Candida* is considered a yeast infection with *Candida albicans* the most common agent in humans. It invades small blood vessels and can be associated with thrombosis and infarction. Neurologic involvement most often takes the form of meningitis that may predispose to basilar artery thrombosis [70]. One affected patient with HIV/acquired immune deficiency virus syndrome (AIDS) and subacute meningitis who was treated empirically for tuberculosis and initiated on HAART therapy developed fatal worsening due to postmortem-proven basilar *Candida* meningitis and cerebral vasculitis characterized by CD8+ T-cell infiltration and microinfarcts, consistent with IRIS [77]. The diagnosis of Candida infection is based on a positive culture and informative PCR, and suggestive findings on antigen assays to mannan and beta-D glucan albeit not routinely performed. Effective treatment depends upon the age and severity of infection with lipid formulations of amphotericin, fluconazole, or echinocandin.

Lipton and colleagues [71] described CNS vasculitis at postmortem examination in 48% of 29 patients with systemic candidiasis, only 21% of whom had suspected antemortem involvement noting that immunosuppression represent a risk factor for both systemic and cerebral mycoses.

Coccidioides immitis

Coccidioides immitis is a soil based fungus endemic to the arid Southwest and Latin America. Infection may be asymptomatic or the cause of mild pulmonary issues such as occurs in valley fever. About one-half of disseminating cases involve the CNS resulting in basilar meningitis with a local vasculitis of small and medium arteries, and occasionally larger ones that is more likely to occur in immunocompromised hosts [72]. Cerebral infarction complicates about 40% of patients with *coccidioides* meningitis leading to alteration of mental status and emergency of focal deficits [4]. Stroke can occur years later following the initial infection [72]. In general, acute infectious related injury can predispose to vasculitic changes that include transmural inflammation with thrombosis and fibrinoid necrosis, while chronic injury leads to intimal thickening, proliferation, and narrowing of the lumen with little or no inflammation.

CSF culture is positive in 33% of cases, often in association with eosinophilic pleocytosis. Complement fixation is positive in about 40% of serum and CSF specimens, but seroconversion can take up to 12 weeks. Treatment involves high-dose fluconazole followed by maintenance therapy. Voriconazole is a second line agent. A self-limited course of corticosteroids can be given in the setting of cerebral infarction to reduce inflammation.

Eron and colleagues [73] described vasculitis and encephaltic as a complications of *Coccidioides immitis* infection of the CNS in six cases of apparent, and four cases of histologically proven vasculitis, including one with vasculitis and encephalitis associated with coccidiodal meningitis. Vasculitic complications includes mental status changes, aphasia, hemianopia, and hemiparesis.

Cryptococcus neoformans

The yeast form, *Cryptococcus neoformans* is the commonest cause of fungal meningitis [4]. Vessels of the circle of Willis are most affected by the resultant basilar exudate. Vascular involvement occurs early or late in 4% to 32% of cases. Diagnosis is made by the presence of CSF cryptococcal antigen, India ink stain, and culture. Treatment involves induction therapy with intravenous amphotericin and flucytosine for 2 weeks followed by consolidation with fluconazole once CSF cultures are negative. Corticosteroids may offer a benefit in the setting of stroke [74].

Exserohilum rostratum

Exserohilum rostratum is a dematiaceous fungus and black mold that does not typically cause human disease. It is a major contaminant in iatrogenic infections due to mold contamination of methylprednisolone acetate. There was one fatal case of meningitis and CNS vasculitis in an immunocompetent host who received a cervical epidural steroid injection for chronic neck pain [80]. The diagnosis is based on culture and PCR of CSF. Recommended therapy is liposomal amphotericin B and voriconazole, with monitoring of drug levels [75].

Lyons and colleagues [76] described angioinvasive septate fungal hyphae associated with diffuse vasculitis at postmortem examination in the brainstem of a patient with fatal

Exserohilum meningitis following cervical epidural methylprednisolone injection for new occipital headaches.

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungus that is endemic in the Ohio and Mississippi River Valley, as well as parts of Latin America, Asia, and Africa [4, 77]. Although infection in immunocompetent hosts may remain asymptomatic or lead to mild lower respiratory tract illness, others can experience disseminated infection with CNS involvement in up to 20% of cases. The latter most commonly manifests meningitis however strokes may accompany associated infective *histoplasma* endocarditis or associated meningovascular disease with ensuing mortality of 11% to 100%. CSF culture and antigen studies which show evidence of CNS infection can be supported by anti-histoplasma antibodies. Treatment includes liposomal amphotericin followed by itraconazole or fluconazole for at least one year.

Mucormycosis

Mucormycosis is due to infection by filamentous fungi of the order *Mucorales* and class *Zygomycetes*. They are ubiquitous organisms in bread mold, soil, manure, and decaying vegetation, and the second commonest invasive mold infection [78, 79]. *Rhizopus, Mucer, and Lichtheimia* are the most common genera to cause mucormycosis. Immunocompromised hosts are at particular risk. Underlying conditions include diabetes mellitus, hematologic malignancy, trauma, solid cancers, and solid organ transplants.

Sites of infection include lung, skin, gastrointestinal tract, and the rhino-orbito-cerebral region. Iron is an important component in this infection. These fungi contain spore coat homolog proteins that are unique, and required for angioinvasion. The result of this blood vessel invasion is vessel thrombosis and tissue necrosis. The rhino-orbito-cerebral form may produce suggestive necrotic nasal or sinus eschars. Patients may experience carotid or basilar artery thrombosis, cavernous sinus thrombosis, or intracerebral hemorrhage [80, 81].

Diagnosis is based on clinical suspicion confirmed by biopsy, scraping, or culture. PCR is being evaluated. Treatment involves a combination of surgery and systemic therapy. Liposomal amphotericin B is favored therapy however thiazoles and posaconazole antibiotics have been used in selected individuals.

PARASITIC PATHOGENS

Taenia solium

Cysticercosis due to infection with the larval stage of the pork cestode tapeworm *Taenia solium* is the commonest CNS parasite accounting for 10% of stroke cases in endemic areas, and a major cause of headache and seizures. Lenticular striate lacunar infarcts are more common than large artery stroke, however TIA and intracranial hemorrhages also occur [4, 82-84]. Among 28 patients with subarachnoid cysticercosis, 15 (53%) had angiographic evidence of cerebral arteritis, 12 (80%) of whom had a stroke syndrome (P=0.02). Eight of the 15 patients (53%) with cerebral arteritis had evidence of cerebral infarction on MRI, whereas only one patient without cerebral arteritis had cerebral infarction (P=0.05). The most commonly

involved vessels were the MCA and posterior cerebral artery (PCA). Small vessels are preferentially affected, with superficial cortical vessel thrombosis, occlusive endarteritis, and focal arteritis. Larger circle of Willis vessels are involved when severe arachnoiditis is present. Diagnosis involves antibody testing and suggestive findings on neuroimaging; however antigen testing is not routinely used. Anti-helminthic therapies include the benzimidazole drug albendazole and the anti-helminthic drug praziquante with corticosteroids.

Plasmodium falciparum

Plasmodium falciparum is a unicellular parasitic protozoan that infects humans causing more severe forms of malaria. The disease is typically transmitted by the bite of an infected female *Anopheles mosquito.* Inoculated sporozoites infect and multiply in liver cells, then differentiate into merozoites that are released and invade red blood cells. Infection leads to expression of adhesive surface proteins that cause the red cells to stick to the walls of small blood vessels. Intercellular adhesion molecule (ICAM)-1 is a major host binding site.

Falciparum malaria is a leading cause of morbidity and mortality in tropical countries. Cerebral malaria is the most sever neurologic manifestation]. It is defined by coma that is not due to seizures, hypoglycemia, or any other identifiable cause, and that is associated with a positive blood smear for parasitized red blood cells.

Pathophysiology is believed to be due to parasitic sequestration in cerebral microvessels. As infected red cells adhere to the endothelium, they cause further erythrocyte agglutination along with platelet clumping. There is endothelial activation, and direct cytotoxic injury. Perfusion is abnormal, and tissue oxygenation is compromised. There may also be injury mediated by soluble factors including various chemokines, cytokines, nitric oxide, and quinolinic acid. Diagnosis is based on blood smear, and antigen-based rapid diagnostic tests. Patients diagnosed with uncomplicated malaria can be effectively treated with the oral antimalarial drug chloroquine phosphate (Aralen™) or hydroxychloroquine (Plaquenil™). Patients who are considered to have severe disease should be treated aggressively with parenteral antimalarial therapy. Treatment of severe malaria involves parenteral quinidine gluconate given by continuous infusion for at least 24 hours in an intensive care setting plus one of the following: doxycycline, tetracycline or clindamycin orally or IV followed by oral administration for a full course of seven days.

There is an investigational new drug protocol that can be obtained by contacting the Centers for Disease Control and Prevention (CDC) that employs artesunate followed by one of the following: atovaquone-proguanil (Malarone™), doxycycline (clindamycin in pregnant women), or mefloquine (Lariam™).

Schistosoma mansoni

This Trematoda infection which involves a flatworm is endemic to sub-Saharan Africa and South America. There is percutaneous penetration of cercariae in the invasive stage followed by mating worms that inhabit the inferior mesenteric veins where they excrete eggs in the adult stage. Neurologic involvement occurs in later stages of infection wherein adult worms can be found in spinal meningeal veins and the intracranial venous system [94]. Ectopic eggs migrate

to the brain provoking granuloma formation. Cerebrovascular lesions are found in 20% of patients from postmortem series.

CNS vasculitis occurs in both early and later stages of *Schistosoma* infection [85, 86] associated with multiple infarctions, marked eosinophilia, and a corticosteroid response reflective of eosinophil-mediated injury. Presumptive diagnosis is suggested by a known travel history and compatible clinical presentation combined with serological testing and documentation of eggs in the stool. Treatment involves praziquantel.

Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular protozoan that causes toxoplasmosis. During the initial acute phase of the infection, rapidly dividing tachyzoites spread throughout the host. The development of an effective cellular immune response suppresses the replication of tachyzoites and eradicates most of them, ending the acute phase of the infection. In the brain, the parasites undergo conversion to bradyzoites, which remain viable in the form of cysts because of the low levels of class I MHC and, in addition, the parasites within the cyst are surrounded by the parasitophorous vacuole that is enclosed by a cyst wall, thus little antigen escape into the cytoplasm of the cyst-containing host cell. The organisms reproduce slowly throughout the life of the host and can remain viable within intact nerve cells. Cyst rupture occurs rarely and, in immunocompetent individuals, a rapid immune response leading eventually to microglial nodule formation limits the damage to small inflammatory foci. However, in immunocompromised hosts, cyst rupture may reactivate the infection, leading to the conversion of bradyzoites to the active and rapidly replicating tachyzoites and development of severe tissue injury. Therefore, the CNS may be affected in congenital toxoplasmosis, as a primary infection in immunocompetent individuals, or as an opportunistic infection in immunosuppressed individuals. Thus, most CNS infections represent reactivation of old lesions and hematogenous spread from prior infections instead of primary infection.

The resulting disease is widely distributed worldwide among domestic animals and humans. The oocyst form is excreted in cat feces and can be the source of infection. Eating infected raw or undercooked meat is another source of infection. Most infections are asymptomatic however immunocompromised hosts are particularly vulnerable to clinical disease. Toxoplasmosis is the leading cause of focal CNS disease in patients with HIV/AIDS and low CD4+ T-cell counts.

Congenital toxoplasmosis causes the characteristic eye lesion termed chorioretinitis, cerebral calcifications, hydrocephalus, and CSF pleocytosis. The pathological features include periventricular microglial nodules surrounded by lymphocytic vasculitis and necrotic foci. Toxoplasma encephalitis shows well circumscribed areas of hemorrhage and necrosis, with vascular thrombosis and present tachyzoites. The resulting clinical presentation is usually headache with constitutional symptoms that progress to encephalopathy and focal neurological deficits.

Toxoplasmosis as an opportunistic infection in immunosuppressed individuals has been reviewed by Pittella [87]. In HIV-infected patients, the disorder presents as a mass lesion, usually multiple, with the basal ganglia, thalamus, and the cerebral gray and white matter junctions being the preferred sites. The lesions consist of well-defined areas of coagulative necrosis, with or without hemorrhage, containing karyorrhectic debris. Blood vessel changes

are common, characterized by necrosis, vasculitis, and thrombosis. Mononuclear inflammatory cells and reactive astrocytes in variable numbers are seen surrounding the necrosis. Bradyzoites and tachyzoites are present in large numbers, the former at the periphery of the lesion and the latter within the necrosis. The immunohistochemical identification of tachyzoites is especially useful when bradyzoites are not seen. In more chronic lesions, macrophages may surround the necrosis associated or not with calcification and parasites are reduced in number. In treated patients, the lesions undergo cystic change and are surrounded by macrophages, scanty inflammatory infiltrate, and astrocytosis.

Serological testing is generally positive, but may not be so in immunocompromised patients. Parasites can sometimes be observed in biopsy-stained tissues and CSF however a positive CSF PCR is helpful. Culture is typically too time-consuming to perform. Compatible features of the disorder on brain MRI include single or multiple lesions in the basal ganglia and white matter, with mass effect and homogeneous or ring enhancing lesions. However, brain neuroimaging may also be normal when there is diffuse CNS involvement.

Treatment includes pyrimethamine, sulfadiazine, and folinic acid administered for six weeks and treatment of any underlying immunocompromised condition. Alternative therapy includes trimethoprim-sulfamethoxazole and clindamycin for patients allergic to sulfa medication.

RICKETTSIAL PATHOGENS

Rickettsiae (*R.*) are obligate intracellular gram negative coccobacillary agents that multiply in eukaryotic cells. Phylogenetically they fall between bacteria and viruses. Both mammals and arthropods are natural hosts. Within the genus *rickettsiae*, there are three biogroups that cause illness: the spotted fever group, the typhus group, and the scrub typhus biogroup. *Rickettsiae* adhere to, and invade endothelium with increased vascular permeability, leakage, edema, and hypotension. They are capable of eliciting a generalized vasculitic response in the CNS.

Rickettsia rickettsiae

R. Rickettsia cause Rocky Mountain spotted fever (RMSF). More than 90% of infections in the United States occur from April through September via tick bite. The tick vectors are larger soft ticks including *Dermacenter andersoni* and *variabilis*; and *Amblyomma americanum*. Within the CNS the vasculitis provokes a damaging immune response that is predominantly cell-mediated. The overall associated mortality rate is about 4%.

Symptomatic infection involves severe headache, abdominal pain, persistent fever, peripheral macular centripetal rash, confusion and myalgia. The classic triad is fever, headache, and rash. Conjunctivitis may also be noted. Neurologic involvement includes meningoencephalitis, focal deficits, and coma. Suggestive laboratory abnormalities are thrombocytopenia, hyponatremia, and elevated liver enzymes. A deficiency of glucose -6-phosphate dehydrogenase enzyme is associated with more severe infection.

Diagnosis is made on clinical grounds, confirmed by positive serology. Therapy involves doxycycline for 7 to 14 days.

Kumar and Pramod [88] described a young Indian male with high fever and severe acute headache followed by mental change who developed facial weakness, hyperreflexia and right posterior cerebral and bilateral thalamopeducular infarcts on computerized tomography (CT) of the brain, with filling defects in the origin in the P1 segment of the right PCA on CTA. CSF showed lymphocytic pleocytosis and a positive Weil-Felix test for the proteus antigen OX19. The patient was diagnosed with cerebral vasculitis, however confirmatory histopathology was not obtained.

Scrub Typhus

Scrub typhus (Tsutsugamushi disease) involves infection with different species of *Orientia tsutsugamushi*. Most cases occur in the southwest Pacific and Southeast Asia. Infection occurs with the bite of the larval form of trombiculid mites or chiggers, resulting in small vessel perivasculitis. The ensuing illness is typically mild and self-limited, but can progress to life-threatening neurological illness [89-91] including meningoencephalitis. Suggestive features of the disorder include necrotic eschar at the site of the mite bite so noted in 50% of case; generalized lymphadenopathy, and mild truncal rash. CSF shows a pattern of aseptic meningitis. Serologic testing is available, and therapy involves doxycycline or another tetracycline.

CONCLUSION

Underlying infections are important to consider in patients with CNS vasculitis and when seriously suspected warrant prompt and thorough investigation. Selected antimicrobial therapy combined with supportive care can be life-saving however a self-limited course of corticosteroids can lead to prompt reduction in associated inflammation and preservation of neurological integrity.

REFERENCES

[1] Scolding, N., Wilson, H., Hohlfeld, R., et al. Chapter 35. Cerebral vasculitis. In: *European Handbook of Neurological Management* 2nd Ed. N. E. Gilhus, M. P. Barnes, M. Brainin, eds. Wiley-Blackwell: New Jersey, 2010; p. 485-489.

[2] Kraemer, M., Berlit, P. Systemic, secondary and infectious causes for cerebral vasculitis: clinical experience with 16 new European cases. *Rheumatol. Int.* 2010; 30: 1471-1476.

[3] Jennette, J. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin. Exp. Nephrol.* 2013; 17:603-606.

[4] Chow, F., Marra, C., Cho, T. Cerebrovascular Disease in Central Nervous System Infections. *Semin. Neurol.* 2011; 31:286-306.

[5] Klein, M., Koedel, U., Pfefferkorn, T., et al. Arterial cerebrovascular complications in 94 adults with acute bacterial meningitis. *Critical Care* 2011; 15:R281.

[6] Kastenbauer, S., Pfister, H. W. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in series of 87 cases. *Brain* 2003; 126:1015-1025.
[7] Panicio, M., Foresto, R., Mateus, L., et al. Pneumococcal Meningitis, Cerebral Venous Thrombosis, and Cervical Arterial Dissection: A Run of Bad Luck? *The Neurohospitalist* 2013; 3:20-23.
[8] Schut, E., Brouwer, M., de Gans, J., et al. Delayed cerebral thrombosis after initial good recovery from pneumococcal meningitis. *Neurology* 2009; 73:1988-1995.
[9] Kato, Y., Takeda, H., Dembo, T., et al. Delayed recurrent ischemic stroke after initial good recovery from pneumococcal meningitis. *Intern. Med.* 2012; 51:647-650.
[10] Choucair, J. Infectious Causes of Vasculitis. In: *Updates in the Diagnosis and Treatment of Vasculitis*. L. I. Sakhas, C. Katsiori eds., 2013; http//dx.doi.org/10.5772/ 55189.
[11] Chaudhary, G., Lee, J. Neurologic complications of infective endocarditis. *Curr. Neurol. Neurosci. Rep.* 2013; 13:380.
[12] Bor, D., Woolhandler, S., Nardin, R., et al. Infective endocarditis in the US, 1998-2009: A nationwide study. *PLOS* 2013; 3(8):e60033.
[13] Hess, A., Klein, I., Lavallee, P., et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. *AJNR Am. J. Neuroradiol.* 2013; 4: 1579-1584.
[14] Ruttmann, E., Willeit, J., Ulmer, H., et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. *Stroke* 2006; 37:2094-2099.
[15] Berit P. Isolated angiits of the CNS and bacterial endocarditis: similarities and differences. *J Neurol* 2009; 256:792-795.
[16] Smith, H. V., Daniel, P. Some clinical and pathological aspects of tuberculosis of the central nervous system. *Tuberculosis* 1947; 28: 64-80.
[17] Thwaites, G., Van Toorn, R., Schoeman, J. Tuberculous meningitis: more questions, still too few answers. *Lancet Neurol.* 2013; 12:999-1010.
[18] Pasticci, M. B., Paciaroni, M., Floridi, P., et al. Stroke in patients with tuberculous meningitis in a low TB endemic country: an increasing medical emergency? *New Microgiologica* 2013; 36:193-198.
[19] Lammie, G., Hewlett, R., Schoeman, J., et al. Tuberculous cerebrovascular disease: a review. *J. Infect.* 2009; 59:156-166.
[20] Thwaites, G. Advances in the diagnosis and treatment of tuberculous meningitis. *Curr. Opin. Neurol.* 2013; 26:295-300.
[21] Cordato, D., Djekic, S., Taneja, S., et al. Prevalence of positive syphilis serology and meningovascular neurosyphilis in patients admitted with stroke and TIA from a culturally diverse population. *J. Clin. Neurosci.* 2013; 20:943-947.
[22] Feng, W., Caplan, M., Matheus, M., et al. Meningovascular syphilis with fatal vertebrobasilar occlusion. *Am. J. Med. Sci*. 2009; 338: 169-171.
[23] Rabinov, K. R. Angiographic findings in a case of brain syphilis. *Radiology* 1963; 80: 622-624.
[24] Veenendaal-Hilbers, J. A., Perquin, W. V. M., Hoogland, P. H., et al. Basal meningovasculitis and occlusion of the basilar artery in two cases of Borrelia burgdorferi infection. *Neurology* 1988; 38: 1317-1319.
[25] Romi, F., Kråkenes, J., Aarli, J., et al. Neuroborreliosis with vasculitis causing stroke-like manifestations. *Eur. Neurol.* 2004; 51:49-50.
[26] Schmiedel, J., Gahn, G., von Kummer, R., et al. Cerebral vasculitis with multiple infarcts caused by Lyme disease. *Cerebrovasc. Dis.* 2004; 17:79-80.

[27] Jacobi, C., Schwark, C., Kress, B., et al. Subarachnoid hemorrhage due to *Borrelia burgdorferi*-associated vasculitis. *Eur. J. Neurol.* 2006; 13:536-538.

[28] Oksi, J., Kalimo, H., Marttila, R. J., et al. Inflammatory brain changes in Lyme borreliosis: a report on three patients and review of literature. *Brain* 1996; 119:2143-2154.

[29] Topakian, R., Stieglbauer, K., Nussbaumer, K., et al. Cerebral vasculitis and stroke in Lyme neuroborreliosis. Two case reports and review of current knowledge. *Cerebrovasc. Dis*. 2008; 26: 455-461.

[30] Miklossy, J., Kuntzer, T., Bogousslavsky, J., et al. Meningovascular form of neuroborreliosis: similarities between neuropathological findings in a case of Lyme disease and those occurring in tertiary neurosyphilis. *Acta Neuropathol*. 1990; 80:568-572.

[31] Oksi, J., Kalimo, H., Marttila, R., et al. Inflammatory brain changes in Lyme borreliosis. *Brain* 1996; 119:2143-2154.

[32] Watt, G., Manaloto, C., Hayes, C. Central nervous system leptospirosis in the Philippines. *Southeast Asian J. Trop. Med. Pub. Health* 1989; 20:265-269.

[33] George, P. Two uncommon manifestations of leptospirosis: Sweet's syndrome and central nervous system vasculitis. *Asian Pacific J. Trop. Med.* 2001; 83-84.

[34] Turhan, V., Senol, M., Sonmez, G., et al. Cerebral venous thrombosis as a complication of leptospirosis. *J. Infection* 2006; 53:e247-e249.

[35] Cadavid, D. Chapter 38 Lyme disease and relapsing fever. In: *Infections of the Central Nervous System*. 3rd Ed. W. M. Sheld, R. J. Whitley, C. M. Marra, eds. Lippincott Williams and Wilkins, Philadelphia, 2004; 659-690.

[36] Rhodes, R., Monastersky, B., Tyagi, R., et al. Mycoplasma cerebral vasculopathy in a lymphoma patient: Presumptive evidence of *Mycoplasma pneumonia* microvascular endothelial cell invasion in a brain biopsy. *J. Neurol. Sci.* 2011; 309:18-25.

[37] Koskiniemi, M. CNS manifestations associated with *Mycoplasma pneumoniae* infections: Summary of cases at the University of Helsinski and review. *Clin. Infect. Dis.* 1993; 17(Suppl. 1):S52-S57.

[38] Rosales RS, Puleio R, Loria GR, et al. Mycoplasmas: Brain invaders? *Res Vet Sci* 2017; 113:56-61.

[39] Spinella, A., Lumetti, F., Sandri, G., et al. Beyond Cat Scratch disease: A case report of *Bartonella* infection mimicking vasculitic disorder. *Case Reports Infect. Dis.* 2012; doi: 10.1155/2012/334625.

[40] Balakrishnan N, Ericson M, Maggi R, et al. Vasculitis, cerebral infarction and persistent Bartonella henselae infection in a child. *Parasit Vectors* 2016; 9:254.

[41] Peters, G., du Plessis, D., Humphrey, P. Cerebral Whipple's disease with a stroke-like presentation and cerebrovascular pathology. *J. Neurol. Neurosurg. Psychiatry* 2002; 73: 336-339.

[42] Compain, C., Sacre, K., Puéchal, X., et al. Central nervous system involvement in Whipple disease: Clinical study of 18 patients and long-term follow-up. *Medicine* 2013; 92:324-330.

[43] El-Helou, J., Saliba, G., Kolev, I., et al. Neuro-Whipple confirmed five years after a presumptive diagnosis of a primitive CNS vasculitis. *J. Neurol.* 2008; 255:925-926.

[44] Famularo G, Minisola G, De Simone C. A patient with cerebral Whipple's disease and a stroke-like syndrome. *Scand J Gstroenterol* 2005; 40:607-609.

[45] Baskin, H., Hedlund, G. Neuroimaging of herpesvirus infections in children. *Pediatr. Radiol.* 2007; 7:949-963.
[46] Breuer, J., Pacou, M., Gauthier, A., et al. Herpes zoster as a risk factor for stroke and TIA. *Neurology* 2014; 82:206-212.
[47] Nagel, M., Cohrs, R., Mahalingam, R., et al. The varicella zoster virus vasculopathies. Clinical, CSF, imaging, and virologic features. *Neurology* 2008; 70:853-860.
[48] Gilden, D., Cohrs, R., Mahalingam, R., et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol.* 2009; 8:731-740.
[49] Eidelberg, D., Sotrel, A., Horoupian, S., et al. Thrombotic cerebral vasculopathy associated with herpes zoster. *Ann. Neurol*. 1985; 19:7-14.
[50] Melanson, M., Chalk, C., Georgevich, L., et al. Varciella-zoster virus DNA in CSF and arteries in delayed contralateral hemiplegia: evidence for viral invasion of cerebral arteries. *Neurology* 1996; 47: 569-570.
[51] Anderson, A., Fountain, J., Green, S., et al. Human immunodeficiency virus-associated cytomegalovirus infection with multiple small vessel cerebral infarcts in the setting of early immune reconstitution. *J. Neurovirol.* 2010; 16:179-184.
[52] Rosales, D., Garcia-Garcia, C., Salgado, E., et al. Primary Central Nervous System Vasculitis Triggered by Cytomegalovirus Encephalitis. *Neurology* 2013; 80:POI.231
[53] Koeppen, A., Lansing, L., Peng, S., et al. Central nervous system vasculitis in cytomegalovirus infection. *J. Neurol. Sci.* 1981; 51:395-410.
[54] Naides, S. Known infectious causes of vasculitis in man. *Clev. Clin. J. Med.* 2002; 69: SII15-19.
[55] Guerrero, W., Dababneh, H., Hedna, S., et al. Vessel wall enhancement in herpes simplex virus central nervous system vasculitis. *J. Clin. Neurosci.* 2013; 20:1318-1319.
[56] Kano K, Katayama T, Takeguchi S, et al. Biopsy-proven case of Epstein-Barr virus (EBV)-associated vasculitis of the central nervous system. *Neuropathology* 2017; 37:259-264.
[57] Benjamin, L., Bryer, A., Emsley, H., et al. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol.* 2012; 11:878-890.
[58] Gray, F., Marie-Claude, L., Keohane, C., et al. Early brain changes in HIV infection: Neuropathological study of 11 HIV seropositive, non-AIDS cases. *J. Neuropathol. Exp. Neurol.* 1992; 51:177-185.
[59] Ma WL, Li CC, Yu SC, et al. Adult T-cell lymphoma/leukemia presenting as isolated central nervous system T-cell lymphoma. *Case Rep Hematol* 2014; 2014:917369.
[60] Semmo, A. N., Baumert, T. F., Kreisel, W. Severe cerebral vasculitis as primary manifestation of hepatitis B-associated polyarteritis nodosa. *J. Hepatol.* 2002; 37:414-416.
[61] Broussalis, E., Trinka, E., Kraus, J., et al. Treatment strategies for vasculitis that affects the nervous system. *Drug Discov. Today* 2013; 18:818-835.
[62] Bilge, I., Sadikoğlu, B., Sevinç, E., et al. Central nervous system vasculitis secondary to parvovirus B19 infection in a pediatric renal transplant patient. *Pediatr. Nephrol.* 2005; 20: 529-533.
[63] Kulsta, A., Wichter, M. West Nile encephalitis presenting as a stroke. *Ann. Emerg. Med.* 2003; 4:283.

[64] Alexander, J., Lasky, A., Graf, W. Stroke associated with central nervous system vasculitis after West Nile virus infection. *J. Child Neurol.* 2006; 21:623-625.

[65] Zafar, S., Dash, D., Chachere, M., et al. West Nile Virus Infection Associated with Central Nervous System Vasculitis and Strokes [Abstract]. *Neurol*ogy 2012; 78: P03. 264.

[66] Younger DS. Epidemiology of Zika virus. *Neurol Clin* 2016; 34:1049-1056.

[67] Abenza-Abildua, M., Fuentes-Gimeno, B., Morales-Bastos, C., et al. Stroke due to septic embolism resulting from *Aspergillus* aortitis in an immunocompetent patient. *J. Neurol. Sci.* 2009; 284:209-210.

[68] Martins, H., Rodgrigo da Silva, T., Scalabrini-Neto, A., et al. Cerebral vasculitis caused by *aspergillus* simulating ischemic stroke in an immunocompetent patient. *J. Emerg. Med.* 2010; 38:597-600.

[69] Laurencikas, E., Sandstedt, B., Söderman, M. Intrathecal aspergillosis and fusiform arterial aneurysms in an immunocompromised child: a clinic-pathological case report. *Childs Nerv. Syst.* 2006; 22:1497-1501.

[70] Grimes, D., Lach, B., Bourque, P. Vasculitic basilar artery thrombosis in chronic Candida albicans meningitis. *Can. J. Neurol. Sci.* 1998; 25:76-78.

[71] Lipton SA, Hickey WF, Morris JH, et al. Candidal infection in the central nervous system. *Am J Med* 1984; 76:101-108.

[72] Williams, P., Johnson, R., Pappagianis, D., et al. Vasculitic and encephalitic complications associated with *Coccidioides immitis* infection of the central nervous system in human: report of 10 cases and review. *Clin. Infect. Dis.* 1992; 14:673-682.

[73] Eron JJ, Morrison J, Aguet J, et al. Vasculitis and encephaltic complications associated with coccidioides immitis infection of the central nervous system in humans: Report of 10 cases and review. *Clinical Infectious Diseases* 1992; 14:673-682

[74] Lane, M., McBride, J., Archer, J. Steroid responsive late deterioration in *Cryptococcus neoformans variety gattii* meningitis. *Neurology* 2004; 63:713-714.

[75] Bell, W., Dalton, J., McCall, C., et al. Iatrogenic *Exserohilum* infection of the central nervous system: mycological identification and histopathological findings. *Modern Pathol.* 2013; 26:166-170.

[76] Lyons JL, Gireesh ED, Trivedi JB, et al. Fatal Exserohilum meningitis and central nervous system vasculitis after cervical epidural methylprednisolone injection. *Ann Intern Med* 2012; 157:835-836

[77] Trofa, D., Nosanchuk, J. Histoplasmosis of the central nervous system. *J. Neuroparasitology* 2012; 3:1-7.

[78] Hong, H., Lee, Y., Kim, T., et al. Risk factors for mortality in patients with invasive mucormycosis. *Infect. Chemother.* 2013; 45:292-298.

[79] Katragkou, A., Walsh, T., Roilides, E. Why is Mucormycosis More Difficult to Cure than More Common Mycoses? *Clin. Microbiol. Infect.* 2013; doi:10.1111/1469-0691. 12466.

[80] Takahashi, S., Horiguchi, T., Mikami, S., et al. Subcortical Intracerebral Hemorrhage Caused by Mucormycosis in a Patient with a History of Bone-marrow Transplantation. *J. Stroke Cerebrovasc. Dis.* 2009; 18;405-406.

[81] Maffini, F., Cocorocchio, E., Pruneri, G., et al. Locked-in syndrome after basilary artery thrombosis by Mucormycosis masquerading as meningoencephalitis in a lymphoma patient. *E Cancer Medical Science* 2013; 7:382.

[82] Alarcón, F., Hidalgo, F., Moncayo, J., et al. Cerebral cysticercosis and stroke. *Stroke* 1992; 23:224-228.
[83] Marquez, J., Arauz, A. Cerebrovascular complications of neurocysticercosis. *Neurologist* 2012; 18:17-22.
[84] Barinagarrementeria, F., Cantú, C. Frequency of cerebral arteritis in subarachnoid cysticercosis: an angiographic study. *Stroke* 1998; 29:123-125.
[85] Camuset, G., Wolff, V., Marescaux, C., et al. Cerebral vasculitis associated with *Schistosoma mansoni* infection. *BMC Infect. Dis.* 2012; 12:220.
[86] Jauréguiberry, S., Ansart, S., Perez, L., et al. Acute neuroschistosomiasis: Two cases associated with cerebral vasculitis. *Am. J. Trop. Med. Hyg.* 2007; 76:964-966.
[87] Pittella JEH. Pathology of CNS parasitic infections. *Handb Clin Neurol* 2013; 114:65-88.
[88] Kumar P, Pramod K. Neurorickettsioses: A rare presentation with stroke in a young adult. *Journal of Clinical and Diagnostic Research*, 2014 Oct, 8:MD03-MD04
[89] Kim, D., Chung, J., Yun, N., et al. Scrub typhus meningitis or meningoencephalitis. *Am. J. Trop. Med. Hyg.* 2013; 89:1206-1211.
[90] Boorugu, H., Chrispal, A., Gopinath, K., et al. Central nervous system involvement in scrub typhus. *Trop. Doct.* 2014; 44:36-37.
[91] Pai, H., Sohn, S., Seong, Y., et al. Central Nervous System Involvement in Patients with Scrub Typhus. *Clin. Infect. Dis.* 1997; 24:436-440.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 11

CENTRAL NERVOUS SYSTEM VASCULITIS DUE TO DRUG ABUSE

David S. Younger**, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology,
New York University School of Medicine,
College of Global Public Health, New York University,
Department of Health Policy and Management,
School of Public Health, City University of New York,
New York, NY, US

ABSTRACT

Illicit drug abuse is a common differential diagnosis of acquired central nervous system vasculitis even though there are only a handful of histopathologically confirmed patients in the literature from among the many potential classes of abused drugs traditionally implicated in this disease. Since publication of the first edition of this chapter, there has been increasing interest in the acute neurotoxicity associated with adulterants. This chapter considers the major classes of illicit drugs in those with and without human immunodeficiency virus type 1 infection and acquired immune deficiency syndrome.

EPIDEMIOLOGY

Drug abuse is a significant public health burden [1]. Globally, it has been estimated that 3.5 to 5.7% of the population age 15 to 64 years, or approximately 250 million persons consumed an illicit drug once in the past year [2]. Taking into account the pattern of drug use, an estimated 16 to 38 million persons are considered regular or frequent uses due to psychic and physical drug dependence or addiction, and an additional 11 to 21 million inject drugs [1]. This wide range of estimations are due to lack of reliable epidemiological data on specific drug abuse, all of which can be cause injury to the central nervous system (CNS) including opiates, heroin, cocaine, amphetamine, and methamphetamine.

* Corresponding Author's Email: youngd01@nyu.edu

The misuse and abuse of drugs in the United States (US) has reached epidemic proportion, and extends to both adolescents and adults. Although individuals with a drug addiction may favor one or another class of illicit drugs, most perform polysubstance abuse. Such a trend was discerned in an analysis of accidental overdose deaths in New York City between 1990 and 1998 due to heroin, cocaine and alcohol. That combination accounted for 97.6% of all deaths, 57% of which were attributed to two or more of these drugs in combination [3] among accidental drug overdose deaths attributed to one drug alone, those positive for cocaine only were the commonest representing 1.93 per 100,000 person-years. In developing countries, illicit use, non-pharmacy sales, counterfeit drugs, and self-treatment complicate the public health concern surrounding substance abuse.

CLASSIFICATION AND NOSOLOGY

The most widely used classification and nosology for the vasculitides is the 2012 Revised International Chapel Hill Consensus Conference [4] Nomenclature. There is a recent review of CNS vasculitis [5].

BLOOD BRAIN BARRIER

The past decade has witnessed extraordinary progress in our understanding of the blood brain barrier (BBB) [6], and progress in its understanding will likely afford new insights into our understanding of cerebral vasculitis. The neurovascular unit (NVU) of the BBB is comprised of capillary endothelial cells, pericytes, smooth muscle cells, astrocytes, and neuronal terminals, and white blood cells in the extended NVU.

Each of the components expresses a wide variety of receptors, ion channels, and transporters that reside in proximity to one another allowing for the dynamic modulation of blood flow, metabolism, and electrophysiologic regulation [7]. Many of the influx and efflux mechanisms of the BBB are present early in the developing brain, encoded by genes at much higher levels than in the adult [8]. The disruption of tight and adherens junctions, enzymatic degradation of the capillary basement membrane, or both, leads to disruption of tight junctions (TJ), altered expression and function of membrane transporters or enzymes, increased passage of inflammatory cells across the BBB from the blood to CNS, and dysfunction of astrocytes and other components [7]. This leads to aberrant angiogenesis and neuroinflammation with concomitant vasogenic edema, accumulation of toxic substances in the brain interstitial fluid, oxidative stress, and impaired ion and water homeostasis.

AMPHETAMINE AND RELATED AGENTS

Background

The earliest reports of misuse of amphetamine sulfate were in late 1930 when students to avoid sleep during examination periods [9] used it. This was followed by reports of death by those who ingested the drug repeatedly as a stimulant for the same purpose [10], in a suicide

attempt that resulted in a fatal intracerebral hemorrhage [11], or accidentally, when dexamphetamine and phenelzine were fatally ingested together decades later [12].

During the Second World War, amphetamine and methamphetamine was used clinically and illicitly but its abuse soared in San Francisco after 1962 where it was illegally produced and distributed [13].

In 2009, the United Nations Office on Drugs and Crime (UNODC) estimated that 16 to 51 million persons between the age of 15 and 64 years consumed amphetamine drugs, with more than half using methamphetamine [14], exceeding the combined consumption of all other drugs of abuse except cannabis [15].

Neuropharmacology

The neuropharmacology of amphetamine, methamphetamine, and their derivatives has been recently reviewed [16, 17]. Such drugs agents comprise a large spectrum of agents [18] available in powder, capsule, tablet, and injectable fluid form that can be swallowed, snorted or taken intra-nasally, smoked or injected with highly variable purity and dosage equivalence. Their potent effects, which include elevation of blood pressure, pulse rate, and increased level of alertness, sometimes in association with insomnia, excitability, panic attacks, and aggressive behavior, can also be associated with seizure and stroke.

The effects of methamphetamine are distributed throughout the brain [19]. Ecstasy refers to the different hallucinogenic amphetamine derivatives that contain 3, 4-methylene-dioxymethamphetamine (MDMA) and 3, 4-methylenedioxyethylamphetamine (MDE) as the main components [20]. Ecstasy alters brain serotonin concentrations, and postsynaptic 5-HT_2 receptors play a role in the regulation of brain microvessels.

The CNS toxic effects are mitigated through blocking of the reuptake of dopamine (DA) and stimulation of the release of DA and norepinephrine (NE), as well as, possible involvement upon serotonergic and endogenous opiate system. There can be DA receptor desensitization with marked reduction of DA transporters and drug levels, as well as other dopaminergic axonal markers. The neurotoxic effects of methamphetamine in particular, are believed to be mediated in addition by multiple additional mechanisms including generation of free radicals, nitric oxide, excitotoxicity, mitochondrial dysfunction, apoptosis, and the induction of immediate early inflammatory genes and transcription factors.

Methamphetamine is the most potent amphetamine and the most commonly abused. All forms of amphetamine administration increase the risk of stroke that may be ischemic, hemorrhagic and intraparenchymal [21], and which may be up to four-fold that of nonusers [22], surpassing the rate of hemorrhagic stroke caused by cocaine use with odds ratios respectively of 4.95 versus 2.33 [23]. Still, amphetamines and methamphetamine are the second commonest cause of all strokes after cocaine, occurring largely in persons younger than 45 years.

Clinicopathological Spectrum of Amphetamine-Related Cerebral Vasculitis

Excluded Literature Patients

Amphetamine was not the definite causative agent of purported cerebral vasculitis in the patient described by Kessler and colleagues [24] with acute intracerebral hemorrhage, or in the patient reported by Bostwick [25] with ischemic stroke in two multi-drug abusers of heroin, cocaine, and amphetamine with beading of small tributaries of the middle cerebral artery (MCA) [24] or occlusion of the right internal carotid artery (ICA) [25]. Postmortem examination in the first patient [24] showed occasional intramural mononuclear and polymorphonuclear cellular infiltration of small leptomeningeal arteries, while histopathology of the second patient [25] was not provided.

Detailed histopathology was lacking in the patient described by Olsen [26] as "vasculitis and cerebritis "as the cause for subarachnoid hemorrhage in a drug abuser who injected Methedrine and soon afterward lapsed into a fatal coma. Cerebral angiography that demonstrated typical features of vasculitis in conjunction with a skin biopsy that revealed granular deposits of IgM and C3 component around the lumina of small vessels of the upper dermis consistent with immune complex disease were the supportive features of cerebral vasculitis in a patient who ingested methamphetamine and later developed headache, nausea and vomiting heralding subarachnoid, without other confirmatory histopathology [27].

Corroborative histopathology was not sought in 10 other often cited patients [28-30] including a young man with presumed cerebral vasculitis attributed to chronic exposure to methylphenidate for 7 years beginning at age 5 to treat hyperactivity and attention deficit disorder. At age 18 years, he was diagnosed with right hemidystonia, whereupon MRI of the brain disclosed chronic infarction in the head of the right caudate, putamen, pallidum, internal capsule and temporal lobe, with occlusion of the left anterior cerebral artery (ACA) and posterior branch of the left MCA on cerebral angiography [28].

Likewise corroborative histopathology was not sought in 8 patients described by Buxton and McConachie [29] who developed presumed intracranial vasculitis as cause for subsequent lobar (5 patients), subarachnoid (2 patients) or brainstem hemorrhage (1 patient) following oral or inhaled amphetamine in whom cerebral angiography showed beading in the one patient with subarachnoid hemorrhage, and normal in 6 others.

Moriya and Hashimoto [31], Shibata and coworkers [32], and Delaney and colleagues [33] each described a patient with fatal intracranial hemorrhages following intravenous injection of amphetamine (2 patients) alone [31, 32] or intranasal injection of methamphetamine (1 patient) [33]. Postmortem examination in one patient [31] did not reveal vascular lesions, while that of another patient [32], with evidence of necrosis of blood vessels walls along named cerebral arteries, failed to reveal cellular infiltration of vessels walls. Detailed gross and microscopic examination of the cerebral vessels in another patient [33] showed no evidence of cerebral vasculitis.

Moreover, there was no mention of vasculitic lesions at postmortem examination of the CNS among 13 patients with purported vasculitis following fatal intravenous injection (1 patient) [34] oral ingestion of methamphetamine (6 patients) [35] or amphetamine sulfate (1 patient) [11], oral ingestion of combination dexamphetamine and phenelzine (1 patient) [12]. There was no evidence of postmortem or brain biopsy studies to investigate the possibility of cerebral vasculitis among 4 other often cited patients [36], 1 of whom was fatally injected with intravenous methamphetamine leading to cerebellar and brainstem hemorrhage; or in 3 other

patients who survived ischemic infarction (2 patients) or lobar hemorrhage (1 patient) associated with inhaled (1 patient) or an unknown mode of administered of methamphetamine ingestion.

Cerebral vasculitis was not mentioned in a recent series of 30 patients, one third each of whom carried the diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage [37]. Nor were the postmortem findings of multiple large intracerebral vessels occlusions attributed to cerebral vasculitis in a patient with a fatal stroke, and attributed instead to accelerated atherosclerosis. Histopathology was not sought in two other fatal strokes or a patient with fatal subarachnoid hemorrhage [37].

Pathologically-Verified Literature Patients

Cerebral vasculitis due to amphetamine, methamphetamine and related agents is exceedingly rare with only 3 histopathologically studied patients in the literature [38, 27]. This is surprising given the number of substances that could cause this disorder if there was a true association. Citron and colleagues [38] in a highly publicized report of 14 Los Angeles multidrug abusers demonstrated amphetamine-related multi-organ arteritis including the CNS. The drug closest to a common denominator was methamphetamine using intravenously by all but two patients and exclusively by one. Acute vessel lesions of fibrinoid necrosis of the media and intima with infiltration by polymorphonuclear cells, eosinophils, lymphocytes and histiocytes, was followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for polyarteritis nodosa (PAN). Two patients one abbreviated D.G. and the other E.V., who injected methamphetamine via intravenous injection had arterial lesions in cerebral and cerebellar (D.G.) and brainstem pontine vessels (D.G. and E.V.), however detailed histopathologic descriptions were not provided. Their report was followed by correspondence by Gocke and Christian [39] who contended that exposure to the Australia antigen of hepatitis B antigen was likely in their cohort [38] conceivably associated with circulating immune complexes and complement activation as had recently been described [40, 41]. The authors [42] responded that no more than 30% of sera from drug abuse patients ultimately tested positive for the Australia antigen. Those with antigen-positive sera who had used drugs others than methamphetamine had no evidence of angiitis when studied angiographically.

Baden [43] wrote that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers. Further, 14 cases were claimed documentation for angiitis was presented in only 4 patients but no substantiation for the diagnosis was given in the remainder except that 5 were asymptomatic, and 5 had a variety of nonspecific systemic signs and symptoms. Citron and Peters [42] responded that evidence of aneurysms so noted in 13 patients, was in their opinion ample evidence of arteritis.

Almost two decades later, cerebral vasculitis was demonstrated in a dubious report [27] of a three-week postpartum woman who took her first over-the-counter Dexatrim diet pill in many months containing phenylpropanolamine, without a history of amphetamine abuse. This was followed 90 minutes later by sudden headache, nausea vomiting and detection of subarachnoid blood on CT neuroimaging and a frontal lobe hematoma. Bilateral carotid angiography demonstrated diffuse segmental narrowing and dilatation of small, medium and large vessels and branches of the anterior and posterior circulation. Evacuation and histopathologic analysis of the hematoma was performed showing necrotizing vasculitis of small arteries and veins with

infiltration of polymorphonuclear leukocytes particularly prominent in the intima with fragmentation of the elastic lamina and areas of vessel occlusion. It was unclear whether the findings were related to primary or drug-related CNS vasculitis. However, treatment with cyclophosphamide for 6 months was associated with almost complete resolution of cerebral angiographic abnormalities.

Etiopathogenic Mechanisms

After the report of Citron and colleagues [38], Rumbaugh and colleagues [44] described the cerebral vascular changes due to methamphetamine abuse in five rhesus monkeys given amphetamine in dose ranges used by human addicts. Two of the five monkeys developed generalized arterial spasm during a two-week period following intravenous injection. Three of the five animals demonstrated decreased caliber of named cerebral artery branches and flow of the contrast agent with normalization one day later while two others showed marked general decrease in small branches and large named vessels that improved in one animal and progressed in another. Histopathologic changes at postmortem examination included microaneurysmal enlargement of arteriolar segments, mononuclear perivascular cuffing of small arterioles, parenchymal necrosis, petechial hemorrhages, and swelling of brain tissue, with most of the hemorrhagic lesions centered on small-size arteriolar and capillary vessels. Although reminiscent of the clinical and histopathologic findings of Citron and colleagues [38], necrotizing arteritis and transmural inflammation were lacking. Five years later, Rumbaugh and coworkers [45] subjected monkeys to short-duration (2 weeks) (5 animals), medium-duration (1 month) (3 monkeys), and long duration (one year) (3 monkeys) of thrice weekly (1.5 mg/kg body weight) intravenous amphetamine and related agents including methamphetamine, secobarbital, methylphenidate, and placebo, with performance of cerebral angiography and documentation of the resulting histopathology. Their studies showed relatively severe vascular injury and brain damage from intravenous methamphetamine that included occlusions and slow blood flow in small cerebral vessels respectively in two each of the five monkeys in the long-term administered drug, and in three each of those given drug for intermediate and short durations, with some animals and controls unaffected. There was less injury caused by secobarbital and methylphenidate. Further, the possibility of vascular spasm due to subarachnoid blood was excluded by lack of blood at postmortem examination in the subarachnoid space in any of the animals.

COCAINE

Background

A classic review of cocaine and stroke describes its abuse potential [46]. Cocaine, which is derived from the leaves of the *Erythroxylum coca* plant found primarily in the eastern mountains of Peru, Ecuador, and Bolivia, is available for abuse as cocaine hydrochloride, a water-soluble white salt in crystal, granular, and white powder that can be sniffed and "snorted" intranasal or injected parenterally [3]. The "free base" alkaloid form is known as "crack" [16]

derives its name from the cracking sound that occurs after dissolution of the hydrochloride salt in water, heated, and mixed with ammonia without or without baking soda. This chemical reaction converts cocaine hydrochloride to a volatile form of the drug, almost pure cocaine. Street cocaine or the non-crack form is highly variable in purity, and often cut with various agents [47]. The alkaloid free-based form, which is inhaled or smoked, is accompanied by higher blood concentrations and more pronounced euphoria.

When smoked as free-base, it is absorbed into the pulmonary circulation and transmitted to the brain in <10 seconds. After appearance in the bloodstream, cocaine is rapidly hydrolyzed to benzoylecgonine [48], which can be accurately tested in the urine; however, levels may persist for up to 27 to 36 hours depending upon the route of administration and host cholinesterase activity [49-51]. In recent years, with increasing availability and purity, and a drop in the price of cocaine from the early 1970s, new cohorts from all socioeconomic backgrounds and age groups have been attracted to this highly addictive drug, and use has continued to expand on a year-by-year basis.

Neuropharmacology

Cocaine is a highly potent central nervous system (CNS) stimulant that rapidly crosses the BBB due to its highly lipophilic properties and is widely distributed through the brain with its major metabolites binding at receptors with varying affinities at presynaptic sites, stimulating the release of dopamine (DA) from synaptic vesicles and blocking DA reuptake resulting in enhanced dopaminergic neurotransmission, in addition to its local anesthetic properties [52-55]. The underlying molecular neurobiology and genetics of cocaine addiction and its treatment with an emphasis reviewed elsewhere [56]. The investigation of single nucleotide polymorphisms (SNP) that encode amino acid substitutions in opioid receptors and ligands implicated in drug addiction, particularly those of the mu opioid receptor (MUP-r) gene system (*OPRM1)* that releases DA from neural synapse when activated, and those of the kappa receptor (KUP-r) that instead lower extracellular dopamine levels, have contributed understanding to the variability in drug addiction among susceptible individuals [57].

Clinicopathological Spectrum of Cocaine-Related Cerebral Vasculitis

Excluded Literature Patients

Since the first reported patient with possible association of cocaine and ischemic stroke [58], both stroke and cerebral vasculitis have been described in the literature as features of cocaine drug abuse. One clinical series of 28 patients [59] and another of 15 patients [60] failed to identify vasculitis by cerebral angiographic data, and in a pathologically studied patient at postmortem examination [59]. Moreover, vasculitis was not suggested in a review of 13 patients from nine published reports by the same authors [61] of cocaine-associated cerebrovascular complications. Other cases of presumed vasculitis suggested by intracranial arterial narrowing [62] in the absence of confirmed histopathology were contested as probably representing vasospasm following subarachnoid hemorrhage [63].

Pathologically-Verified Literature Patients

Only ten histologically verified patients, including six men and 4 women, age 21 to 39 (mean age 28 years) occurred in the absence of other possible known causes including concomitant infection by human immunodeficiency virus type 1 (HIV-1 or HIV) infection and known causative coinfections [25, 64-70]. In all but 1 patient [68] who had a long-standing cocaine habit with abuse sometime in the 6 months before admission, onset of neurological symptoms immediately followed cocaine use that was intranasal cocaine in 6 patients [66-70], intravenous in 2 [64, 65], smoked in 1 [64], and acquired via unknown modality in 1 [64]. Cerebral vasculitis was associated with cerebral hemorrhage in 3 patients [67, 68] and ischemia in the 7 patients [25, 64-66, 69, 70] that typically presented with abrupt onset of headache and focal hemiparesis so noted in 6 patients [67, 68, 25, 64], confusion or agitation [65, 66, 68-70], and grand mal seizures [66] that progressed to stupor, coma and death in 3 patients [25, 64, 66]. Lumbar CSF analysis showed lymphocytic pleocytosis of 10 to 65 cells/ cm^3 with elevation of the protein content from 185 to 630 mg/dL [65, 70], and was completely normal in 2 other patients [64, 68]. Cerebral angiography performed in 7 patients showed an avascular mass in the patient with a putaminal hemorrhage [67], abnormal large named vessel occlusions or segmental narrowing in 3 patients [64, 68, 25], poor filling and irregularities in vessel appearance in 2 [69, 70], and normal in one patient [65].

The pathology of cerebral vasculitis was established by brain and meningeal biopsy in seven patients [64, 65, 67-70], at postmortem examination in two patients [25, 66], and by both in one patient [64]. The underlying pathology of cerebral vasculitis was non-necrotizing with transmural mononuclear cell inflammation affecting small arteries and veins in three patients [64, 66, 67] or veins alone in three patients [68-70], and perivascular cuffing of small arteries and veins in another [65]. In two patients, there was necrosis of small cerebral vessels associated with polymorphonuclear cell inflammation of small arteries and veins [68] or large named vessels [25]. Among three patients so studied at postmortem examination, non-necrotizing small vessel vasculitis was noted in the brains of two patients without evidence of systemic involvement [64, 66], while necrotizing large vessel vasculitis was found in both the brain and systemic organs [25].

Treatment consisting of corticosteroid was administered to seven patients, five of whom improved [64, 65, 68, 70] and two who died with refractory seizures despite anticonvulsant medication [64] or because of infection, coma and decerebration [25]. There was no mention of treatment or outcome in 3 patients, [66, 67, 69] including two patients who succumbed to coma, hypoxic ischemic decerebration, and death [66, 67].

Etiopathogenic Mechanisms

Although cocaine-associated cerebral vasculitis has not been rigorously studied, several independent lines of experimental evidence suggest possible etiopathogenic mechanisms in susceptible individuals.

The first was the observed effects of cocaine in the induction of adhesion molecules and endothelial leukocyte migration across cerebral blood vessel endothelia walls particularly under inflammatory conditions, which may disturb the function of the blood brain barrier.

Cocaine increased the expression of the endothelial adhesion molecules intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and endothelial leukocyte adhesion molecule (ELAM)-1 on BMVEC with a peak effect on ICAM-1 expression between 6 and 18 hours after treatment in human brain microvascular endothelial cells (BMVEC) cultures and increased monocyte migration in an *in vitro* BBB model [71-74] constructed with BMVEC and astrocytes [75]. These effects of cocaine, exerted through a cascade of augmented expression of inflammatory cytokines and endothelia adhesion molecules, may contribute to the known cerebrovascular complications of cocaine abuse.

The second is the effect of cocaine on endothelial cell permeability and apoptosis as well as the induction of chemokines and cytokines. The immunomodulatory effects of cocaine on brain microvascular endothelial cells and its proinflammatory effects on induction of proinflammatory cytokines and chemokines was investigated using a human BBB model that included HIV neuroinvasion [76]. Cocaine increased the *in vitro* permeability of endothelial cells of the BBB model and induced apoptosis of mouse thymocytes in cultures of BMVEC and monocytes using an enzyme-linked immunosorbent assay (ELISA) of generated accompanied by up-regulation of macrophage inflammatory protein (MIP)-1, MIP-1α, inducible protein (IP)-10, and interleukin (IL)-8 and TNF-α expression.

A third line of investigation has been the observed synergy of cocaine in facilitating pathogenic retroviral neuroinvasion, which may confer an independent risk factor for cerebral vasculitis. Both *in vitro* and *in vivo* studies have provided valuable tools in exploring the role of cocaine in mediating HIV-1-associated neuropathogenesis. The importance of drug abuse in conjunction with HIV-1 has been underscored by the ability of cocaine to induce retroviral replication in mononuclear cells [77] and enhance gp120-induced neurotoxicity [78].

OPIOIDS

Background

The opioid drugs comprise a large number of agonists, antagonists and mixed agonist-antagonists. Opioid overdose accounts for at least 16,000 deaths annually in the US [79] and occurs across sex, ethnic, age and geographic strata, and involves both medical and nonmedical opioid uses.

According to the Centers for Disease Control and Prevention (CDC), since 2003, opioid analgesic abuse [80] overdose deaths involving opioid analgesics exceeded those due to cocaine. For every unintentional overdose death related to an opioid analgesic, nine persons were admitted for substance abuse treatment, 161 reported drug abuse or dependency, and 461 reported nonmedical uses of opioid analgesic drugs [81].

Also known as diacetylmorphine, heroin was first synthesized by the Bayer Company in 1889 as a less addictive morphine sulfate substitute [82], however it has since become cheaper and more readily available.

There is extensive literature relating to the outcome of heroin abuse and overdose [83-87] with a reported the average mortality rate of 2% in regularly injecting persons, half of which is attributable to overdose and equal to 20 times the mortality rate expected in non-drug using peers.

Neuropharmacology

Opioids or narcotic drugs have pharmacologic properties similar to those of morphine that include the derivatives morphine, hydrocodone, oxycodone, hydromorphone, codeine, fentanyl, meperidine, methadone, and opium. Whereas the source of opioids is the exudate of seed from the poppy plant, heroin is derived from acetylation of morphine [21]. Heroin is administered intravenously, intranasal and subcutaneously.

A higher bioavailability of heroin is present after heating on foil for inhalation compared to smoking after heating. Intravenous injection leads to extreme euphoria that peaks at 10 minutes followed by profound sedation and analgesia that lasts for up to one hour. Opiate overdose produces the triad of coma, respiratory depression and meiosis. The medical complications of long-term heroin exposure includes endocarditis, pulmonary complications of embolism, pneumonia and granulomatosis or fibrosis, nephropathy, immunodepression, infection at the site of injection due to cellulitis, thrombophlebitis, and bacteremia, and hepatitis due to needle sharing [88].

It binds to endogenous opiate mu_1 receptors, which are responsible for most of the analgesic effects, and for the actions of the central nervous system and cardiovascular system leading to bradycardia, hypotension, and respiratory depression. Agonist actions at mu_2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, meiosis, and physical dependence.

Agonist actions at kappa receptors lead to separate analgesia. Circulating serum morphine is transformed into morphine-3-glucuronide or morphine-6-glucuronide by the liver and the kidney. Most fatal and nonfatal overdoses occur when heroin is administered intravenously.

Clinicopathological Spectrum of Opioid-Related Cerebral Vasculitis

Excluded Literature Patients

Four often cited Brust, coworkers [58], Adle-Biassette, and colleagues [89] described patients with heroin abuse and cerebral vasculitis studied after death. In three patients [58] cerebral vasculitis was considered possible after exclusion of bacterial or fungal endocarditis, focal ischemic during a period of shock after overdosage and hypoventilation, concomitant methamphetamine, drug allergy, and likely adulterants. One reported patient [58] died in methadone detoxification and postmortem revealed a massive hemorrhage of the right basal ganglia however, intracranial vessels were not examined. A second reported patient [58] developed unconscious followed by seizures, global aphasia and right hemiparesis in association with multiple occlusions on cerebral angiography before expiring, however neuropathological postmortem examination was not performed. A third reported heroin addict [58] who presented comatose with xanthochromic and bloody cerebrospinal fluid and died, was found to have a left intracerebral hemorrhage with normal large vessels on postmortem examination however, the smaller cerebral vessels were not commented upon.

Another often-cited pathological case [89] of possible cerebral infarction following inhalation of heroin in who was found dead one morning after the usual signs of recent heroin intake had ischemic cardiac lesions of varying ages and cortical watershed infarcts, reportedly had normal intracranial vessels at postmortem examination.

Confirmatory pathology was not sought among 5 often cited surviving heroin abusers [90-94] who presented with focal strokes on neuroimaging after inhalation [93, 94] or intravenous [90, 91] evidencing likely cerebral vasculitis on cerebral angiography; [90, 92], one of whom admitted to intermittent lysergic acid diethylamide (LSD) use [90]. All of the patients who had employed only heroin, cocaine or marihuana described by Halpern and Citron [38] in a report of necrotizing angiitis associated with drug abuse were included in the category of normal angiographic examinations, and their supporting pathology, even if available, was not described in the paper.

Pathologically-Verified Literature Patients

This author could not identify any pathologically confirmed cases of heroin induced cerebral vasculitis reported in the literature, nor was cerebral vasculitis suggested as a likely occurrence in heroin abuse [95], heroin addiction [88, 96], or acute overdose [83]. Moreover, detailed neuropathological studies carried out on 134 victims of acute heroin intoxication including 18 who survived for periods of hours or days [97], who respectively demonstrated cerebral edema in conjunction with vascular congestion, capillary engorgement, and perivascular bleeding attributed to toxic primary respiratory failure; and ischemic nerve cell damage resembling systemic hypoxia, showed no evidence of cerebral vasculitis, and only one focus of lymphocytic perivascular inflammation. The brains of 10 intravenous drug abusers who died from heroin overdoses, including one due to gunshot injury [98] likewise showed no evidence of cerebral vasculitis at postmortem examination, manifesting only a few perivascular mononuclear cells associated with pigment deposition.

Etiopathogenic Mechanisms

The postulated mechanisms of opioid related neuronal and CNS vascular injury include increased oxidative stress, induction of inflammatory cytokines, and increased permeability of the BBB especially in intravenous drug abuse. Ramage and colleagues [99] described increased deposition of hyperphosphorylated tau in entorhinal cortex and subiculum of the hippocampus, AT8-positive neurofibrillary tangles in entorhinal cortex, and increase in β-amyloid precursor protein (βAPP) in both the hippocampus and brainstem of drug abusers compared to controls. Several postulated causative mechanisms included repeated head injury, hypoxic-ischemic injury associated with opioid induced respiratory depression, microglial associated cytokine release, and drug-associated neurotoxicity.

DRUG ABUSE AND HIV/AIDS

Background

Recognition of the propensity for cerebral vascular inflammation in association with HIV/acquired immune deficiency syndrome (AIDS) and drug abuse has provided new insights into the mechanisms of cerebral vasculitis.

Early in the HIV/AIDs epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections [100]. Among 50 patients with AIDS and neurological complication, six HIV-1 infected patients described by Snider and colleagues [101] were intravenous drug users (IVDU), the others being male homosexuals and recently arrived Haitian refugees. The two postulated periods in the neurobiology of HIV-1 when autoimmune disease manifestations can occur that appear to be significant for the development of cerebral vasculitis were shortly after seroconversion and before the spread of productive infection [98, 102]; and after initiation of highly active antiretroviral therapy (HAART) in association with the immune reconstitution syndrome (IRIS) [103]. The impact of IVDU in the development of cerebral vasculitis and other autoimmune sequel is not well understood. However there an extensive literature suggesting an independent contribution of IVDU to immune suppression, breakdown of the BBB, microglial activation, and neuronal injury [104-110] and an additive or synergistic reinforcement of HIV-related brain damage by IVDU [111].

The timing of early HIV invasion has been difficult to ascertain based on the presence of one or more well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis [112] HIV-associated dementia [113], and AIDS-dementia complex [114], all of which are indicative of symptomatic infection. HIV encephalitis is initially associated with myelin pallor and gliosis of the centrum semiovale found in more than 90% of brains from patients dying with AIDS [115]. With increasing severity of symptomatic disease, multiple glial nodules with the multinucleated cells characteristic of HIV encephalitis occur throughout the white matter, basal ganglia, cerebral and cerebellar cortex, brainstem and spinal cord. HIV has been demonstrated in monocytes and multinucleated giant cells by electron microscopy, immunocytochemical techniques and in situ hybridization. Guillevin [116] reviewed vasculitides in the context of HIV infection.

Clinicopathological Spectrum of Drug Abuse and HIV/AIDS

HIV-Seropositive, Pre-AIDS Literature Patients

It has long been recognized that HIV antigens may be identified in CSF at, or shortly after seroconversion [117-119], and asymptomatic HIV-positive subjects [120] including seropositive men with normal CD4+ cell counts, neuropsychological, and neuroimaging, and normal neurophysiological investigations [121]. The examination of presymptomatic individuals has been virtually confined to intravenous drug abusers since other risk groups have a very low mortality before development of AIDS [106]. Gray and colleagues [122] described six patients with non-necrotizing cerebral vasculitis in a postmortem series of presymptomatic HIV-seropositive drug abusers, and Yankner and coworkers [123] with rapidly fatal necrotizing granulomatous angiitis of the brain without evidence of acquired immune deficiency, circulating HTLV-III or HIV-1 antibodies, described an analogous patient. Seven other patients were described by Bell and colleagues with lymphocytic infiltration of the walls of leptomeningeal and subarachnoid veins, without specific reference of cerebral vasculitis [102]. Gray and colleagues [122] studied two cohorts of 11patients, one HIV-seropositive and non-AIDS, and the other HIV-seronegative heroin abusers, 10 patients of each died from heroin overdose and another of a fatal gunshot wound.

Neuropathological studies [122] showed varying degrees of vascular inflammation including "true vasculitis" exemplified by dense vascular inflammation extending through the vessel wall, associated with leptomeningitis in six of the 11 HIV-seropositive AIDS-negative patients. However, there was no mention as to whether inflammatory process involved arteries and vein or the vessel caliber. Vascular inflammation was comparatively mild or absent and restricted to a few perivascular mononucleated cells associated with pigment deposition, without transmural vascular inflammation or meningitis in the HIV-seronegative cohort. HIV immunocytochemistry was negative in both cohorts and multinucleated giant cells, considered the hallmark of productive HIV infection in the brain and an essential neuropathological feature of HIV encephalitis, were not seen. One year later, Bell and coworkers [102] described the neuropathological findings of 23 intravenous drug users from the Edinburgh HIV Autopsy Cohort who died suddenly after seroconversion but while still in the presymptomatic stage of HIV infection in comparison to 10 HIV-negative intravenous drug users, 12 non-intravenous drug user controls, and 9 patients with full-blown AIDS, who also died suddenly. Seven of the presymptomatic HIV-positive patients showed infiltration of T-cells in the walls of veins in association with low-grade lymphocytic meningitis; seven others demonstrated isolated lymphocytic meningitis, and one patient had focal perivascular lymphocytic cuffing and macrophage collections throughout the central white matter tissue of the brain and in basal ganglia. Neither conspicuous perivascular lymphocytic infiltration nor lymphocytic meningitis was noted in HIV-negative intravenous drug user controls or in those with no drug association, or others with full-blown AIDS.

Neuropathological examination in presymptomatic HIV-seropositive patients failed to reveal characteristic lesions of HIV encephalitis and none of the subjects showed immunocytochemical evidence of p24 antigen in brain tissue. Nearly a decade later, Bell and colleagues [105] reiterated that in more than 50% of pre-AIDS cases so studied, the brain was characterized by a low-grade lymphocytic meningoencephalitis in which T-cell infiltration was present in leptomeninges and the perivascular compartment, with an occasional HIV-p24 positive lymphocyte in the lymphocytic infiltrate, but not in brain parenchyma. According to the same authors [105] there was conversely no clear evidence of vasculitis among intravenous drug users with HIV encephalitis in the Edinburgh HIV autopsy cohort [124]. Yankner and colleagues [123] reported the clinicopathologic findings of a homosexual man with rapidly fatal cerebral granulomatous angiitis of the brain associated with isolation of human T-lymphotropic virus type III (HTLV-III) in CSF and brain tissue. Mononuclear cellular infiltrates were present at postmortem examination in the walls of affected large named arteries without involvement of small arteries and veins, and with rare microglial nodules and multinucleated giant cells.

The early CNS changes of HIV infection were investigated among hemophiliacs examined after sudden death from intracranial hemorrhage and liver cirrhosis [125] and in experimental animal models of simian immunodeficiency virus (SIV) syndrome [126] and feline immunodeficiency virus (FIV) infection [127]. They have comparable neuropathological changes of gliosis, occasional microglial nodules, perivascular mononuclear infiltrates, and occasional leptomeningeal meningitis in all three, characteristically without multinucleated giant cells or evidence of HIV in the brain [125-127]. HIV-infected cells were mainly perivascular and expressed macrophage markers in the SIV model [126] suggesting transit of virus across the BBB as the main source of entry into the CNS.

Moreover, the comparatively less pronounced vascular inflammation than that described in early HIV-infection associated with drug abuse, suggests that intravenous drug abuse contributes to vascular inflammation.

HIV/AIDS-Associated-IRIS Literature Patients

The introduction of HAART has changes the incidence, course and prognosis of the neurological complications of HIV infection concomitant with almost undetectable viral load in plasma and a rise in circulating T-lymphocytes [128]. One pathologically confirmed patient with cerebral vasculitis and van der Ven and colleagues [129] described IRIS. This HIV-seropositive homosexual man developed dysarthria and dysphagia after HAART with worsening and appearance of limb paresis after discontinuation of the medication. Treatment with corticosteroids preceded recommencement of HAART but there was worsening with discontinuation of corticosteroids. Biopsy of a hyperintense fronto-parietal lesion on T_2-weighted MRI showed small vessel lymphocytic vasculitis, with microglial activation in the surrounding parenchyma. A severe demyelinating leukoencephalopathy in association with intense perivascular infiltration by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes was described by Langford and colleagues [130] in seven postmortem patients. All were severely immunosuppressed and treated with HAART with presumed IRIS however, high not low levels of HIV replication were noted. However, there was no consideration of cerebral vasculitis. Confirmatory neuropathology was not sought however in a patient described by Patel and coworkers [131] with HIV-seropositive man who developed encephalitis 10 months after HAART in association with a lower thoracic dermatomal varicella zoster virus (VZV) rash.

Levamisole

Background

The anti-helminthic agent levamisole, first introduced for use in veterinary medicine was later discovered to have potent immunomodulation properties, prompting its application in inflammatory and oncologic conditions including rheumatoid arthritis, aphthous ulcers, and melanoma (132). The U.S. Food and Drug Administration as adjuvant therapy for the treatment of inflammatory conditions and cancer approved Levamisole. In Asia, it has been used as an anti-helminthic and pesticide agent.

Epidemiology

Levamisole was detected in cocaine bricks by the U.S. Drug Enforcement Agency in 2003 (133), noting an increase from 44.1% of specimens in 2008 to 73.2% in 2009 (134), signaling a rising public health problem. In 2011, Buchman and co-workers (135) reported a prevalence of 68% employing a combination of immunoassay and gas chromatolography-mass spectroscopy detection methodologies. Other drugs noted in positive urine specimens included the opioid analgesics methadone (45%), codeine (16%). heroin/6-monoacetylmorphine (6%), and morphine or oxycodone (5%). The importance of detecting levamisole in urine concomitantly with cocaine in affected cases is in being able to ascertain its separate contribution to the observed neurotoxicity in suspected cases.

Neuropharmacology

Levamisole is 100- to 300-fold less potent than cocaine in blocking norepinephrine and dopamine uptake, and has a very low affinity for the serotonin transporter; and it does not trigger an appreciable substrate efflux. Nevertheless, the desired neuropharmacologic effects leads to its widespread contamination in cocaine production. It potentiates the euphoric effects of cocaine by inhibiting dopamine reuptake and forming amphetamine-like metabolites. Hofmaier and colleagues (136) studied the allosteric effects of levamisole and cocaine at 30 uM, a concentration at which levamisole displayed already mild effects on norepinephrine transport but without an inhibitory action on cocaine. Levamisole metabolized to aminorex, an amphetamine-like substance that exerted strong effects on dopamine, serotonin and norepinephrine transporters in a manner that resembled amphetamine. They concluded that while the adulterant levamisole itself had only moderate effects on neurotransmission, its metabolite, aminorex, nonetheless exerted distinct psychostimulant effects and that after the cocaine effect "fades out," the levamisole/aminorex effects "kicks in."

Clinicopathologic Manifestations

Exposure to levamisole-adulterated cocaine is associated with a variety of well-described hematological, skin, renal and pulmonary pathologies (137) often in association with positive antineutrophil cytoplasmic antibody (ANCA) serology. Hematologic abnormalities include agranulocytosis and neutropenia, which occurs in a dose dependent fashion, which is not commonly associated with pure cocaine-linked side or a characteristic of drug-induced vasculitis. A distinguishing feature of levamisole-adulterated cocaine exposure is small vessel vasculitis (SVV) which involves the ear lobes and the skin overlying zygomatic arch or lower extremities, often with purpuric plaques in a retiform pattern or central necrosis. Skin biopsy shows pathological involvement of superficial and deep dermal vessels associated with numerous neutrophils and eosinophils that surrounding and invade the walls of dermal vessels with extravasation of red blood cells, leukocyclastic debris (nuclear dust), and fibrinoid necrosis on hematoxylin and eosin-stained tissue sections. Such findings are similar to children with chronic levamisole treated for nephrotic syndrome so noted in a minority of children who developed purpuric lesions of at least the ears and biopsies revealing cutaneous vasculitis (138). Although organ involvement has not been characteristic of levamisole-adulterated cocaine-induced autoimmune disease, there is an established association with proteinuria or hematuria, acute renal injury, focal necrotizing and crescentic pauciimmune glomerulonephritis in some cases, and increased titers to p-ANCA. As in other drug-induced vasculitides, pulmonary involvement can complete the triad of skin, kidney and lung pathology in the form of diffuse alveolar hemorrhages, idiopathic pulmonary hypertension, or other clinicopathologic presentations.

Multifocal Inflammatory Leukoencephalopathy

It has taken 25 years to recognize the causal association of levamisole-associated MIL in cocaine users. In 1992, Hook and colleagues (139) described three patients, ages 45 to 74 years, who developed a cerebral demyelinating disease within 3 to 5 months of beginning adjuvant therapy with 5-fluroouracil (5-FU) and levamisole. Two patients presented with progressive encephalopathy and ataxia, and a third had unexplained loss of consciousness. Brain MRI revealed multiple gadolinium-enhanced white matter lesions, predominantly in a

periventricular distribution. Cerebrospinal fluid obtained in two patients showed oligoclonal bands (two patients) and pleocytosis (one patient). Pathological studies of brain biopsy specimens from two patients revealed cerebral demyelination and perivascular inflammation similar to multiple sclerosis (MS). There was clear improvement after discontinuation of chemotherapy and administration of corticosteroids. The pathogenesis was unclear, and the authors considered the etiological basis to be 5-FU toxicity although the role of levamisole was not excluded.

Three years later, Kimmel and colleagues (140) described a patient age 57 years, who developed progressive confusion and ataxia over a three-week period, five weeks after adjuvant therapy with levamisole for malignant melanoma. Brain MRI showed multifocal enhancing white matter lesions. Cerebrospinal fluid showed pleocytosis with an increased IgG index. The patient improved with a three-month tapering course of corticosteroids. The cause of the leukoencephalopathy in previously described cases (139) of 5-FU and levamisole was assigned at least in part, to levamisole.

One year later, Luppi and colleagues (141) described two patients, age 54 and 60 years, treated with adjuvant 5-FU and levamisole for colon cancer, who after 10 weeks and 6 weeks respectively from onset of treatment noted confusion, aphasia, ataxia, and progressive obtundation leading to decerebration (Case 1) and nasogastric feeding (Case 2). Brain MRI in both showed widespread bilaterally symmetric periventricular and hemispheric white matter hyperintensities compatible with MIL. Treatment with parenteral corticosteroids (Case 2) led to clinical improvement.

A decade later, Wu and coworkers (142) described a series of 31 patients with levamisole-induced MIL, including 7 from their institution and twenty-four from the medical literature, treated with a combination of levamisole and 5-FU adjuvant therapy (21 patients) or levamisole alone (10 patients) for malignant cancer, most commonly colon cancer.

Onset of gait ataxia in two-thirds of cases, was delayed in those treated with combination 5-FU and levamisole compared with levamisole alone (11.7 weeks vs. 2.5 weeks). Brain MRI showed enhancing periventricular or supratentorial white matter lesions. Cerebrospinal fluid showed lymphocytic pleocytosis in 47% of cases. Treatment with corticosteroids and intravenous immunoglobulin (Ig) led to improved clinical status in 29 (94%) cases.

In 2009, Xu and coworkers (143) described the clinical and neuroradiological findings in 16 patients, age 8 to 52 years, treated with levamisole for recurrent aphthous ulcers or ascarsis infections noting weakness (75%), aphasia (50%), neurocognitive (50%), and facial palsy (44%) as the main presenting clinical features. Brain MRI showed typical plaque and round or oval demyelinating enhancing white matter lesions and hyperintense signal on T_2/FLAIR images. Brain biopsy in one case showed multifocal demyelinating lesions with lymphocytic perivascular cuffs. Treatment with corticosteroids and hyperbaric oxygen led was associated with full recovery.

In 2012, Blanc and colleagues (144) described a 29-year-old woman and active crack cocaine abuser with acquired immune deficiency syndrome (AIDS) presented with fever, malaise, and back pain and an unremarkable neurological examination. Cerebrospinal fluid showed acellular fluid with increased protein content and oligoclonal bands. A urine drug screen showed cocaine and opiates. Brain MRI showed lesions consistent with MIL. Sera later tested for both cocaine and levamisole by gas chromatolography-mass spectroscopy were negative. The authors speculated that levamisole contamination was responsible for MIL citing

that urine testing for levamisole would have been positive if performed at the time of cocaine detection.

In 2013, Yan and colleagues (145) described the clinical and neuroradiologic features of 15 patients, age 31 to 54 years, treated with levamisole for worm expulsion for two weeks to two months prior to onset of fever, headache, dizziness, neurocognitive disturbance, weakness, and visual impairment. Nine patients who underwent CSF examination showed only pleocytosis. Electroencephalography in all 15 showed high amplitude slow waves. Brain MRI showed multiple hyperintense T2/FLAIR bilateral centrum semiovale and periventricular lesions (all patients), while two-thirds showed lesions in basal ganglia; with lesser frequency in the frontal (26%), occipital (6%), and temporal lobes (6%), brainstem or cerebellum (6%). Treatment with "hormone therapy" was effective in all patients.

In the same year, 2013, Gonzáález-Duarte and Williams (146) described a 40-year-old woman with chronic daily use of cocaine admitted for acute confusion, aphasia, and fever. Cerebrospinal fluid showed neutrophilic pleocytosis. Brain MRI showed hyperintense signal in left parietal lobe white matter on T_2/FLAIR images. She developed sudden visual changes and hemiparesis 10 days later, and a week after, a new episode of expressive aphasia each associated with respective right and left frontal white matter lesions reminiscent of MIL. Complete recovery occurred in two weeks and she remained stable without further new episodes despite continued cocaine abuse. The authors speculated a relationship to levamisole adulteration.

In 2015, Vosoughi and Schmidt (147) described MIL in two cocaine abusers, age 25 and 41 years, who presented respectively with unilateral progressing to bilateral sensorimotor deficits; and confusion with impaired balance. Serial brain MRI in the first patient showed increasing bilateral T_2/FLAIR enhancing white matter hyperintensities in periventricular white matter, pons and cerebellar peduncles, with similar presenting features in the second patients. Both patients improved with corticosteroids and plasma exchange. Urinary levamisole was not tested in either patient although the authors concluded that it was a likely cause of MIL in their cases.

Finally, Vitt and colleagues (148) described a case of MIL with positive urine testing for cocaine and levamisole in a cocaine abuser with a history of hepatitis C infection. This a 63-year-old woman presented with three days of progressive confusion, fever, and headache. Over two days she developed spastic quadriparesis and stupor. Cocaine tested positive in the urine. Brain MRI revealed T_2/FLAIR hyperintensities and incomplete ring-enhancement in periventricular subcortical white matter, many of which were ovoid shaped. Cerebrospinal fluid showed a lymphocytic pleocytosis and elevated protein content without oligoclonal bands. Gas chromatolography-mass spectroscopy detected levamisole in the urine. High-dose intravenous methylprednisolone for five days followed by plasmapheresis was ineffective. The patient received intravenous cyclophosphamide with stabilization. Ten months later, the patient was minimally conscious with mutism and generalized spasticity.

Immunopathogenic Mechanism

The mechanisms underlying levamisole-adulterated cocaine-induced systemic pathology are not well understood but a causal relation to ANCA-associated disease is suggested by the correlation of disease pathology, clinical relapse with detectable autoantibodies, sensitivity to immune modulatory and immunosuppressive therapy, and predictable levamisole-induced histopathology. Levamisole potentiates the production of interferon-α and interleukin-2 as well as increases T-cell activation and proliferation, neutrophil mobility, adherence, and chemotaxis

and increases the formation of antibodies to antigens (132). Is acts as a hapten, triggering an immune response resulting in opsonization and leukocyte destruction. Levamisole may interact with neutrophil extracellular traps (NET) composed of a complex of deoxyribonucleic acid (DNA), histones, and neutrophil granules including myeloperoxidase (MPO), proteinease-3 (PR3, and human neutrophil elastase (HNE). Neutrophil extracellular traps release in response to stress and provide a source of antigen that can activate the immune system (137). Although there has not been a postmortem-studied case of MIL, for unclear reasons, such patients fail to demonstrate vasculitis in brain biopsy tissue or symptomatic vasculitic skin pathology, renal, hematologic, or pulmonary involvement in life

CONCLUSION

Drug abuse is a rare cause of histopathologically verified CNS vasculitis. Nonetheless, the complications of illicit substance use on the cerebral circulation can be highly lethal with secondary vasculopathy, hemorrhage and aneurysm formation especially when the illicit substances are delivered parenterally. With only a handful of confirmed patients in the literature, and rare association if ever, with progressive neurological deficits, there is generally little justification for invasive laboratory investigation, especially given the availability of highly accurate vascular neuroimaging techniques. Management rests upon avoidance of further exposure and minimizing the secondary neurotoxic effects of the abused substances and polypharmacy use.

REFERENCES

[1] Wu, L. T. Substance abuse and rehabilitation: responding to the global burden of diseases attributable to substance abuse. *Subst. Abuse Rehabil.* 2010; 5-11.

[2] United Nations Office on Drugs and Crime. *World Drug Report 2010*. New York, NY: United Nations; 2010.

[3] Coffin, P. O., Galea, S., Ahern, J., et al. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990-98. *Addiction* 2003; 98:739-747.

[4] Jennette, J. C., Falk, R. J., Bacon, P. A., et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013; 65:1-11.

[5] Younger, D. Y., APJ. CNS Vasculitis. In: Coyle, P. R. S., editor. *Clinical Neuroimmunology: Multiple Sclerosis and Related Disorders: Springer*.

[6] Abbott, N. J., Patabendige, A. A., Dolman, D. E., et al. Structure and function of the blood-brain barrier. *Neurobiol. Dis*. 2010; 37:13-25.

[7] Benarroch, E. E. Blood-brain barrier: recent developments and clinical correlations. *Neurology*. 2012; 78:1268-1276.

[8] Ek, C. J., Dziegielewska, K. M., Habgood, M. D., et al. Barriers in the developing brain and Neurotoxicology. *Neurotoxicology*. 2012; 33:586-604.

[9] Benzedrine sulfate “pep pills" [Editorial]. *JAMA* 1937; 108:1973-1974.

[10] Smith, L. Collapse with death following the use of amphetamine sulfate. *AJAM*. 1939; 113:1022-1023.

[11] Gericke, O. Suicide by ingestion of amphetamine sulfate. *JAMA: The Journal of the American Medical Association*. 1945;128:1098-1099.

[12] Lloyd, J. T., Walker, D. R. Death after combined dexamphetamine and phenelzine. *Br. Med. J.* 1965; 2:168-169.

[13] Anglin, M. D., Burke, C., Perrochet, B., et al. History of the methamphetamine problem. *J. Psychactive Drugs* 2000; 32:137-141.

[14] United Nations Office on Drugs and Crime. *UNODC 2009 World Drug Report*. Vienne, Austria: United Nations; 2009.

[15] United Nations Office on Drugs and Crime. *World Drug Report 2000*. New York, NY: United Nations; 2000.

[16] Buttner, A. Review: The neuropathology of drug abuse. *Neuropathol. Appl. Neurobiol.* 2011; 37:118-134.

[17] Schep, L. J., Slaughter, R. J., Beasley, D. M. The clinical toxicology of methamfetamine. *Clin. Toxicol.* 2010; 48:675-694.

[18] Christophersen, A. S. Amphetamine designer drugs-an overview and epidemiology. *Toxicol. Lett.* 2000; 112-113:127-131.

[19] Kalasinsky, K. S., Bosy, T. Z., Schmunk, G. A., et al. Regional distribution of methamphetamine in autopsied brain of chronic human methamphetamine users. *Forensic Sci. Int.* 2001; 116:163-169.

[20] Parrott, A. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology* 2004; 173:234-241.

[21] Fonseca, A. C., Ferro, J. M. Drug abuse and stroke. *Curr. Neurol. Neurosci. Rep.* 2013; 13:325.

[22] Petitti, D. B., Sidney, S., Quesenberry, C., et al. Stroke and cocaine or amphetamine use. *Epidemiology* 1998; 9:596-600.

[23] Westover, A. N., McBride, S., Haley, R. W. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Archives of General Psychiatry*. 2007; 64:495-502.

[24] Kessler, J. T., Jortner, B. S., Adapon, B. D. Cerebral vasculitis in a drug abuser. *J. Clin. Psychiatry* 1978; 39:559-564.

[25] Bostwick, D. G. Amphetamine induced cerebral vasculitis. *Hum. Pathol.* 1981; 12: 1031-1033.

[26] Olsen, E. R. Intracranial hemorrhage and amphetamine usage. Review of the effects of amphetamines on the central nervous system. *Angiology* 1977; 28:464-471.

[27] Glick, R., Hoying, J., Cerullo, L., et al. Phenylpropanolamine: an over-the-counter drug causing central nervous system vasculitis and intracerebral hemorrhage. Case report and review. *Neurosurgery* 1987; 20:969-974.

[28] Trugman, J. Cerebral arteritis and oral methylampenidate. *Lancet* 1988; 1:584-585.

[29] Buxton, N., McConachie, N. S. Amphetamine abuse and intracranial haemorrhage. *J. R. Soc. Med.* 2000; 93:472-477.

[30] Coroner's Report. Amphetamine overdose kills boy. *The Pharmaceutical Journal* 1976; 198:172.

[31] Moriya, F. H., Hashimoto, Y. A case of fatal hemorrhage in the cerebral ventricles following intravenous use of methamphetamine. *Forensic Sci. Int.* 2002; 129:104-109.

[32] Shibata, S., Mori, K., Sekine, I., et al. [An autopsy case of subarachnoid and intracerebral hemorrhage and necrotizing angitis associated with methamphetamine abuse]. *No To Shinkei* 1988; 40:1089-1094.

[33] Delaney, P., Estes, M. Intracranial hemorrhage with amphetamine abuse. *Neurology* 1980; 30:1125-1128.

[34] Hall, C. B., Blanton, D. E., Scatliff, J. H., et al. Speed kills: fatality from the self-administration of methamphetamine intravenously. *South. Med. J.* 1973; 66:650-652.

[35] Byard, R. W., Gilbert, J., James, R., et al. Amphetamine derivative fatalities in South Australia--is "Ecstasy" the culprit? *Am. J. Forensic Med. Pathol.* 1998; 19:261-265.

[36] Perez, J. A. Jr., Arsura, E. L., Strategos, S. Methamphetamine-related stroke: four cases. *J. Emerg. Med.* 1999; 17:469-471.

[37] Ho, E. L., Josephson, S. A., Lee, H. S., et al. Cerebrovascular complications of methamphetamine abuse. *Neurocrit. Care* 2009; 10:295-305.

[38] Citron, B. P., Halpern, M., McCarron, M., et al. Necrotizing angiitis associated with drug abuse. *N. Enlg. J. Med.* 1970; 283:1003-1011.

[39] Gocke, D. C., CI. Angitiis in drug abusers [Letter]. *N. Engl. J. Med.* 1971;284:112.

[40] Gocke, D. J., Howe C. Rapid detection of Australian antigen by counterimmunoelectrophoresis. *J Immunol* 1970; 104:1031-1034.

[41] Gocke, D. J. Hsu, K., Morgan, C., et al. Association of polyarteritis and Australia antigen. *Lancet* 1970; 2:1149-1153.

[42] Citron, B., Peters, R. Angiitis in drug abusers [Letter]. *N. Engl. J. Med.* 1971; 1971; 284:111-113.

[43] Baden, M. Angiitis in drug abusers. *N. Engl. J. Med.* 1971; 284:111.

[44] Rumbaugh, C. L., Bergeron, R. T., Scanlan, R. L., et al. Cerebral vascular changes secondary to amphetamine abuse in the experimental animal. *Radiology*. 1971; 101: 345-351.

[45] Rumbaugh, C. L., Fang, H. C., Higgins, R. E., et al. Cerebral microvascular injury in experimental drug abuse. *Invest. Radiol.* 1976; 11:282-294.

[46] Levine, S. R., Welch, K. M. Cocaine and stroke. *Stroke* 1988; 19:779-783.

[47] Gay, G. R. Clinical management of acute and chronic cocaine poisoning. *Ann. Emerg. Med.* 1982; 11:562-572.

[48] Spiehler, V. R., Reed, D. Brain concentrations of cocaine and benzoylecgonine in fatal cases. *J. Forensic Sci.* 1985; 30:1003-1011.

[49] Barnett, G., Hawks, R., Resnick, R. Cocaine pharmacokinetics in humans. *J. Ethnopharmacol.* 1981; 3:353-66.

[50] Cregler, L. L., Mark, H. Medical complications of cocaine abuse. *N. Engl. J. Med.* 1986; 315:1495-1500.

[51] Ambre, J. R., Ruo, T. I., Smith, G. L., et al. Ecgonine methylester, a major metabolite of cocaine. *J. Anal. Toxicol.* 1982; 6:26-29.

[52] Quinn, D. I., Wodak, A., Day, R. O. Pharmacokinetic and pharmacodynamics principles of illicit drug use and treatment of illicit drug users. *Clin. Pharmacokinet.* 1997; 33:344-400.

[53] White, S. M., Lambe, C. J. The pathophysiology of cocaine abuse. *J. Clin. Forensic Med.* 2003; 10:27-39.

[54] Biegon, A., Dillon, K., Volkow, N. D., et al. Quantitative autoradiography of cocaine binding sites in human brain postmortem. *Synapse* 1992; 10:126-130.

[55] Kalasinsky, K. S., Bosy, T. Z., Schmunk, G. A., et al. Regional distribution of cocaine in postmortem brain of chronic human cocaine abusers. *J. Forensic Sci.* 2000; 45:1041-1048.

[56] Kreek, M. J., Levran, O., Reed, B., et al. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. *J. Clin. Invest.* 2012; 122:3387-3393.

[57] Kreek, M. J., Bart, G., Lilly, C., et al. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. *Pharmacol. Rev.* 2005;57:1-26.

[58] Brust, J. C., Richter, R. W. Stroke associated with cocaine abuse--? *NY State J. Med.* 1977; 77:1473-1475.

[59] Levine, S. R., Brust, J. C. M., Futrell, N., et al. Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N. Engl. J. Med.* 1990; 323:699-704.

[60] Daras, M., Tuchman, A. J., Marks, S. Central nervous system infarction related to cocaine abuse. *Stroke* 1991; 22:1320-1325.

[61] Nolte, K. B., Gelman, B. B. Intracerebral hemorrhage associated with cocaine abuse. *Arch. Pathol. Lab. Med.* 1989; 113:812-813.

[62] Kaye, B. R., Fainstat, M. Cerebral vasculitis associated with cocaine abuse. *JAMA* 1987; 258:2104-2106.

[63] Levine, S., JCM B, Welch, K. Cerebral vasculitis associated with cocaine abuse or subarachnoid hemorrhage?. *JAMA* 1988; 259:1648-1649.

[64] Krendel, D. A., Ditter, S. M., Frankel, M. R., et al. Biopsy-proven cerebral vasculitis associated with cocaine abuse. *Neurology*. 1990; 40:1092-1094.

[65] Fredericks, R. K., Lefkowitz, D. S., Challa, V. R., et al. Cerebral vasculitis associated with cocaine abuse. *Stroke* 1991; 22:1437-1439.

[66] Morrow, P. L., McQuillen, J. B. Cerebral vasculitis associated with cocaine abuse. *J. Forensic Sci.* 1993; 38:732-738.

[67] Tapia, J. F., JM S. Case 27-1993-A 32- year-old man with the sudden onset of a right-sided headache and left hemiplegia and hemianesthesia. *N. Engl. J. Med.* 1993; 329: 117-124.

[68] Merkel, P. A., Koroshetz, W. J., Irizarry, M. C., et al. Cocaine-associated cerebral vasculitis. *Semin. Arthritis Rheum.* 1995; 25:172-183.

[69] Martinez, N., Diez-Tejedor, E., Frank, A. Vasospasm/thrombus in cerebral ischemia related to cocaine abuse [Letter]. *Stroke* 1996; 27:147-148.

[70] Diez-Tejedor, E., Frank, A., Gutierrez, M., et al. Encephalopathy and biopsy-proven cerebrovascular inflammatory changes in a cocaine abuser. *Eur. J. Neurol.* 1998; 5:103-107.

[71] Fiala, M., Gan, X. H., Zhang, L., et al. Cocaine enhances monocyte migration across the blood-brain barrier. Cocaine's connection to AIDS dementia and vasculitis? *Adv. Exp. Med. Biol.* 1998; 437:199-205.

[72] Fiala, M., Gan, X.-H., Newton, T., et al. Divergent effects of cocaine on cytokine production by lymphocytes and monocytes/macrophages. *Adv. Exp. Med. Biol.* 1996; 402:145-156.

[73] Fiala, M., Looney, D. J., Stins, M., et al. TNF- α opens a paracellular route for HIV-1 invasion across the blood-brain barrier. *Mol. Med.* 1997; 3:553-564.

[74] Fiala, M., Rhodes, R. H., Shapshak, P., et al. Regulation of HIV-1 in astrocytes: expression of Nef-α and IL-6 is enhanced in coculture of astrocytes and macrophages. *J. Neurovirol.* 1996; 2:158-166.

[75] Gan, X., Zhang, L., Berger, O., et al. Cocaine enhances brain endothelial adhesion molecules and leukocyte migration. *Clin. Immunol.* 1999; 91:68-76.

[76] Zhang, L., Looney, D., Taub, D., et al. Cocaine opens the blood-brain barrier to HIV-1 invasion. *J. Neurovirol.* 1998; 4:619-626.

[77] Bagasra, O., Pomerantz, R. J. Human immunodeficiency virus type 1 replication in peripheral blood mononuclear cells in the presence of cocaine. *J. Infect. Dis.* 1993; 168: 1157-1164.

[78] Buch, S., Yao, H., Guo, M., et al. Cocaine and HIV-1 interplay in CNS: cellular and molecular mechanisms. *Curr. HIV Res.* 2012; 10:425-428.

[79] Beletsky, L., Rich, J. D., Walley, A. Y. Prevention of fatal opioid overdose. *JAMA* 2012; 308:1863-1864.

[80] Centers for Disease Control and Prevention. CDC grand rounds: prescription drug overdoses-a U.S. epidemic. *MMWR Morb. Mortal Wkly. Rep.* 2012; 61:10-13.

[81] Substance Abuse and Mental Health Services Administration. *Results from the 2009 national survey on drug use and health: Volume 1: Summary of national findings*. Substance Abuse and Mental Health Services Administration. Rockville, MD 2010.

[82] De Ridder, M. Heroin: new facts about an old myth. *J. Psychoactive Drugs* 1994; 26: 65-68.

[83] Sporer, K. A. Acute heroin overdose. *Ann. Intern. Med.* 1999; 130:584-590.

[84] Joe, G. W., Simpson, D. D. Mortality rates among opioid addicts in a longitudinal study. *Am. J. Public Health* 1987;77:347-348.

[85] Vaillant, G. A 20 year followup of New York narcotic addicts. *Arch. Gen. Psychiatry* 1973; 29:237-241.

[86] Oppenheimer, E., Tobutt, C., Taylor, C., et al. Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. *Addiction* 1994; 89:1299-1308.

[87] Davoli, M., Perucci, C. A., Forastiere, F., et al. Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users. *Int. J. Epidemiol.* 1993; 22: 273-277.

[88] Louria, D. B., Hensle, T., Rose, T. The major medical complications of heroin addiction. *Ann. Intern. Med.* 1967; 67:1-22.

[89] Adle-Biassette, H., Marc, B., Benhaiem-Sigaux, N., et al. Cerebral infarctions in a drug addict inhaling heroin. *Arch. Anat. Cytol. Pathol*. 1996; 44:12-17.

[90] Lignelli, G. J., WA B. Angiitis in drug abusers [Letter]. *N. Engl. J. Med.* 1971; 284: 112-113.

[91] Woods, B. T., Strewler, G. J. Hemiparesis occurring six hours after intravenous heroin injection. *Neurology* 1972; 22:863-866.

[92] Niehaus, L., Meyer, B. U. Bilateral borderzone brain infarctions in association with heroin abuse. *J. Neuroll. Sci.* 1998; 160:180-182.

[93] Benoilid, A., Collongues, N., de Seze, J., et al. Heroin inhalation-induced unilateral complete hippocampal stroke. *Neurocase* 2012; 19: 313-315.

[94] Bartolomei, F., Nicoli, F., Swiader, L., et al. [Ischemic cerebral vascular stroke after heroin sniffing. A new case]. *Presse Medicale* 1992; 21:983-986.

[95] Caplan, L. R., Hier, D. B., Banks, G. Current concepts of cerebrovascular disease--stroke: stroke and drug abuse. *Stroke* 1982; 13:869-872.

[96] Richter, R. W., Pearson, J., Bruun, B., et al. Neurological complications of addictions to heroin. *Bull. NY Acad. Med.* 1973; 49:3-21.

[97] Oehmichen, M., Meissner, C., Reiter, A., et al. Neuropathology in non-human immunodeficiency virus-infected drug addicts: hypoxic brain damage after chronic intravenous drug abuse. *Acta Neuropathol.* 1996; 91:642-646.

[98] Gray, F., Lescs, M. C., Keohane, C., et al. Early brain changes in HIV infection: neuropathological study of 11 HIV seropositive, non-AIDS cases. *J. Neuropathol. Exp. Neurol.* 1992; 51:177-185.

[99] Ramage, S. N., Anthony, I. C., Carnie, F. W., et al. Hyperphosphorylated tau and amyloid precursor protein deposition is increased in the brains of young drug abusers. *Neuropathol. Appl. Neurobiol.* 2005; 31:439-448.

[100] UNAIDS/WHO. *AIDS epidemic update 2005. 2005.*

[101] Snider, W. D., Simpson, D. M., Nielsen, S., et al. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann. Neurol.* 1983; 14: 403-418.

[102] Bell, J. E., Busuttil, A., Ironside, J. W., et al. Human immunodeficiency virus and the brain: investigation of virus load and neuropathologic changes in pre-AIDS subjects. *J. Infect. Dis.* 1993; 168:818-824.

[103] Nachega, J. B., Morroni, C., Chaisson, R. E., et al. Impact of immune reconstitution inflammatory syndrome on antiretroviral therapy adherence. *Patient Prefer Adherence* 2012; 6:887-891.

[104] Kumar, A. HIV and substance abuse. *Curr. HIV Res.* 2012; 10:365.

[105] Bell, J. E., Arango, J. C., Robertson, R., et al. HIV and drug misuse in the Edinburgh cohort. *J. Acq. Immune Defic. Syndr.* 2002; 31 (Suppl. 2):S35-S42.

[106] Bell, J. E., Arango, J. C., Anthony, I. C. Neurobiology of multiple insults: HIV-1-associated brain disorders in those who use illicit drugs. *J. Neuroimmune Pharmacol.* 2006; 1:182-191.

[107] Donahoe, R. M., Vlahov, D. Opiates as potential cofactors in progression of HIV-1 infections to AIDS. *J. Neuroimmunol.* 1998; 83:77-87.

[108] Bane, A., Annessley-Williams, D., Sweeney, E., et al. Cerebral vasculitis and haemorrhage in a HIV positive intravenous drug abuser. *Ir. Med. J.* 1999; 92:340.

[109] Tomlinson, G. S., Simmonds, P., Busuttil, A., et al. Upregulation of microglia in drug users with and without pre-symptomatic HIV infection. *Neuropathol. Appl. Neurobiol.* 1999; 25:369-379.

[110] Gosztonyi, G., Schmidt, V., Nickel, R., et al. Neuropathologic analysis of postmortal brain samples of HIV-seropositive and -seronegative i.v. drug addicts. *Forensic Sci. Int.* 1993; 62:101-105.

[111] Bell, J. E., Donaldson, Y. K., Lowrie, S., et al. Influence of risk group and zidovudine therapy on the development of HIV encephalitis and cognitive impairment in AIDS patients. *AIDS* 1996; 10:493-499.

[112] Sharer, L. R., Kapila, R. Neuropathologic observations in acquired immunodeficiency syndrome (AIDS). *Acta Neuropathol.* 1985; 66:188-198.

[113] McArthur, J. C., Haughey, N., Gartner, S., et al. Human immunodeficiency virus-associated dementia: an evolving disease. *J. Neurovirol.* 2003; 9:205-221.

[114] Price, R. W., Brew, B., Sidtis, J., et al. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science* 1988; 239:586-592.

[115] Petito, C. K. Review of central nervous system pathology in human immunodeficiency virus infection. *Ann. Neurol.* 1988; 23(Suppl.):S54-S57.

[116] Guillevin, L. Vasculitis in the context of HIV infection. *AIDS* 2008; 22(Suppl. 3):S27-S33.

[117] Ho, D. D., Sarngadharan, M. G., Resnick, L., et al. Primary human T-lymphotrophic virus type III infection. *Ann. Intern. Med.* 1985; 103:880-883.

[118] Albert, J., Gaines, H., Sonnerborg, A., et al. Isolation of human immunodeficiency virus (HIV) from plasma during primary HIV infection. *J. Med. Virol.* 1987; 23:67-73.

[119] Janssen, R. S., Cornblath, D. R., Epstein, L. G., et al. Human immunodeficiency virus (HIV) infection and the nervous system: report from the American Academy of Neurology AIDS Task Force. *Neurology* 1989; 39:119-122.

[120] Shaunak, S., Albright, R. E., Klotman, M. E., et al. Amplification of HIV-1 provirus from cerebrospinal fluid and its correlation with neurologic disease. *J. Infect. Dis.* 1990; 161:1068-1072.

[121] Koralnik, I. J., Beaumanoir, A., Häusler, R., et al. A controlled study of early neurological abnormalities in men with asymptomatic human immunodeficiency virus infection. *N. Engl. J. Med.* 1990; 323:864-870.

[122] Gray, F., Lescs, M. C., Keohane, C., et al. Early brain changes in HIV infection: neuropathological study of 11 HIV seropostive, non-AIDS cases. *Journal of Neuropathology and Experimental Neurology* 1992; 51:177-185.

[123] Yankner, B. A., Skolnik, P. R., Shoukimas, G. M., et al. Cerebral granulomatous angiitis associated with isolation of human T-lymphotropic virus type III from the central nervous system. *Ann. Neurol.* 1986; 20:362-364.

[124] Connor, M. D., Lammie, G. A., Bell, J. E., et al. Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV Autopsy Cohort. *Stroke* 2000; 31:2117-2126.

[125] Esiri, M. M., Scaravilli, F., Millard, P. R., et al. Neuropathology of HIV infection in haemophiliacs: comparative necropsy study. *BMJ* 1989; 299:1312-1315.

[126] Sharer, L. R., Michaels, J., Murphey-Corb, M., et al. Serial pathogenesis study of SIV brain infection. *J. Med. Primatol.* 1991; 20:211-217.

[127] Hurtrel, M., Ganiere, J. P., Guelfi, J. F., et al. Comparison of early and late feline immunodeficiency virus encephalopathies. *AIDS* 1992; 6:399-406.

[128] Gray, F., Keohane, C. The neuropathology of HIV infection in the era of Highly Active AntiRetroviral Therapy (HAART). *Brain Pathol.* 2003; 13:79-83.

[129] Van der Ven, A. J., van Oostenbrugge, R. J., Kubat, B., et al. Cerebral vasculitis after initiation antiretroviral therapy. *AIDS* 2002; 16:2362-2364.

[130] Langford, T. D., Letendre, S. L., Marcotte, T. D., et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. *AIDS* 2002; 16:1019-1029.

[131] Patel, A. K., Patel, K. K., Shah, S. D., et al. Immune reconstitution syndrome presenting with cerebral varicella zoster vasculitis in HIV-1-infected patient: a case report. *J. Int. Assoc. Physicians AIDS Care* 2006; 5:157-160.

[132] Amery WR, Bruynseels JP. Levamisole, the story and the lessons. *Int J Immunopharmacol* 1992;14:481-486.

[133] Valentino AM, Fuentecilla K. Levamisole: an analytical profile. *Microgram J* 2005; 3:134-137.

[134] Drug Intelligence brief: *Cocaine containing levamisole adversely affecting drug users in the United States* (DEA-10001-levamisode). Drug Enforcement Administration, Intelligence Production Unit. January 2010.

[135] Buchman JA, Heard K, Burbach C, et al. Prevlence of levamisole in urine toxicology screens positive for cocaine in an inner-city hospital. *JAMA* 2011; 305:16571658.

[136] Hofmaier T, Luf, Seddik A, et al. Aminorex, a metabolite of the cocaine adulterant levamisole, exerts amphetamine like actions at monoamine transporters. *Neurochem Int* 2014; 73:32-41.

[137] Nolan AI, Kuang-Yu J. Pathologic manfiestations of levamisole-adulterated cocaine exposure. *Diagnostic Pathology* 2015; 10:48.

[138] Rongioletti F, Chio L, Ginevi F, et al. Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. *Br J Dermatol* 1999; 140:948-951.

[139] Hook CC, Kimmel DW, Kvols LK, et al. Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992; 31:262-267.

[140] Kimmel DW, Wijdicks FM, Rodriguez M. Multifocal inflammatory leukoencephalopathy associated with levamisole therapy. *Neurology* 1995; 45:374-376.

[141] Luppi G, Zoboli A, Barbieri F, et al. Multifocal leukoencephalopathy associated with 5-flurouracil and levamisole adjuvant therapy for colon cancer. A report of two cases and review of the literature. *Ann Oncol* 1996; 7:412-415.

[142] Wu VC, Huang JW, Lien HC, et al. Levamisole-induced multifocal inflammatory leukoencephalopathy. Clinical characteristics, outcome, an dimpact of treatment in 31 patients. *Medicine* 2006; 85:203-213.

[143] Zu N, Zhou W, Shuyu Li, et al. Clinical and MRI characteristics of levamisole-induced leukoencephalopathy in 16 patients. *J Neuroimmaging* 2009; 19:326-331.

[144] Blanc PD, Chin C, Lynch KL. Multifocal inflammatory leukoencephalopathy associated with cocaine abuse: Is levamisole responsible? *Clinical Toxicology* 2012; 50:534-535.

[145] Yan R, Wu Q, Ren J, et al. Clinical features and magnetic image analysis of 15 cases of demyelinating leukoencephalopathy induced by levamisole. *Exp Ther Med* 2013; 6:71-74.

[146] Gonzáález-Duarte A, Williams R. Cocaine-induced recurrent leukoencephalopathy. The *Neuroradiology Journal* 2013; 26:511-513.

[147] Vosoughi R, Schmidt BJ. Multifocal leukoencephalopathy in cocaine users: a report of two cases and review of the literature. *BMC Neurology* 2015; 15:208.

[148] Vitt JR, Brown EG, Chow DS, et al. Confirmed case of levamisole-assocaited multofical inflammatory leukoencephalopathy in a cocaine user. *J Immunol* 2017; 305:128-130.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 12

PERIPHERAL NERVE VASCULITIS: CLASSIFICATION AND DISEASE ASSOCIATIONS

Kelly G. Gwathmey[1], MD, Jennifer A. Tracy[2], MD and P. James B. Dyck[2,*], MD

[1]Department of Neurology
Division of Neuromuscular Medicine
Virginia Commonwealth University Medical Center
Richmond, VA, US
[2]The Peripheral Neuropathy Research Center,
Mayo Clinic, Rochester, MN, US

ABSTRACT

The vasculitides are diverse disorders characterized by inflammation of vessel walls resulting in damage to the mural structures and ischemic injury. Necrotizing vasculitic lesions of peripheral nerve microvessels measuring 75 to 300 microns in diameter impact small arteries, large arterioles, and variably smaller vessels in the majority of primary and secondary systemic vasculitis. Microvasculitis is distinguished by transmural non-necrotizing inflammatory lesions affecting the smallest arterioles typically less than 40 microns, impacting smaller arterioles, endoneurial capillaries, and venules. These histopathological features are characteristic of several primary and secondary disorders, including nonsystemic vasculitic neuropathy and the interrelated disorders of diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, diabetic cervical radiculoplexus neuropathy, and painless diabetic motor neuropathy. The resultant clinical features in each of these vasculitic entities depend on the size of the vessels involved, the severity of the inflammatory process, and the location and cumulative extent of the lesions along the peripheral nerve.

In light of these observations, we favor a simplified binary clinicopathological classification of vasculitic neuropathy based upon the size of the affected vessels, and the separation into the broad categories of nerve large arteriole vasculitis and microvasculitis.

* Corresponding Author's Email: DyckPJames@mayo.edu.

Such categorization informs prognosis and the approach to treatment. This chapter reviews the essential aspects of the nosology and classification, clinicopathologic aspects, prognosis and selected management of the representative vasculitides.

Keywords: primary, secondary, vasculitic, systemic, non-systemic, radiculoplexus, diabetic, painless, motor, lumbosacral, microvasculitis

INTRODUCTION

Vasculitis of the peripheral nerves occurs when the walls of arteriae nervorum and other nerve microvessels are infiltrated and damaged by inflammatory cells with secondary ischemic injury [1]. Vasculitic processes may be systemic or restricted to the nerves. Systemic vasculitis is primary or secondary to other disorders such as a connective tissue disease, infectious process, paraneoplastic syndrome, or drugs [2, 3]. This chapter examines the classification, diagnosis, clinical features, and treatment of common primary and secondary systemic vasculitic neuropathy (SVN), non-systemic vasculitic neuropathy (NSVN), and other recently described radiculoplexus neuropathies, including diabetic lumbosacral radiculoplexus neuropathy (DLRPN) and non-diabetic LRPN, diabetic cervical radiculoplexus neuropathy (DCRPN), and painless diabetic motor neuropathy (PDMN).

Classification

There are several accepted classification schemes for systemic vasculitic neuropathy based on the clinical characteristics, histopathological features and underlying mechanisms. Over the last several decades the classification schemes have become gradually more complex due to the increasing number of disorders considered to be vasculitic [4–9]. Additional studies to further define the optimal classification scheme are ongoing (10).

In 2010, the Peripheral Nerve Society Task Force [4] proposed a classification scheme that categorized SVN into primary and secondary forms, NSVN, and other localized presentations (Table 1). In this classification pathologically-definite vasculitic neuropathy must meet the pathological criteria for an active or chronic lesion. The former required demonstration of cellular invasion of the walls of blood vessels and one or more signs of active vascular damage, including fibrinoid necrosis, endothelial loss/disruption, internal lamina loss/fragmentation, smooth muscle media loss/fragmentation/separation, acute thrombosis, vascular/perivascular hemorrhage or leukocytoclasia (Figure 1). Chronic vasculitic lesions require demonstration of chronic vascular damage with repair, including intimal hyperplasia, fibrosis of media, adventitial/periadventitial fibrosis or chronic thrombosis with recanalization. Non-systemic vasculitic neuropathy require pathology to be isolated to the peripheral nerves. The Peripheral Nerve Society guideline group adopted two new exclusionary criteria for NSVN, both with >95% specificity for SVN, namely antineutrophil cytoplasmic antibodies (ANCA) and erythrocyte sedimentation rate (ESR) >/100 mm/h [4].

Table 1. Classification of Peripheral Neuropathy-Associated Vasculitides

I. Primary systemic vasculitides
- 1. Predominantly small vessel vasculitis
  - a. Microscopic polyangiitis
  - b. Eosinophilic granulomatosis with polyangiitis
  - c. Granulomatosis with polyangiitis
  - d. Essential mixed cryoglobulinemia (non-HCV)
  - e. IgA vasculitis
- 2. Predominantly medium vessel vasculitis
  - a. Polyarteritis nodosa
- 3. Predominantly large vessel vasculitis
  - a. Giant cell arteritis

II. Secondary systemic vasculitides associated with one of the following
- 1. Connective tissue diseases
  - a. Rheumatoid arthritis
  - b. Systemic lupus erythematosus
  - c. Sjögren syndrome
  - d. Systemic sclerosis
  - e. Dermatomyositis
  - f. Mixed connective tissue disease
- 2. Sarcoidosis
- 3. Behcet disease
- 4. Infection due to HBV, HCV, HIV, CMV, leprosy, Lyme disease, and HTLV-I
- 5. Drugs
- 6. Malignancy
- 7. Inflammatory bowel disease
- 8. Hypocomplementemic urticarial vasculitis syndrome

III. Non-systemic/localized vasculitis
- 1. Non-systemic vasculitic neuropathy, including non-diabetic radiculoplexus neuropathy and some cases of Wartenberg migrant sensory neuritis
- 2. Diabetic radiculoplexus neuropathy
  - a. Diabetic lumbosacral radiculoplexus neuropathy
  - b. Diabetic cervical radiculoplexus neuropathy
  - c. Diabetic thoracic radiculopathy
  - d. Painless diabetic motor neuropathy
- 3. Localized cutaneous/neuropathic vasculitis
  - a. Cutaneous polyarteritis nodosa
  - b. Others

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

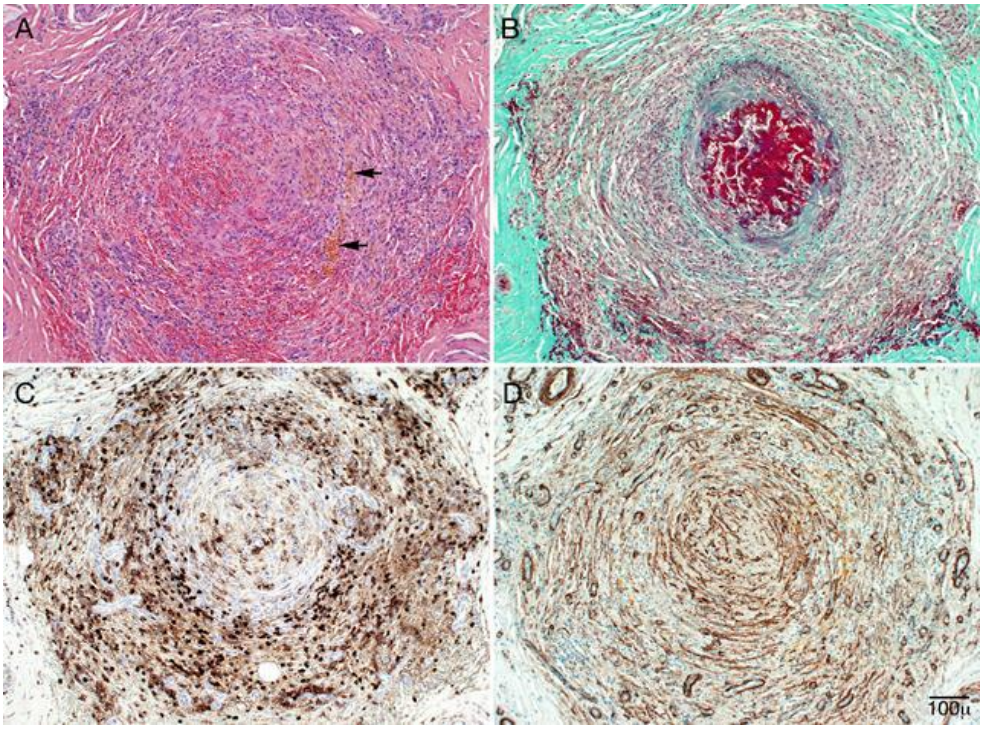


Figure 1. Serial tranverse paraffin sections of a sural nerve biopsy showing larger arteriole necrotizing vasculitis: Panel A (H&E) and B (Mason's trichrome) shows fibrinoid necrosis of the mural elements with inflammatory infiltration, orange discoloration (arrows), luminal occlusion and vessel wall destruction. Panel C (CD45) confirms the leukocyte infiltration and panel D (smooth muscle actin) shows the fragmentation and destruction of muscle layers with loss of normal architecture.

The Revised 2012 Chapel Hill Consensus Conference (CHCC) [5], which categorized the diverse forms of primary and secondary systemic vasculitis based upon the caliber of the vessels involved and the associated clinicopathologic features, did not directly consider NSVN. However, under their nosology [5], NSVN would be designated a single-organ vasculitis (SOV) of the peripheral nervous system (PNS), analogous to primary central nervous system (PCNS) vasculitis. Peripheral nerve involvement is distinctly uncommon in large vessel vasculitis that affects the aorta, its major branches and analogous veins. It is more prevalent in polyarteritis nodosa (PAN) which involves medium and small caliber vessels, notably visceral arteries and veins and their initial branches and small vessel vasculitis in association with ANCA and immune complexes, with involvement of intraparenchymal arteries, arterioles, capillaries, veins and venules. The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA), while vasculitic disorders associated with immune complexes include IgA vasculitis, cryoglobulinemic vasculitis, and hypocomplementemia urticarial vasculitis associated with C1q antibodies. There were in addition, separate categories for vasculitis associated with specific systemic connective tissue disorders such as rheumatoid arthritis and Sjögren syndrome, and disorders associated with a known systemic disorder such as might occur in paraneoplastic and infection-related vasculitis. Drug-related vasculitic neuropathies comprise a separate secondary systemic vasculitic neuropathy category.

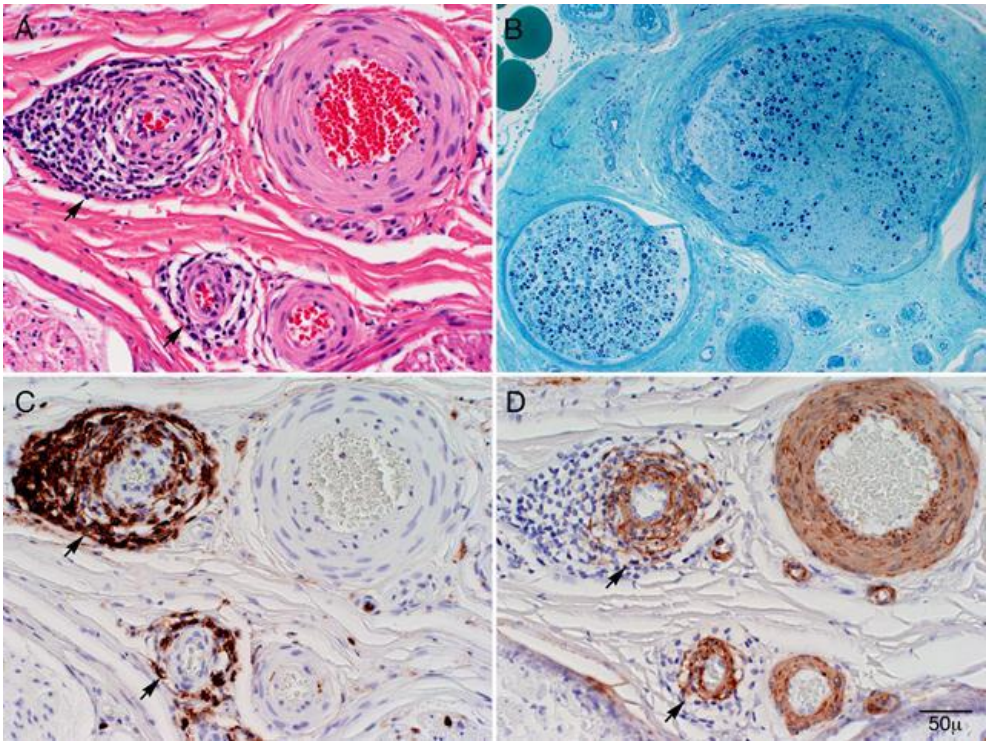


Figure 2. Serial transverse paraffin sections (panels A, C, and D) and an epoxy section (panel B) of a sural nerve showing nerve microvasculitis: Panel A (H&E) shows inflammation surrounding and involving two vessel walls (arrows), panel B (methylene blue) shows multifocal fiber loss with the upper right fascicle showing fiber degeneration and loss (typical ischemic injury) that can result from both large arteriole necrotizing vasculitis and microvasculitis, panel C (CD45) shows the transmural inflammation is mostly leukocytes (lymphocytes [arrows]), and panel D (smooth muscle actin) shows fragmentation and disruption of the muscular layers of vessel walls (arrows).

We favor a simplified binary classification of vasculitic neuropathies based on the size of the affected vessels into nerve large arteriole vasculitides and microvasculitis. This classification scheme is valuable as the prognosis and treatment approach differs between these two groups. The former category, which affects vessels ranging from 75 to 300 microns in diameter, involves small arteries, large arterioles and variably smaller vessels. As virtually all peripheral nerve vessels, even the largest intraneural arteries, can in a general sense be considered small vessels, it is possible to group most patients with PAN, AAV, and secondary vasculitis associated with connective tissue disease, infection and paraneoplasia in nerve large arteriole vasculitis [7]. By comparison, nerve microvasculitis, which includes DLRPN, LRPN, DCRPN and PDMN, involves small arterioles, endoneurial microvessels, capillaries and venules all measuring less than 40 microns. Nerve large arteriole vasculitis typically demonstrates fibrinoid necrosis, whereas microvasculitis is differentiated by inflammation in the vessel wall with fragmentation and necrosis of the tunica media (Figure 2). Common features to both forms of vasculitis include multifocal fiber loss, perineurial thickening, hemosiderin-laden macrophages, active Wallerian degeneration, neovascularization, and immune deposits of IgM, complement proteins, and fibrinogen in the epineurial vessel walls. The overlap of vessel size in NSVN was anticipated in the Revised 2012 CHCC (5), nonetheless

most cases of NSVN fit better into the microvasculitis than the nerve large arteriole vasculitis category.

Clinical Features

The clinical presentation of a vasculitic neuropathy depends on the distribution and severity of blood vessel involvement. Patients with primary and secondary systemic vasculitis typically manifest severe multiorgan symptoms that can overshadow the peripheral nervous system involvement. However, one-quarter of patients with PAN and AAV may have neuropathy as a heralding feature [11]. Patients typically display constitutional symptoms including weight loss, fatigue, fever, rash or night sweats. Other organs may also be involved with evidence of respiratory symptoms, skin manifestations, gastrointestinal symptoms, and hematuria [12–15]. In contrast, NSVN is not accompanied by extraneural involvement, although constitutional symptoms such as fatigue, weight loss, arthralgia, and myalgia occur in up to one-third of patients [4, 9].

Patients with both SVN and NSVN will typically present with acute to subacute onset of painful sensory or sensorimotor mononeuropathies followed by stepwise involvement of other nerves resulting in mononeuropathy multiplex (otherwise known as multiple mononeuropathy. Some patients have a fulminant presentation, whereas others have a more slowly progressive form and may go undiagnosed for up to a decade or longer, especially those reported with NSVN [16, 17]. Although vasculitic neuropathies are classically associated with a multiple mononeuropathy presentation, a given patient may demonstrate overlapping mononeuropathies that instead resemble distal predominant symmetrical or asymmetrical polyneuropathy [2, 13]. The pattern frequencies are multifocal neuropathy, 45%; asymmetric neuropathy, 35%; and distal symmetric polyneuropathy, 20% (4,18). One-third of patients present with slowly progressive neuropathy that does not develop in a stepwise fashion [19–21]. Vasculitis has a predilection for particular nerves including the common fibular mixed nerve, the fibular division of the sciatic nerve in the legs, and the ulnar nerve in the arm [22, 23]. Cranial neuropathy, which occurs infrequently in NSVN, may be seen in those with EGPA [24] and less often in GPA [25, 26].

NERVE LARGE ARTERIOLES VASCULITIS

Primary Systemic Vasculitis

Polyarteritis Nodosa

This multisystem disorder affects both small and medium-sized arteries and is the commonest type of primary vasculitic neuropathy so noted in up to 70% of patients [27, 28]. The skin and peripheral nervous system are the two organs most commonly involved (27). Renal arteritis, hepatitis B virus (HBV) infection and antigenemia, and visceral microaneurysms can all fall in the clinical spectrum of PAN [27, 29]. In contrast to AAV, PAN spares the lungs [30].

ANCA-Associated Vasculitis

Microscopic Polyangiitis

This AAV affects large arterioles and is associated with p-ANCA (or myeloperoxidase [MPO]-ANCA) in 50 to 70% of patients, and c-ANCA (or proteinase 3 [PR3]-ANCA) in 20 to 30% [31]. This disorder is differentiated from other AAV by the absence of granulomas. The incidence of MPA in Europe ranges from 3 to 10 per million [32] with a usual age at diagnosis of 60 to 70 years [33, 34]. Most patients have constitutional symptoms at the time of diagnosis. Renal involvement, notably progressive glomerulonephritis occurs in 80% of patients, while peripheral neuropathy occurs in about 50% of patients [18, 35, 36]. Estimates of pulmonary involvement vary widely ranging from 25-92% [37, 38]. Alveolar hemorrhage caused by pulmonary capillaritis is the classic manifestation and is reported in up to 55% of patients [39, 40]. Skin lesions such as palpable purpura and gastrointestinal symptoms such as abdominal pain occur nearly 50% of the time (Greco 2015).

Eosinophilic Granulomatosis with Polyangiitis

This category of AAV affects small-sized vessels and large arterioles. The Lanham clinical diagnostic criteria required asthma, eosinophilia of greater than 1500/mm^3, and vasculitis involving two or more non-pulmonary sites, not uncommonly in association with sinusitis [41]. The American College of Rheumatology 1990 Criteria requires 4 out of 6 of the following: asthma, eosinophilia, history of allergy, pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils [42]. The disorder affects younger people with a mean age at diagnosis of 48 to 52 years [12, 43–46]. Neuropathy occurs in 60 to 70% of patients with infrequent cranial nerve involvement [12, 36, 41, 44, 45, 47, 48]. About 30 to 40% of patients display ANCA-seropositivity, typically p-ANCA [12, 41, 49]. ANCA-positive patients are more likely to have peripheral nerve involvement and glomerular nephritis whereas cardiomyopathy is more common in ANCA-negative patients [12, 44, 50].

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis primarily affects the lungs and kidneys [51–53], though the skin, heart and GI tract may also be involved [54]. The disease presents in two stages, first with localized granulomatous inflammation of the respiratory tracts resulting in nasal ulceration, nasoseptal perforation, sinusitis, conductive hearing loss and otitis media. The next stage is generalized vasculitis heralded by constitutional symptoms and vasculitic involvement of the upper respiratory tract, lungs, kidneys and eyes [18, 52]. Neuropathy occurs in approximately 25% of patients [55]. With cranial involvement in between 15% to 33% of patients with GPA [14, 25, 56, 57]. GPA has an estimated relapse rate of 50% [51, 58].

Secondary Systemic Vasculitis

Rheumatoid Vasculitis

Rheumatoid vasculitis (RV) typically affects small to medium-sized arteries, including smaller arterioles, capillaries and venules [59], and is typically a late manifestation of severe seropositive RA. Vasculitic neuropathy occurs in 40 to 50% of patients with RV and in about

10% of patients with RA [47, 60]. Smoking, vascular disease and severity of RA are risk factors for RV [61]. Despite aggressive treatment, mortality rates remain high at approximately 25% over 5 years [61]. Central fascicular fiber degeneration distal to the site of ischemia with multifocal fiber loss and axonal degeneration was found among more than 15,000 serial skip sections in tissue sections of the roots, lumbosacral plexus, fibular and tibial nerves at postmortem examination of a patient with RV and peripheral neuropathy [18]. In spite of necrotizing vasculitis of small arteries and large arterioles, there was no evidence of ischemic nerve injury until the mid-sciatic vascular watershed zone, the latter of which is now regarded as the initial site of nerve infarction in many forms of vasculitic neuropathy.

Sjögren Syndrome

Estimates of peripheral nerve involvement in Sjögren syndrome vary from 2 to 64% [62] with presentation of trigeminal sensory neuropathy, distal sensorimotor neuropathy, small or large fiber sensory neuronopathy, autonomic neuropathy, and multiple mononeuropathy [47, 63, 64]. The latter neuropathy was encountered in 3 to 12% of patients as a manifestation of vasculitic neuropathy [47, 64]. Sjögren syndrome may be associated with either nerve large arteriole or microvasculitis with perivascular cellular invasion as the most common histological feature in one series [64].

Viral Infection

Certain viral infections which persist in the body for long periods of time, such as HBV, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Parvovirus B19, demonstrate good associations with vasculitis and vasculitic neuropathies [65–67]. Those with HBV infection who also go on to develop PAN typically do so within the first 9 months of the acute hepatitis [68]. Moreover, circulating HBV surface antigenemia, so noted in 10 to 50% of patients with PAN, does not distinguish the 1 to 5% who go on to develop PAN (69). Hepatitis is often undiagnosed prior to the onset of PAN when clinically latent. Although clinical symptoms may be similar, peripheral neuropathy was more common in HBV-related PAN than those without concomitant HBV infection, so noted by Pagnoux and colleagues [27] in 85% of patients with HBV-related PAN.

Chronic HCV infection is a determinant of cryoglobulinemic vasculitis (CV) [70], with up to 65% of patients with HCV-related CV developing clinically significant peripheral neuropathy. Affected patients present with palpable purpura, glomerulonephritis, leg ulcers, arthritis, and sicca syndrome. Tissue damage in CV results from complement-dependent immune complex mediated inflammation of small blood vessels [71] with 85% of patients manifesting overtly abnormal electrodiagnostic findings [72]. In one relatively large series of patients, CV neuropathy comprised of only 8% of 71 patients with cryoglobulinemic neuropathy [73]. Patients with HCV-associated PAN similarly also develop vasculitic neuropathy in the absence of cryoglobulinemia [74]. In contrast to HCV-associated CV, HCV-associated PAN patients had a higher incidence of constitutional symptoms, multiple mononeuropathy, livedo, hypertension and GI tract involvement [74].

Paraneoplastic Vasculitis

Paraneoplastic vasculitic neuropathy occurs in the setting of hematologic tumors, thymoma, and small cell lung cancer with lesions confined to the peripheral nerves and muscles

in biopsy and postmortem tissue sections [75, 76]. Anti-Hu or serum antineuronal nuclear antigen-2 (ANNA-2) autoantibodies are associated with paraneoplastic vasculitic peripheral neuropathies [77] In contrast to paraneoplastic vasculitis, solid tumors are more often associated with paraneoplastic vasculitic neuropathies than hematological malignancies [78]. Sensory ataxia and autonomic dysfunction may occur in patients who harbor anti-Hu antibodies.

Drug-Induced Vasculitis

Several drugs have recently been associated with vasculitic neuropathies. Minocycline, which is a tetracycline derivative used for acne vulgaris, has been reported to trigger a vasculitic neuropathy in several patients [79, 80]. The time course from time of initiation of the minocycline to development of peripheral nerve vasculitis is variable. Discontinuation of minocycline and initiation of corticosteroids and other immunosuppressant drugs results in improvement. Minocycline has interestingly also been associated with CNS vasculitis [81].

Cocaine has been implicated as a trigger in AAV [82]. Cocaine may actually spark a pseudovasculitis rather than the true vasculitis seen in systemic AAV [83]. Patients will have sinus involvement, a vasculitic purpuric rash, inflammatory arthritis and peripheral neuropathy. ANCA positivity may be c-ANCA or p-ANCA [82]. Corticosteroids and steroid sparing agents may be used.

Anti-programmed death 1 (PD-1) antibodies, such as pembrolizumab or nivolumab, are used in the treatment of solid-organ tumors and hematological cancers [84]. These immune checkpoint inhibitors have been associated with various autoimmune complications including two cases of vasculitic neuropathy [84, 85] In addition to discontinuation of the antibody treatment, additional immunotherapy may be necessary [84].

MICROVASCULITIS

Non-Systemic Vasculitic Neuropathy

NSVN differs from SVN in its restriction to the nerves secondarily affecting muscle, the slow progression, and non-fatal outcome [47]. There are typically less severe constitutional symptoms or less markedly abnormal laboratory studies. Approximately one-third of patients report a weight loss and 10 to 13% note fever [9]. As a result of slow, progressive development of asymmetric and multifocal neurological deficits, there is often a longer delay, in some reports up to 14 years, to diagnosis than systemic vasculitic neuropathy [16, 17, 86, 87]. Overall, 45% have an asymmetric neuropathy, 33% multifocal neuropathy and 23% symmetric polyneuropathy [9]. Patients with NSVN typically present with pain and weakness that commences unilaterally and spreads to the contralateral side in 80 to 90% of patients. Twenty percent of patients will have no pain [9]. Affected patients classically manifest sensorimotor symptoms and signs, with 15% of patients presenting a sensory-predominant syndrome depending upon both the precise location and extent of the vasculitic lesion in the mixed nerve and selective involvement of sensory branches [18]. Continued monitoring is recommended for those with NSVN since 10% of affected patients may evolve into SVN. Most patients continue to be ambulatory and independent in activities of daily living [9]. Sugiura and colleagues [88]

considered NSVN, noting the clinicopathologic similarity to MPA, in spite of restriction of relapses to the PNS, the absence of ANCA-seropositivity, and overall improved prognosis of the former. Takahashi and colleagues, however, demonstrated a distinct pathogenesis in NSVN and MPA [89]. In both ANCA-positive and ANCA-negative MPA, neutrophils attach to vascular endothelial cells, whereas complement plays more integral role in NSVN with C3d deposition in epineurial small vessels. The antigens most often identified in the inflammatory lymphocytic infiltrates in NSVN include CD52, BAFF, and CD49d which were expressed in the epineurial, perivascular and intramural lymphocytes in all 20 treatment-naïve sural nerve biopsies in one series [90].

Diabetic Lumbosacral Radiculoplexus Neuropathy

Dyck and coworkers [91] described monophasic severe lower leg pain and weakness that commenced unilaterally, with delayed involvement of the other leg in an asymmetrical pattern affecting both the proximal and distal lower extremities in middle to later age type 2 diabetics with relatively good glycemic control. The onset of pain and weakness is often heralded by significant weight loss, a median of 30 pounds in the Dyck study [91]. There is generally a lack of correlation between developing DLRPN and a greater duration or severity of diabetes mellitus, as opposed to cases of typical diabetic polyneuropathy. Sharp, lancinating allodynic pain and burning sensations along the legs are typical presenting features. Sensory impairments become overshadowed by leg weakness, which is the most disabling feature, prompting use of ambulatory aids including wheelchairs in one-half of patients [91]. The non-diabetic form "LRPN" has an identical presentation of monophasic severe lower leg pain and weakness [92, 93]. Unlike other forms of vasculitic neuropathy, multiple leg and thigh nerves, lumbosacral plexus and nerve roots are affected. Electrodiagnostic studies reveal active axonal features and acute spontaneous activity in multiple proximal and distal lower leg muscles and in lumbosacral paraspinal muscles, and motor unit potential changes consistent with a radiculoplexus (involving root, plexus and peripheral nerve) neuropathy as the term LRPN implies. Autonomic nervous system (ANS) involvement occurs in approximately one-half of patients. There may be associated thoracic radiculopathy and mononeuropathy of the arms, and less commonly cervical radiculoplexus neuropathy [91]. An etiopathogenesis attributed to microvasculitis-induced ischemic injury was postulated in a series of 33 prospectively studied patients with DLRPN [91] in whom biopsy of a distal cutaneous nerve revealed neovascularization, injury neuroma, perineurial thickening, multifocal fiber loss and abnormal amounts of inflammation, one-half of the biopsied nerves showed findings diagnostic or suggestive of microvasculitis. Further in support of a vasculitic ischemic etiopathogenesis, was the finding of necrotizing arteritis in biopsy tissue of the superficial fibular cutaneous nerve of a patient with clinically apparent DLRPN [94] in whom postmortem examination also showed epineurial perivascular inflammation of the femoral nerve, lumbar plexus and roots. Although spontaneous improvement is expected, recovery is often incomplete with foot drop being the most common long-term sequela.

Diabetic Cervical Radiculoplexus Neuropathy

Massie and colleagues [95] reported a series of 85 patients with DCRPN, most of whom were type 2 diabetics, with a mean age of 62 years. The commonest presenting symptoms were pain noted in 69 (81%), and numbness in 56 (66%) of patients, which were overshadowed by weakness noted in all but one patient. In contrast to DLRPN, the presentation was more acute

and clinical deficits peaked in the first week. Moreover, unlike brachial plexus neuritis, which typically manifests upper trunk involvement, the upper, middle and lower plexuses are equally affected in DCRPN, with about 30% of patients demonstrating pan-plexus involvement. Electrodiagnostic studies showed axonal neuropathy in all 80 patients studied, with evidence of paraspinal denervation in 32%, with abnormal ANS testing (evaluating cardiovagal, cardioadrenergic, and post-ganglionic sudomotor function) in 96%, and abnormal quantitative sensory testing in 77%. Altogether, 44 (52%) patients had one or more additional body regions affected including 30 contralateral cervical, 20 lumbosacral, and 16 thoracic regions. Evidence of ischemic nerve injury was the predominant feature in cutaneous nerve biopsy tissues, within which epineurial perivascular inflammation was seen in all 22 specimens, microvasculitis in 5 (23%), multifocal nerve fiber loss in 15 (68%) and inflammation involving vessel walls in 14 (64%). The pathological findings were essentially the same as found in diabetic and non-diabetic LRPN. Given the clinicopathologic similarity to DLRPN these two disorders are categorized together in the spectrum of diabetic radiculoplexus neuropathy.

Painless Diabetic Motor Neuropathy

Garces-Sanchez and colleagues [96] described painless diabetic motor and lower limb-predominant neuropathy among 23 patients of mean age 62 years, 22 (96%) of whom had type 2 diabetes. Similar to those with DLRPN and LRPN, chronic diabetic complications were uncommon and weight loss was typical. Most patients had gradual onset of bilateral foot-drop that spread to the proximal legs and occasionally the arms. However, in comparison to DLRPN, the neurological deficits of those with PDMN were more severe with over one-half of patients confined to a wheelchair by the time of presentation. Despite the motor-predominant presentation, most had sensory symptoms, less than one-half of affected patients had ANS involvement, and significantly more patients had arm involvement compared to patients with DLRPN. Electrodiagnostic studies showed pan-modality sensory loss, ANS abnormalities, and axonal polyradiculopathy with lumbosacral paraspinal muscle denervation. Cutaneous nerve biopsy findings showed ischemic injury like other radiculoplexus neuropathies, with evidence of epineurial perivascular inflammation in all 23, with vessel wall invasion in 15 (65%) and microvasculitis in 4 (13%) of nerves. Given the absence of ischemic injury and microvasculitis in nerve biopsy specimens of analogous patients with diabetic chronic inflammatory demyelinating polyradiculopathy (CIDP), the authors (96) concluded that the patients with PDMN were best classified as a form of radiculoplexus neuropathy rather than a form of diabetic CIDP.

DIAGNOSIS

There is general agreement on four principles in the diagnosis of vasculitis which are applicable to peripheral nerve vasculitis [1]. First, vasculitis is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction. Therefore, prompt recognition of the typical neurologic manifestations of peripheral nerve vasculitis is key to placing it high up in the differential etiologic diagnosis of peripheral neuropathy. Second, undiagnosed and therefore untreated, there is a likelihood of excess morbidity. Third, a favorable response to an empiric course of immunosuppressive and immunomodulating therapy

should never be considered a substitute for the absolute proof of the laboratory diagnosis of vasculitis. Fourth, histopathologic confirmation of vasculitis is essential for the accurate diagnosis of peripheral nerve vasculitis, such as by analysis of nerve and muscle biopsy tissue when PNS involvement is postulated.

All patients with peripheral neuropathy due to suspected primary or secondary peripheral nerve vasculitis should be thoroughly evaluated for systemic involvement including disease-specific serological studies guided by the clinical presentation and postulated etiologic diagnosis to avoid excessive cost and spurious results. ANCA serology is mandatory in the evaluation of suspected SVN. ANCA are a family of autoantibodies that react with proteins that are expressed in cytoplasmic granules of polymorphonuclear cells. The presumptive ANCA autoimmune response, which is regarded as a multifactorial process that includes genetic predisposition, environmental factors, an initiating antigen, and altered T-cell regulation, primes neutrophils by binding to certain antigens expressed on their surface, and ANCA-activated neutrophils contribute to an inflammatory amplification loop that recruits other effector cells leading to granuloma formation [97]. However, there are significant differences in sensitivity, specificity and predictive value among commercially-available ANCA enzyme-linked immunosorbent assay (ELISA) kits. An International Consensus Statement [98, 99] suggested guidelines for ANCA testing recommending screening by standard immunofluorescence tests (IFT) and mandatory antigen-specific ELISA for positive IFT tests. The three major IFT patterns [100] including, granular cytoplasmic neutrophil fluorescence with central interlobular accentuation, perinuclear neutrophil staining often with nuclear extension, and another comprising a mix of cytoplasmic and perinuclear fluorescence, correlate respectively with C-ANCA, P-ANCA, and atypical ANCA with multiple specificities. C-ANCA-seropositivity typically occurs in patients with active generalized GPA, whereas P-ANCA occurs in patients with MPA and EGPA; ANCA with multiple antigen specificities often occurs in the absence of vasculitis. Autoantibodies with specificity for myeloperoxidase are referred to as MPO-ANCA and those against proteinase-3 are PR3-ANCA. The c-ANCA pattern is in most cases caused by antibodies to PR3. P-ANCA pattern is less specific, but MPO is an antigen associated with this pattern [101].

Biomarkers are emerging as potentially useful predictors of disease activity including neurofilament light chain and VEGF [102, 103]. There are published consensus recommendations for the laboratory investigation of suspected vasculitic neuropathy (Table 2) [4].

Table 2. Recommended laboratory studies in suspected vasculitic neuropathy

Initial studies: Complete blood count with differential (for eosinophil count), comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate, C-reactive protein, anti-neutrophil cytoplasmic antibodies (autoantibodies to proteinase-3 and myeloperoxidase), serum protein electrophoresis, complement levels (including C3, C4, and total), glycosylated hemoglobin, or 2 hour glucose tolerance test, hepatitis B surface antigen, hepatitis C antibodies, cryoglobulins, chest x-ray, and urinalysis.
Additional studies: Extractable nuclear antigen profile (including SSA/SSB antibodies), double-stranded DNA antibodies, rheumatoid factor, cyclic citrullinated peptide antibodies, angiotensin converting enzyme, human immunodeficiency virus antibodies, paraneoplastic autoantibodies, salivary gland biopsy, and malignancy imaging.

Electrodiagnostic studies are useful in the initial investigation of vasculitis because they can identify areas of asymptomatic involvement, sites for muscle and nerve biopsy, and when combined with the clinical and laboratory evaluation, support the specific neuropathic syndrome with a high degree of certainty. A wide sampling of nerves and muscles should be examined, both distal and proximal, with side-to-side comparisons. Most patients with peripheral nerve vasculitis will have multiple, acute or subacute, axonal mononeuropathies. Over time, a distal symmetric or asymmetric pattern due to the confluent nature of additional superimposed vasculitic lesions may be appreciated.

In patients suspected to have a vasculitic neuropathy, open biopsy of a cutaneous sensory nerve and companion muscle tissue are indispensable in the evaluation of primary and secondary peripheral nerve vasculitis. However, they should only be performed at major neuromuscular centers to assure that all necessary specimens are obtained, and they are processed correctly for light microscopy of cryostat- and paraffin-stained hematoxylin and eosin (H&E) sections, supplemented by plastic embedded, 1-mm semithin sections, and teased nerve fiber analysis. Such studies generally show evidence of axonopathy with Wallerian degeneration due to nerve ischemia and vasculitis supported by the presence of myelin ovoids, myelin debris, macrophage recruitment along the course of degenerated fibers, marked fascicular depletion of myelinated and unmyelinated nerve fibers, and endoneurial fibrosis. Immunocytochemical studies including lymphocyte cell marker analysis and complement immunofluorescence can be performed to identify activated components of the cell-mediated and humoral immune system. Cutaneous nerve biopsy is generally unnecessary in those with obvious DLRPN, LRPN, DCRPN and new-onset of multifocal neuropathy and known systemic vasculitis. However, cutaneous nerve biopsy may be useful in cases of prolonged DLRPN, LRPN and DCRPN where the disease course is protracted a year or more, and the treating physician needs to know if there is active microvasculitis. It may also be beneficial in cases with atypical clinical, electrophysiological, and magnetic resonance imaging (MRI) features, to accurately confirm the diagnosis. The sural nerve and superficial fibular sensory nerves are the commonest nerves studied in the legs, likewise the superficial radial sensory nerve for the evaluation of vasculitis in the upper limbs [2]. The addition of soleus or peroneus brevis muscle from the same incision as the sural and superficial fibular sensory nerves increased the yield of vasculitis by 15 to 25%, to an estimated overall sensitivity of 50 to 60% in several series [2, 104, 105]. Deprez and coworkers [106] studied clinicopathologic correlations in 355 retrospective patients with peripheral neuropathies noting a greater yield of nerve biopsy in those with multifocal and asymmetrical patterns, and a clinical onset-to-biopsy interval of less than six months. Chalk and colleagues [107] studied the diagnostic usefulness of ANCA serology in 166 consecutive patients, noting ANCA-seropositivity in four of six patients with vasculitic neuropathy; however, false-positive results limits its diagnostic usefulness in peripheral neuropathy.

TREATMENT

Treatment of vasculitic neuropathy can be divided into 3 broad categories including treatment of non-infectious nerve large arteriole vasculitis (including primary SVN and secondary SVN); treatment of infectious nerve large arteriole vasculitis, and treatment of

NSVN and other microvasculitides. Treatment of SVN should be initiated immediately as the one-year mortality rate approaches 90% in untreated patients with GPA and PAN compared to 12 to 20% among those promptly treated [4, 108]. The usual approach to treatment is induction of remission followed by long-term maintenance therapy which is continued for 18 to 24 months [109–113]. Corticosteroids are standard initial therapy for both SVN and NSVN. The addition of cyclophosphamide is usually necessary in those with MPA and GPA, and in others with NSVN who progress while on corticosteroids alone. A good tool for assessing response to treatment is the Neuropathy Impairment Score (NIS) because it combines weakness, reflex changes and sensory loss, as well as a standard neurological examination and follow up electrodiagnostic studies. The 1996 and 2009 revised Five-Factor Score (FFS) can help prognosticate in patients with PAN, MPA, EGPA, and GPA [114, 115]. Four factors are each allocated one point: renal insufficiency, cardiomyopathy, severe gastrointestinal manifestations, and age >65. ENT involvement, the fifth factor, is considered protective, so if absent, is allocated one point. The fifth factor is only used for EGPA and GPA. Five-year mortality rates for scores of 0, 1, and >/2 were 9%, 21%, and 40% respectively. Neuropathy itself does not affect survival. If new neurological deficits develop, treatment should be escalated [3, 4, 7, 27, 116–118], The starting dose of prednisone is 1.0 mg/kg/day and in severe cases is administered intravenously as methylprednisolone at a dose of 1000 mg for 3 to 5 days, followed by oral prednisone [119]. Oral prednisone is slowly tapered by 5 to 10 mg every few weeks after one to two months depending on the patient's response and severity of the disease [7, 120]. The erythrocyte sedimentation rate (ESR) and other markers of acute inflammation [2], including ANCA levels in those with AAV [121], should be monitored at baseline and with treatment. Maximal improvement occurs in 6 to 24 months after initiation of corticosteroids due to the slow pace of axonal regeneration. When needed, cyclophosphamide can be administered as an intravenous pulsed dose or as daily oral therapy with anticipated equal efficacy, however oral cyclophosphamide is associated with a higher incidence of side effects [122–127]. Intravenous pulse therapy is associated with higher relapse rate upon follow up [127]. Once remission is achieved with cyclophosphamide and prednisone, methotrexate or azathioprine can be substituted for the cyclophosphamide [128–130]. Patients with refractory disease despite treatment with cyclophosphamide and corticosteroids can be treated effectively with rituximab [4, 131–133]. Newer treatment protocols that combine rituximab, intravenous cyclophosphamide and oral prednisone in AAV have recently been published [134]. There is continued research to determine the best regimen for AAV patients [135] with rituximab emerging as likely first line therapy [136]. Other options include intravenous immune globulin (IVIg), plasma exchange, and mycophenolate mofetil.

Azathioprine is used as alternative maintenance therapy to cyclophosphamide in those with SVN and NSVN especially those in whom remission has been induced with cyclophosphamide. The timing of discontinuation of azathioprine does not clearly influence the relapse rate in AAV [137]. Azathioprine should not be added to corticosteroids to induce remission in AAV as it does not improve remission rates, lower the risk of relapse, or spare steroids [138]. Methotrexate can be used with corticosteroids for induction of remission in mild, non-life-threatening AAV and in patients with SVN and typical NSVN in lieu of azathioprine for remission maintenance following cyclophosphamide induction [7]. Methotrexate should be continued for 18 to 24 months prior to attempted tapering. Methotrexate has been found to be non-inferior to cyclophosphamide in remission maintenance [139]. IVIG was found to be

effective in patients with diverse forms of vasculitic neuropathy and in those with AAV refractory to standard therapy [140–143].

The chimeric anti-CD20 monoclonal immunoglobulin rituximab is first-line therapy for induction of remission in patients with GPA and MPA instead of cyclophosphamide [136]. It is also effective in patients with CV and RV [144–150]. Nearly 90% of patients with treatment-refractory AAV improved following rituximab treatment in uncontrolled series [72, 136]. Plasma exchange is an option in patients with fulminant vasculitis and significant organ impairment, as well as, in HBV-associated PAN, HCV-associated CV, and HIV-associated systemic vasculitis [151–156].

For most HCV genotypes a combination of interferon-free antiviral drugs (sofosbuvir and ribavirin), immunosuppressive drugs, with or without plasmapheresis should be used [157, 158]. If the patient has HCV genotype 6, direct-acting antiviral drugs, such as pegylated interferon injections are used [158]. Rituximab may be more effective in patients with severe cryoglobulinemic vasculitis [71, 72, 146, 159]. For non-cytomegalovirus-related HIV vasculitis, treatment is similar to HBV-associated PAN using antiviral therapy and plasma exchange, although in clinical practice most use corticosteroids [28, 160]. The current recommendation is to treat HBV-associated PAN with lamivudine, corticosteroids and in severe cases, plasma exchange [161, 162]. Prolonged corticosteroid treatment should be avoided as it favors viral replication (163). The French Vasculitis Study Group [65, 155] treatment protocol for HBV-related PAN that included antiviral agents, therapeutic plasma exchange to remove circulating immune complexes followed by two weeks of corticosteroids to treat the severe symptoms, induced complete remission in 80 to 90% of patients.

The 2010 Peripheral Nerve Society published guidelines for the immunosuppressive therapy of classic NSVN [4] Since that time, most experts now recommend initiation of combination therapy (corticosteroids with cyclophosphamide, methotrexate, or rituximab) [9]. Azathioprine should not be used as induction therapy but can be used as maintenance therapy. Rituximab can be also be used as maintenance therapy [9].

Patients with progressive symptoms early in the course of DLRPN or LRPN are candidates for immunotherapy [166]. One prospective, randomized, double-blind, multicenter- controlled trial employing intravenous methylprednisolone in patients with DLRPN found improvements in indices of pain but not neurological function [167]. However, a concern is that patients may have been enrolled and treated too late in the disease course to affect impairment, and may not reflect a true degree of benefit of early treatment in a monophasic inflammatory disorder. One open uncontrolled study employing intravenous methylprednisolone in patients with clinically deteriorating LRPN, showed improvement in NIS commensurate with clinical improvement in all patients [168, 169]. While case series of patients [169–171] with radiculoplexus neuropathies suggest improvement in pain and strength with IVIg, there have been no randomized trials of plasma exchange in DLRPN or LRPN. One case series of five patients with DLRPN treated with plasma exchange demonstrated improvement [172]. Considering that DLRPN and LRPN are subtypes of NSVN, a similar treatment regimen for patients with LRPN should be undertaken.

Pain control is of utmost importance in vasculitic neuropathy and the usual medications employed include tricyclic antidepressants, pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, valproate, carbamazepine, tramadol, topical lidocaine, topical capsaicin, and narcotics [173]. Continued pain without progressive neurologic deficits is not an indication for high-dose corticosteroids.

CONCLUSION

Peripheral nerve vasculitis is commonly encountered in patients with primary systemic vasculitis, but may also be secondary to viral infections, malignancy, and concomitant connective tissue disease. All peripheral nerve vasculitic neuropathies involve small blood vessels and classification is based upon separation into nerve large arteriole vasculitis (which typically has fibrinoid necrosis of the involved vessel) and nerve microvasculitis (which typically does not have fibrinoid necrosis). Primary and secondary systemic vasculitic neuropathies are forms of nerve large arteriole vasculitis. Non-systemic vasculitic neuropathy accounts for up to 30% of all vasculitic neuropathies. Altogether, NSVN, as well as some forms of secondary systemic vasculitic, and the radiculoplexus neuropathies including DLRPN, LRPN, DCRPN, and PDMN, the latter of which may be considered localized forms of vasculitic neuropathy, will likely be associated with peripheral nerve microvasculitis. Treatment employing corticosteroids, systemic immunosuppressive agents, and immune modulation with plasma exchange and intravenous immune globulin, all suitable options in patients with severe and progressive neurological deterioration, especially to reduce excess morbidity and mortality.

REFERENCES

[1] Younger DS. Vasculitis of the nervous system. *Curr Opin Neurol.* 2004 Jun;17(3):317–36.

[2] Said G, Lacroix C. Primary and secondary vasculitic neuropathy. *J Neurol.* 2005 Jun;252(6):633–41.

[3] Schaublin G a, Michet CJ, Dyck PJB, Burns TM. An update on the classification and treatment of vasculitic neuropathy. *Lancet Neurol.* 2005 Dec;4(12):853–65.

[4] Collins MP, Dyck PJB, Gronseth GS, Guillevin L, Hadden RDM, Heuss D, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. *J Peripher Nerv Syst*. 2010 Sep;15(3):176–84.

[5] Jennette JC, Falk RJ, Bacon P a, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013 Jan;65(1):1–11.

[6] Lie JT. Nomenclature and classification of vasculitis: plus ça change, plus c'est la même chose. [what goes around comes around.] *Arthritis Rheum.* 1994 Feb;37(2):181–6.

[7] Burns TM, Schaublin GA, Dyck PJB. Vasculitic neuropathies. *Neurol Clin*. 2007 Feb;25(1):89–113.

[8] Dyck P, Englestad J, Dyck P. Microvasculitis. In: Dyck P, Thomas P, editors. *Peripheral Neuropathy*. 4th ed. Philadelphia: Elsevier; 2005.

[9] Collins MP, Hadden RD. The nonsystemic vasculitic neuropathies. *Nat Rev Neurol.* 2017 Apr 27;13(5):302–16.

[10] Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). *Clin Exp Nephrol*. 2013 Oct;17(5):619–21.

[11] Wolf J, Schmitt V, Palm F, Grau AJ, Bergner R. Peripheral neuropathy as initial manifestation of primary systemic vasculitides. *J Neurol.* 2013 Apr;260(4): 1061–70.

[12] Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum*. 2013 Jan;65(1):270–81.

[13] Lacomis D, Zivković S a. Approach to vasculitic neuropathies. *J Clin Neuromuscul Dis.* 2007 Sep;9(1):265–76.

[14] Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol.* 1993 Jan;33(1):4–9.

[15] Guillevin L, Le Thi Huong DU, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. *Br J Rheumatol.* 1988 Aug;27(4):258–64.

[16] Cassereau J, Baguenier-Desormeaux C, Letournel F, Lavigne C, Leclech C, Dubas F, et al. Necrotizing vasculitis revealed in a case of multiple mononeuropathy after a 14-year course of spontaneous remissions and relapses. *Clin Neurol Neurosurg*. 2012 Apr;114(3):290–3.

[17] Üçeyler N, Geng A, Reiners K, Toyka KV, Sommer C. Non-systemic vasculitic neuropathy: single-center follow-up of 60 patients. *J Neurol*. 2015 Sep;262(9):2092–100.

[18] Collins MP, Arnold WD, Kissel JT. The neuropathies of vasculitis. *Neurol Clin*. 2013 May;31(2):557–95.

[19] Agadi JB, Raghav G, Mahadevan A, Shankar SK. Usefulness of superficial peroneal nerve/peroneus brevis muscle biopsy in the diagnosis of vasculitic neuropathy. *J Clin Neurosci*. 2012 Oct;19(10):1392–6.

[20] Collins MP, Mendell JR, Periquet MI, Sahenk Z, Amato a a, Gronseth GS, et al. Superficial peroneal nerve/peroneus brevis muscle biopsy in vasculitic neuropathy. *Neurology*. 2000 Sep 12;55(5):636–43.

[21] Bennett DLH, Groves M, Blake J, Holton JL, King RHM, Orrell RW, et al. The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. *J Neurol Neurosurg Psychiatry.* 2008 Dec;79(12):1376–81.

[22] Dyck PJ, Conn DL, Okazaki H. Necrotizing angiopathic neuropathy. Three-dimensional morphology of fiber degeneration related to sites of occluded vessels. *Mayo Clin Proc.* 1972 Jul;47(7):461–75.

[23] Collins M, Kissel JT. Vasculitic neuropathies and neuropathies of connective tissue diseases. In: Katirji B, Kaminski HJ, Ruff RL E, editor. N*euromuscular disorders in clinical practice.* 2nd ed. New York: Springer; 2013.

[24] André R, Cottin V, Saraux JL, Blaison G, Bienvenu B, Cathebras P, et al. Central nervous system involvement in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Report of 26 patients and review of the literature. *Autoimmun Rev*. 2017 Sep;16(9):963–9.

[25] Lee E, Park J, Choi SH, Park SH. Seronegative granulomatosis with polyangiitis presenting with multiple cranial nerve palsies. *Neuropathology*. 2017 Nov 14;

[26] Kim SH, Park J, Bae JH, Cho MS, Park KD, Jeong JH. ANCA-negative Wegener's granulomatosis with multiple lower cranial nerve palsies. *J Korean Med Sci.* 2013 Nov;28(11):1690–6.

[27] Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010 Feb;62(2):616–26.

[28] Collins M, Kissel J. Neuropathies with systemic vasculitis. In: Dyck P, Thomas PK, editors. *Peripheral Neuropathy*. 4th ed. Philadelphia: Elsevier Inc.; 2005. p. 2335–404.

[29] Stone JH. Polyarteritis nodosa. *JAMA*. 2002 Oct 2;288(13):1632–9.

[30] Forbess L, Bannykh S. Polyarteritis nodosa. *Rheum Dis Clin North Am.* 2015;41(1):33–46, vii.

[31] Wiik AS. Autoantibodies in ANCA-associated vasculitis. *Rheum Dis Clin North Am.* 2010 Aug;36(3):479–89.

[32] Ntatsaki E, Watts RA, Scott DGI. Epidemiology of ANCA-associated vasculitis. *Rheum Dis Clin North Am.* 2010 Aug;36(3):447–61.

[33] Mahr AD. Epidemiological features of Wegener's granulomatosis and microscopic polyangiitis: two diseases or one "anti-neutrophil cytoplasm antibodies-associated vasculitis" entity? *APMIS Suppl.* 2009 Jun;117(127):41–7.

[34] Mohammad AJ, Jacobsson LTH, Westman KWA, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. *Rheumatology* (Oxford). 2009 Dec;48(12):1560–5.

[35] Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum*. 1999 Mar;42(3):421–30.

[36] Cattaneo L, Chierici E, Pavone L, Grasselli C, Manganelli P, Buzio C, et al. Peripheral neuropathy in Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. *J Neurol Neurosurg Psychiatry*. 2007 Oct;78(10):1119–23.

[37] Chung S a, Seo P. Microscopic polyangiitis. *Rheum Dis Clin North Am*. 2010 Aug;36(3):545–58.

[38] Wilke L, Prince-Fiocco M, Fiocco GP. Microscopic polyangiitis: a large single-center series. *J Clin Rheumatol.* 2014 Jun;20(4):179–82.

[39] Lauque D, Cadranel J, Lazor R, Pourrat J, Ronco P, Guillevin L, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires [Study and

Research Group on Pulmonary "Orphan" Disease] (GERM"O"P). *Medicine* (Baltimore). 2000 Jul;79(4):222–33.

[40] Collins CE, Quismorio FP. Pulmonary involvement in microscopic polyangiitis. *Curr Opin Pulm Med*. 2005 Sep;11(5):447–51.

[41] Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* (Baltimore). 1984 Mar;63(2):65–81.

[42] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum*. 1990 Aug;33(8):1094–100.

[43] Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med.* 2003 Sep;115(4):284–90.

[44] Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.* 2005 Sep;52(9):2926–35.

[45] Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis*. 2013 Jun;72(6):1011–7.

[46] Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine* (Baltimore). 1999 Jan;78(1):26–37.

[47] Collins MP, Periquet MI. Isolated vasculitis of the peripheral nervous system. *Clin Exp Rheumatol.* 2008;26(3 Suppl 49):S118-30.

[48] Vinit J, Muller G, Bielefeld P, Pfitzenmeyer P, Bonniaud P, Lorcerie B, et al. Churg-Strauss syndrome: retrospective study in Burgundian population in France in past 10 years. *Rheumatol Int.* 2011 May;31(5):587–93.

[49] Dunogué B, Pagnoux C, Guillevin L. Churg-strauss syndrome: clinical symptoms, complementary investigations, prognosis and outcome, and treatment. *Semin Respir Crit Care Med*. 2011 Jun;32(3):298–309.

[50] Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med.* 2005 Nov 1;143(9):632–8.

[51] Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992 Mar 15;116(6):488–98.

[52] Holle JU, Laudien M, Gross WL. Clinical manifestations and treatment of Wegener's granulomatosis. *Rheum Dis Clin North Am*. 2010 Aug;36(3):507–26.

[53] Holle JU, Gross WL, Latza U, Nölle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. *Arthritis Rheum*. 2011 Jan;63(1):257–66.

[54] Lutalo PMK, D'Cruz DP. Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). *J Autoimmun.* 48–49:94–8.

[55] Collins MP, Periquet MI. Prevalence of vasculitic neuropathy in Wegener granulomatosis. *Arch Neurol*. 2002 Aug;59(8):1333–4; author reply 1334.

[56] Zhang W, Zhou G, Shi Q, Zhang X, Zeng X-F, Zhang F-C. Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides. *Clin Exp Rheumatol.* 2009;27(1 Suppl 52):S65-9.

[57] Suppiah R, Hadden RDM, Batra R, Arden NK, Collins MP, Guillevin L, et al. Peripheral neuropathy in ANCA-associated vasculitis: outcomes from the European Vasculitis Study Group trials. *Rheumatology* (Oxford). 2011 Dec;50(12):2214–22.

[58] Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol.* 2011 Jan;23(1):7–11.

[59] Scott DG, Bacon PA, Tribe CR. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. *Medicine* (Baltimore). 1981 Jul;60(4):288–97.

[60] Dyck PJ, Benstead TJ, Conn DL, Stevens JC, Windebank AJ, Low PA. Nonsystemic vasculitic neuropathy. *Brain*. 1987 Aug;110 (Pt 4:843–53).

[61] Makol A, Crowson CS, Wetter DA, Sokumbi O, Matteson EL, Warrington KJ. Vasculitis associated with rheumatoid arthritis: a case-control study. *Rheumatology* (Oxford). 2014 May;53(5):890–9.

[62] Pavlakis PP, Alexopoulos H, Kosmidis ML, Mamali I, Moutsopoulos HM, Tzioufas AG, et al. Peripheral neuropathies in Sjögren's syndrome: a critical update on clinical features and pathogenetic mechanisms. *J Autoimmun*. 2012 Aug;39(1–2):27–33.

[63] Rosenbaum R. Neuromuscular complications of connective tissue diseases. *Muscle Nerve.* 2001 Feb;24(2):154–69.

[64] Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain.* 2005 Nov;128(Pt 11):2518–34.

[65] Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. *Clin Exp Rheumatol.* 2006; Mar-Apr 24((2 Suppl 41)):S71-81.

[66] Lidar M, Lipschitz N, Langevitz P, Shoenfeld Y. The infectious etiology of vasculitis. *Autoimmunity*. 2009 Aug;42(5):432–8.

[67] Lenglet T, Haroche J, Schnuriger A, Maisonobe T, Viala K, Michel Y, et al. Mononeuropathy multiplex associated with acute parvovirus B19 infection: characteristics, treatment and outcome. *J Neurol*. 2011 Jul;258(7):1321–6.

[68] Guillevin L. Infections in vasculitis. *Best Pract Res Clin Rheumatol*. 2013 Feb;27(1):19–31.

[69] Han S-HB. Extrahepatic manifestations of chronic hepatitis B. *Clin Liver Dis*. 2004 May;8(2):403–18.

[70] Khella SL, Souayah N. Hepatitis C: a review of its neurologic complications. *Neurologist.* 2002 Mar;8(2):101–6.

[71] Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. *Lancet.* 2012 Jan 28;379(9813):348–60.

[72] Collins MP. The vasculitic neuropathies: an update. *Curr Opin Neuro*l. 2012 Oct;25(5):573–85.

[73] Gemignani F, Brindani F, Alfieri S, Giuberti T, Allegri I, Ferrari C, et al. Clinical spectrum of cryoglobulinaemic neuropathy. *J Neurol Neurosurg Psychiatry*. 2005 Oct;76(10):1410–4.

[74] Saadoun D, Terrier B, Semoun O, Sene D, Maisonobe T, Musset L, et al. Hepatitis C virus-associated polyarteritis nodosa. *Arthritis Care Res* (Hoboken). 2011 Mar;63(3):427–35.

[75] Kannan MA, Challa S, Kandadai RM, Uppin MS, Jabeen SA, Borgohain R. Series of paraneoplastic vasculitic neuropathy: a rare, potentially treatable neuropathy. *Neurol India.* 63(1):30–4.

[76] Oh SJ. Paraneoplastic vasculitis of the peripheral nervous system. *Neurol Clin.* 1997 Nov;15(4):849–63.

[77] Eggers C, Hagel C, Pfeiffer G. Anti-Hu-associated paraneoplastic sensory neuropathy with peripheral nerve demyelination and microvasculitis. *J Neurol Sci*. 1998 Mar 5;155(2):178–81.

[78] Fain O, Hamidou M, Cacoub P, Godeau B, Wechsler B, Pariès J, et al. Vasculitides associated with malignancies: analysis of sixty patients. *Arthritis Rheum*. 2007 Dec 15;57(8):1473–80.

[79] Kang MK, Gupta RK, Srinivasan J. Peripheral Vasculitic Neuropathy Associated With Minocycline Use. *J Clin Neuromuscul Dis.* 2018 Mar;19(3):138–41.

[80] Baratta JM, Dyck PJB, Brand P, Thaisetthawatkul P, Dyck PJ, Engelstad JK, et al. Vasculitic neuropathy following exposure to minocycline. *Neurol Neuroimmunol neuroinflammation*. 2016 Feb;3(1):e180.

[81] Kermani TA, Ham EK, Camilleri MJ, Warrington KJ. Polyarteritis nodosa-like vasculitis in association with minocycline use: a single-center case series. *Semin* A*rthritis Rheum.* 2012 Oct;42(2):213–21.

[82] Subesinghe S, van Leuven S, Yalakki L, Sangle S, D'Cruz D. Cocaine and ANCA associated vasculitis-like syndromes - A case series. *Autoimmun Rev*. 2018 Jan;17(1):73–7.

[83] Friedman DR, Wolfsthal SD. Cocaine-induced pseudovasculitis. *Mayo Clin Proc*. 2005 May;80(5):671–3.

[84] Kao JC, Liao B, Markovic SN, Klein CJ, Naddaf E, Staff NP, et al. Neurological Complications Associated With Anti-Programmed Death 1 (PD-1) Antibodies. *JAMA Neurol.* 2017 Oct 1;74(10):1216–22.

[85] Aya F, Ruiz-Esquide V, Viladot M, Font C, Prieto-González S, Prat A, et al. Vasculitic neuropathy induced by pembrolizumab. *Ann Oncol Off J Eur Soc Med* Oncol. 2017;28(2):433–4.

[86] Kissel JT, Slivka AP, Warmolts JR, Mendell JR. The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. *Ann Neurol*. 1985 Aug;18(2):251–7.

[87] Davies L, Spies JM, Pollard JD, McLeod JG. Vasculitis confined to peripheral nerves. *Brain.* 1996 Oct;119 (Pt 5:1441–8).

[88] Sugiura M, Koike H, Iijima M, Mori K, Hattori N, Katsuno M, et al. Clinicopathologic features of nonsystemic vasculitic neuropathy and microscopic polyangiitis-associated neuropathy: a comparative study. *J Neurol Sci.* 2006 Mar 15;241(1–2):31–7.

[89] Takahashi M, Koike H, Ikeda S, Kawagashira Y, Iijima M, Hashizume A, et al. Distinct pathogenesis in nonsystemic vasculitic neuropathy and microscopic polyangiitis. *Neurol Neuroimmunol neuroinflammation.* 2017 Nov;4(6):e407.

[90] Schneider C, Wunderlich G, Bleistein J, Fink GR, Deckert M, Brunn A, et al. Lymphocyte antigens targetable by monoclonal antibodies in non-systemic vasculitic neuropathy. *J Neurol Neurosurg Psychiatry*. 2017 Sep;88(9):756–60.

[91] Dyck PJ, Norell JE. Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. *Neurology.* 1999 Dec 10;53(9):2113–21.

[92] Dyck PJB, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. *Muscle Nerve.* 2002 Apr;25(4):477–91.

[93] Dyck PJ, Norell JE, Dyck PJ. Non-diabetic lumbosacral radiculoplexus neuropathy: natural history, outcome and comparison with the diabetic variety. *Brain.* 2001 Jun;124(Pt 6):1197–207.

[94] Younger DS. Diabetic lumbosacral radiculoplexus neuropathy: a postmortem studied patient and review of the literature. *J Neurol.* 2011 Jul;258(7):1364–7.

[95] Massie R, Mauermann ML, Staff NP, Amrami KK, Mandrekar JN, Dyck PJ, et al. Diabetic cervical radiculoplexus neuropathy: a distinct syndrome expanding the spectrum of diabetic radiculoplexus neuropathies. *Brain.* 2012 Oct;135(Pt 10):3074–88.

[96] Garces-Sanchez M, Laughlin RS, Dyck PJB, Engelstad JK, Norell JE. Painless diabetic motor neuropathy: a variant of diabetic lumbosacral radiculoplexus Neuropathy? *Ann Neurol*. 2011 Jun;69(6):1043–54.

[97] Jennette JC, Falk RJ, Hu P, Xiao H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. *Annu Rev Pathol.* 2013 Jan 24;8:139–60.

[98] Savige J, Gillis D, Benson E, Davies D, Esnault V, Falk RJ, et al. International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). *Am J Clin Pathol*. 1999 Apr;111(4):507–13.

[99] Csernok E, Holle JU. Twenty-eight years with antineutrophil cytoplasmic antibodies (ANCA): how to test for ANCA - evidence-based immunology? *Auto- Immun highlights.* 2010 May;1(1):39–43.

[100] Csernok E, Lamprecht P, Gross WL. Diagnostic significance of ANCA in vasculitis. *Nat Clin Pract Rheumatol.* 2006 Apr;2(4):174–5.

[101] Weiner M, Segelmark M. The clinical presentation and therapy of diseases related to anti-neutrophil cytoplasmic antibodies (ANCA). *Autoimmun Rev.* 2016 Oct;15(10):978–82.

[102] Bischof A, Manigold T, Barro C, Heijnen I, Berger CT, Derfuss T, et al. Serum neurofilament light chain: a biomarker of neuronal injury in vasculitic neuropathy. *Ann Rheum Dis*. 2017 Jul 25;

[103] Manolov V, Petrova I, Vasilev V. VEGF levels in diagnosis of vasculitic neuropathy. *Clin Lab.* 2014;60(9):1573–7.

[104] Vrancken AFJE, Gathier CS, Cats EA, Notermans NC, Collins MP. The additional yield of combined nerve/muscle biopsy in vasculitic neuropathy. *Eur J Neurol.* 2011 Jan;18(1):49–58.

[105] Vital C, Vital A, Canron MH, Jaffré A, Viallard JF, Ragnaud JM, et al. Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases. *J Peripher Nerv Syst.* 2006 Mar;11(1):20–9.

[106] Deprez M, de Groote CC, Gollogly L, Reznik M, Martin JJ. Clinical and neuropathological parameters affecting the diagnostic yield of nerve biopsy. *Neuromuscul Disord.* 2000 Feb;10(2):92–8.

[107] Chalk CH, Homburger HA, Dyck PJ. Anti-neutrophil cytoplasmic antibodies in vasculitis peripheral neuropathy. *Neurology.* 1993 Sep;43(9):1826–7.

[108] Watts R a, Scott DG, Pusey CD, Lockwood CM. Vasculitis-aims of therapy. An overview. *Rheumatology* (Oxford). 2000 Mar;39(3):229–32.

[109] Pagnoux C, Guillevin L. Peripheral neuropathy in systemic vasculitides. *Curr Opin Rheumatol.* 2005 Jan;17(1):41–8.

[110] Gorson KC. Vasculitic neuropathies: an update. *Neurologist.* 2007 Jan;13(1):12–9.

[111] Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. *Rheumatology* (Oxford). 2007 Oct;46(10):1615–6.

[112] Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis.* 2009 Mar;68(3):310–7.

[113] Smith RM, Jones RB, Jayne DRW. Progress in treatment of ANCA-associated vasculitis. *Arthritis Res Ther.* 2012 Jan;14(2):210.

[114] Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore). 1996 Jan;75(1):17–28.

[115] Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore). 2011 Jan;90(1):19–27.

[116] Gorson KC, Natarajan N, Ropper AH, Weinstein R. Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial. *Muscle Nerve.* 2007 Jan;35(1):66–9.

[117] Stasi R, Stipa E, Del Poeta G, Amadori S, Newland a C, Provan D. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology* (Oxford). 2006 Nov;45(11):1432–6.

[118] Dyck PJ, Engelstad J, Norell J. Microvasculitis in non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN): similarity to the diabetic variety (DLSRPN). *J Neuropathol Exp Neurol.* 2000 Jun;59(6):525–38.

[119] Naddaf E, Dyck PJB. Vasculitic Neuropathies. *Curr Treat Options Neurol*. 2015 Oct;17(10):374.

[120] Gorson KC. Therapy for vasculitic neuropathies. *Curr Treat Options Neurol.* 2006 Mar;8(2):105–17.

[121] Tervaert JW, Limburg PC, Elema JD, Huitema MG, Horst G, The TH, et al. Detection of autoantibodies against myeloid lysosomal enzymes: a useful adjunct to classification of patients with biopsy-proven necrotizing arteritis. *Am J Med*. 1991 Jul;91(1):59–66.

[122] Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. *Br J Rheumatol*. 1997 Dec;36(12):1290–7.

[123] de Groot K, Harper L, Jayne DRW, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2009 May 19;150(10):670–80.

[124] Haubitz M, Schellong S, Göbel U, Schurek HJ, Schaumann D, Koch KM, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum.* 1998 Oct;41(10):1835–44.

[125] Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum*. 1997 Dec;40(12):2187–98.

[126] Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *QJM*. 1997 Jun;90(6):401–9.

[127] Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis.* 2012 Jun;71(6):955–60.

[128] Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JWC, Dadoniené J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003 Jul 3;349(1):36–44.

[129] Gold R, Fontana A, Zierz S. Therapy of neurological disorders in systemic vasculitis. *Semin Neurol*. 2003 Jun;23(2):207–14.

[130] Langford C a. 15. Vasculitis. *J Allergy Clin Immunol*. 2003 Feb;111(2):S602–12.

[131] Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis.* 2007 May;66(5):605–17.

[132] Jones RB, Tervaert JWC, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med.* 2010 Jul 15;363(3):211–20.

[133] Stone JH, Merkel P a, Spiera R, Seo P, Langford C a, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010 Jul 15;363(3):221–32.

[134] McAdoo SP, Medjeral-Thomas N, Gopaluni S, Tanna A, Mansfield N, Galliford J, et al. Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephrol Dial Transplant.* 2018 Feb 14;

[135] Furuta S, Sugiyama T, Umibe T, Kaneko Y, Amano K, Kurasawa K, et al. Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS): protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open.* 2017;7(12):e018748.

[136] Ayan G, Esatoglu SN, Hatemi G, Ugurlu S, Seyahi E, Melikoglu M, et al. Rituximab for anti-neutrophil cytoplasmic antibodies-associated vasculitis: experience of a single center and systematic review of non-randomized studies. *Rheumatol Int*. 2018 Apr;38(4):607–22.

[137] de Joode AAE, Sanders JSF, Puéchal X, Guillevin LP, Hiemstra TF, Flossmann O, et al. Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data. *Rheumatology* (Oxford). 2017 Nov 1;56(11):1894–901.

[138] Puéchal X, Pagnoux C, Baron G, Quémeneur T, Néel A, Agard C, et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. *Arthritis Rheumatol* (Hoboken, NJ). 2017;69(11):2175–86.

[139] Maritati F, Alberici F, Oliva E, Urban ML, Palmisano A, Santarsia F, et al. Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial. *PLoS One.* 2017;12(10):e0185880.

[140] Levy Y, Uziel Y, Zandman G, Rotman P, Amital H, Sherer Y, et al. Response of vasculitic peripheral neuropathy to intravenous immunoglobulin. A*nn N Y Acad Sci.* 2005 Jun;1051:779–86.

[141] Tsurikisawa N, Taniguchi M, Saito H, Himeno H, Ishibashi A, Suzuki S, et al. Treatment of Churg-Strauss syndrome with high-dose intravenous immunoglobulin. *Ann Allergy Asthma Immunol.* 2004 Jan;92(1):80–7.

[142] Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, et al. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. *Arthritis Rheum*. 2008 Jan;58(1):308–17.

[143] Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM.* 2000 Jul;93(7):433–9.

[144] Lamprecht P. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. *Ann Rheum Dis*. 2003 Dec 1;62(12):1230–3.

[145] De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum*. 2012 Mar;64(3):843–53.

[146] Saadoun D, Resche Rigon M, Sene D, Terrier B, Karras A, Perard L, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood*. 2010 Jul 22;116(3):326-34; quiz 504-5.

[147] Pietrogrande M, De Vita S, Zignego AL, Pioltelli P, Sansonno D, Sollima S, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. *Autoimmun Rev*. 2011 Jun;10(8):444–54.

[148] Ferri C, Cacoub P, Mazzaro C, Roccatello D, Scaini P, Sebastiani M, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. *Autoimmun Rev.* 2011 Nov;11(1):48–55.

[149] De Vita S, Quartuccio L, Fabris M. Rituximab in mixed cryoglobulinemia: increased experience and perspectives. *Dig Liver Dis.* 2007 Sep;39 Suppl 1:S122-8.

[150] Puéchal X, Gottenberg JE, Berthelot JM, Gossec L, Meyer O, Morel J, et al. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis: Results from the AutoImmunity and Rituximab Registry. *Arthritis Care Res* (Hoboken). 2012 Mar;64(3):331–9.

[151] Murai H, Inaba S, Kira J, Yamamoto A, Ohno M, Goto I. Hepatitis C virus associated cryoglobulinemic neuropathy successfully treated with plasma exchange. *Artif Organs.* 1995 Apr;19(4):334–8.

[152] Scarpato S, Tirri E, Naclerio C, Moscato P, Salvati G. Plasmapheresis in cryoglobulinemic neuropathy: a clinical study. *Dig Liver Dis.* 2007 Sep;39 Suppl 1:S136-7.

[153] Braun A, Neumann T, Oelzner P, Hein G, Gröne H-J, Ziemer M, et al. Cryoglobulinaemia type III with severe neuropathy and immune complex glomerulonephritis: remission after plasmapheresis and rituximab. *Rheumatol Int.* 2008 Mar;28(5):503–6.

[154] Guillevin L, Pagnoux C. Indication for plasma exchange for systemic necrotizing vasculidities. *Transfus Apher Sci*. 2007 Apr;36(2):179–85.

[155] Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine* (Baltimore). 2005 Sep;84(5):313–22.

[156] de Luna G, Chauveau D, Aniort J, Carron P-L, Gobert P, Karras A, et al. Plasma exchanges for the treatment of severe systemic necrotizing vasculitides in clinical daily practice: Data from the French Vasculitis Study Group. *J Autoimmun*. 2015 Dec;65:49–55.

[157] Saadoun D, Thibault V, Si Ahmed SN, Alric L, Mallet M, Guillaud C, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. *Ann Rheum Dis.* 2016 Oct;75(10):1777–82.

[158] Ostojic P, Jeremic IR. Managing refractory cryoglobulinemic vasculitis: challenges and solutions. *J Inflamm Res*. 2017;10:49–54.

[159] Dammacco F, Tucci FA, Lauletta G, Gatti P, De Re V, Conteduca V, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. *Blood*. 2010 Jul 22;116(3):343–53.

[160] Patel N, Patel N, Khan T, Patel N, Espinoza LR. HIV infection and clinical spectrum of associated vasculitides. C*urr Rheumatol Rep*. 2011 Dec;13(6):506–12.

[161] Farrell GC, Teoh NC. Management of chronic hepatitis B virus infection: a new era of disease control. *Intern Med J.* 2006 Feb;36(2):100–13.

[162] De Virgilio A, Greco A, Magliulo G, Gallo A, Ruoppolo G, Conte M, et al. Polyarteritis nodosa: A contemporary overview. *Autoimmun Rev.* 2016 Jun;15(6):564–70.

[163] Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. *N Engl J Med.* 1981 Feb 12;304(7):380–6.

[164] Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. *Clin Exp Rheumatol.* 24(2 Suppl 41):S71-81.

[165] Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine* (Baltimore). 2005 Sep;84(5):313–22.

[166] Thaisetthawatkul P, Dyck PJB. Treatment of diabetic and nondiabetic lumbosacral radiculoplexus neuropathy. *Curr Treat Options Neurol*. 2010 Mar;12(2):95–9.

[167] Dyck PJB, O'Brien P, Bosch P et al. The multi-center double-blind controlled trial of IV methylprednisolone in diabetic lumbosacral radiculoplexus neuropathy [abstract]. *Neurology*. 2006;66 (5 supp:A191.

[168] Dyck PJ, Norell JE. Methylprednisolone may improve lumbosacral radiculoplexus neuropathy. *Can J Neurol Sci.* 2001 Aug;28(3):224–7.

[169] Tamburin S, Zanette G. Intravenous immunoglobulin for the treatment of diabetic lumbosacral radiculoplexus neuropathy. *Pain Med.* 2009 Nov;10(8):1476–80.

[170] Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. *Arch Neurol*. 1995 Nov;52(11):1053–61.

[171] Kilfoyle D, Kelkar P, Parry GJ. Pulsed methylprednisolone is a safe and effective treatment for diabetic amyotrophy. *J Clin Neuromuscul Dis*. 2003 Jun;4(4):168–70.

[172] Pascoe MK, Low P a., Windebank AJ, Litchy WJ. Subacute diabetic proximal neuropathy. *Mayo Clin Proc*. 1997 Dec;72(12):1123–32.

[173] Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain.* 2010 Sep;150(3):573–81.

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 13

AUTOIMMUNE ENCEPHALITIDES

David S. Younger*[*]*, MD, MPH, MS
Department of Neurology, Division of Neuroepidemiology, New York University School of Medicine, and the College of Global Public Health, New York University;
Department of Health Policy and Management, School of Public Health
City University of New York, New York, NY, US

ABSTRACT

Autoimmune encephalitis is a severe inflammatory disorder of the brain with diverse causes and a complex differential diagnosis including central nervous system vasculitis. Recent advances in the past decade has led to the identification of new syndromes and biological markers of limbic encephalitis, the commonest presentation of autoimmune encephalitis. Autoimmune encephalitis is associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens against constituents of the limbic system neuropil. This has led to a reconsideration of a number of neuropsychiatric and neurocognitive disorders as having shared mechanisms of origin. The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment has resulted in relatively few biopsy and postmortem examinations. In those available, there can be variable infiltrating inflammatory T-cells with cytotoxic granules in close apposition to neurons, analogous to microscopic vasculitis.

Keywords: autoimmune, encephalitis, hashimoto, encephalopathy

INTRODUCTION

According to Dalmau [1], for many years, the only know disorders associated with autoantibodies were myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS). These two predominantly B-cell peripheral nervous system (PNS) disorders targeted acetylcholine receptors or voltage-gated calcium channels resulting in reversible

[*] Corresponding Author's E-mail: youngd01@nyu.edu

neuromuscular alterations that fully accounted for the observed symptoms and signs. In the central nervous system (CNS), paraneoplastic disorders associated with onconeural antibodies were cross-reactive with tumor nuclear and cytoplasmic neuronal antigens mediated by cytotoxic T-cells not B-cells. With the large group of undiagnosed encephalopathies, in particular syndromes characterized by limbic encephalitis, investigators returned to the laboratory to study the patterns of brain neuropil reactivity of newly recognized autoantibodies [2]. The result has been the recognition of newly characterized childhood and adult neurological and neuropsychiatric disorders termed autoimmune encephalitis (AE) or encephalopathy, mediated by antibodies against surface and intracellular antigens [3]. The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment has resulted in relatively few biopsy and postmortem examinations. In those available however, the resulting neurodegeneration associated with autoantibodies appears to result from infiltrating inflammatory T-cells, especially those with cytotoxic granules in close apposition to neurons, analogous but distinct from microscopic vasculitis. With the ease of screening the serum and cerebrospinal fluid for a panel of pathogenic autoantibodies, and obtaining detailed morphologic and metabolic images of the brain specific for the disorders, autoimmune encephalitis is in the differential diagnosis of childhood and adult primary central nervous system angiitis [4, 5, 6], particularly before brain tissue biopsy is considered, or to avoid potentially harmful empiric immunosuppressant therapy [7]. This chapter reviews their historical background, epidemiology, clinical presentation, laboratory evaluation, histopathology, diagnosis and management of the autoimmune encephalitides.

HISTORICAL PERSPECTIVE

In 1968, Corsellis and colleagues [8] coined the term limbic encephalitis (LE) noting a relation to bronchial cancer in three patients in the sixth to eighth decade of life. All three cases had subacute temporal lobe seizures, neuropsychiatric, and memory disturbances for two years before death. Postmortem examination revealed inflammatory lesions in limbic grey matter sections of the brain, notably in medial temporal lobe structures of the uncus and amygdala nuclei, and in the hippocampal, cingulum and dentate gyri. Case 2 had an undifferentiated non-metastatic lung carcinoma removed six months after onset of neurological symptoms, while two others had clinically unsuspected cancer at postmortem examination. Case 1 had a bronchial carcinoma restricted to a mediastinal lymph node without a primary lesion, while Case 3 had an unsuspected oat cell carcinoma infiltrating the main bronchi of both lungs and adjacent mediastinal nodes. Over the ensuing decades, attention turned away from limbic encephalitis and toward neurological autoimmune paraneoplastic syndromes with the discovery of several neuronal target antigens including Hu (ANNA-1) responsible for paraneoplastic encephalomyelitis (PEM) [9] in association with small cell lung cancer (SCLC); Ri (ANNA-2) responsible for paraneoplastic cerebellar degeneration [10] and motor neuronopathy [11] in association with breast cancer; and PCA-1 responsible for paraneoplastic cerebellar degeneration [12] in association with gynecologic tumors. Other syndromes associated with paraneoplastic encephalitis were elucidated by Dalmau and colleagues [13, 14] in

their descriptions of anti-MA1 and MA2 and testicular cancer; and the collapsin response mediator protein-5 (CRMP5/Cv2) in association with thymoma. Each with an intracellular target antigen, the resultant histopathology of these antibodies generally consisted of infiltrative cytotoxic (CD8+) T-cell destruction of neurons, with variable IgG and complement deposits in the CNS, with less helper (CD4+) T-cells, and generally absent B-cells. Bernal and colleagues [15] illustrated the role of infiltrating CD8+ T-cells in cell death by showing their close apposition to neurons.

In 2000, Bien and colleagues [16] revisited non-cancerous cases of LE in its relation to temporal lobe epilepsy. The interface of strictly paraneoplastic and autoimmune mechanisms was subsequently highlighted in the characterization of patients with stiff-person syndrome (SPS) associated with antibodies to glutamic acid decarboxylase (GAD); and the clinical neurological syndromes associated with voltage-gated potassium channel (VGKC)-complex antibodies. Solimena and colleagues [17] investigated the existence of non-paraneoplastic CNS autoimmunity in a patient with SPS, epilepsy and type-1 diabetes (T1D, and increased titers of oligoclonal CSF IgG. Both the serum and CSF produced identical intense staining of all gray-matter regions. GAD65 was thence an important autoantigen in T1D, being highly expressed in the cytoplasm of pancreatic β cells. GAD-derived peptides were presentable by main histocompatibility complex (MHC) class I molecules and recognized by CD8+ T-cells on the surface of β cells. Activation of CD8+ GAD-specific T-cells further differentiated into memory cells suggesting a pathogenic role in T1D. However, only patients with very high titers of GAD were associated with LE; and they typically presented with recent-onset temporal lobe epilepsy (TLE) and intrathecal secretion, defining a form of non-paraneoplastic LE. Other patients within the SPS spectrum harbored antibodies against other proteins of the GABAergic synapse, including amphiphysin and gephyrin, which were found to associate with lymphoma, and malignant tumors of the breast, colon, lung, and thymus [18].

Contemporaneously, the clinical phenotypes associated with autoantibodies to VGKC-complex ranged from peripheral nerve hyperexcitability (PNH), to Morvan's syndrome (MoS), and LE and autoimmune epilepsy [19, 20]. VGKC-complex antibodies were subsequently described in 2 patients with reversible LE [21]. Both patients were negative for typical paraneoplastic antibodies and with near-complete recovery, including one with recurrent thymoma after plasma exchange (PE), while the other patient recovered spontaneously without specific immunotherapy. The immunoprecipitation of VGKC-complexes linked a number of clinical syndromes that might otherwise have remained separate.

By 2010, Graus and colleagues [22] classified neuronal antibodies associated with syndromes resulting from CNS neuronal dysfunction into two groups according to the location of the target antigen. One group of well-characterized autoantibodies that recognized intracellular neuronal antigens included Ri, Yo, Hu, Ma2, CRMP5/Cv2 and GAD. These so called onconeural antibodies were useful in the designation of a specific paraneoplastic neurological disorder. Bien and colleagues [23] described qualitative and quantitative immunopathologic features of biopsy or postmortem brain tissue in 17 cases of AE associated with intracellular (IAg) (Hu, Ma2, GAD) or surface antigens (SAg) (VGKC-C and NMDA). Their studies noted higher CD8+/CD3+ ratio and more frequentappositions of granzyme-B (GrB))(+) cytotoxic T-cells to neurons, with associated cell loss in the IAg-onconeural group compared to those in the SAg group. The exceptions were GAD cases that showed less intense inflammation and relatively low CD8/CD3 ratios compared to the IAg-onconeural cases. A role

for T-cell-mediated neuronal cytotoxicity was found in encephalitides with antibodies against IAg, whereas a complement-mediated humoral immune mechanism was suggested in VDKC-complex encephalitis. There was apparent absence of both mechanisms in NMDA receptor encephalitis.

Bauer and Bien [24] suggested that neurodegeneration in brains of patients with antibodies against IAg was not simply induced by antibody reactivity with the target antigen, but rather by the inflammatory T-cells. To be pathogenic, they pointed out, the imputed antibody first had to transit the blood-brain barrier (BBB) and then the cell membrane of the target cell to a location where it could bind the pathogenic intracellular antigen. Depending upon protein conformation and folding, the antigenic site might be readily accessible before inactivation and ensuing irreparable cell damage. It is difficult to imagine that an intracellular antibody could easily overcome each of these obstacles. A major concern in managing these disorders has not only been prompt treatment of the tumor, but commencement of effective immunotherapy targeting mainly cytotoxic T-cells [25]. Vasculitis has not been a recognized mechanism of injury in intraneuronal antibodies, either in life or at postmortem examination [26].

The past decade witnessed the emergency of serum autoantibodies against SAg and synaptic-enriched regions leading to LE that spares the cytoplasm and nuclei of neurons such as those against GluN1 or GluN2/3 synaptic subunits of *N*-methyl-D-aspartate (NMDA) and glycine receptors; and to the amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; and other novel neuropil antigens that localize to the cell surface of neurons and dendrites colocalized with synaptophysin and spinophilin [27, 28, 29, 30]. All supportive of LE or AE, these new antibodies share the property of strong immunolabeling of areas of dense dendritic network and synaptic-enriched regions in the neuropil of hippocampus. The clinical phenotype associated with the novel neuropil antibodies include dominant behavioral and psychiatric symptoms and seizures. With inconstant features of cognition and memory, brain-magnetic resonance imaging (MRI) and 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG PET) abnormalities were less frequently restricted to the medial temporal lobe than in patients with classical paraneoplastic and VGKC-complex antibodies.

A role for the autoimmune dysfunction in neuropsychiatric illness has been sought since the 1930s when autoantibodies were first reported in a schizophrenia patient [31]. Since that time, there have been reports of specific autoimmune responses to self-antigens in psychosis, affective disorders, and other neurobehavioral abnormalities [32, 33]. Clinical neurologists, neuroscientists and psychiatrists, all have a stake in the emerging link between autoimmunity and resulting neurologic and psychiatric disorders in AE [34].

AUTOIMMUNE LIMBIC ENCEPHALITIDES

Three autoantibodies found in children and adults with LE target intracellular GAD65, and surface antigens of the NMDAR and VGKC-complex. Classically, the associated symptoms, which evolve over days to weeks, include short-term memory loss, sleep disturbances, seizures, irritability, depression, hallucinations, and personality change.

Anti-GAD65 Encephalitis

Background

Autoimmunity targeting the 65 kilodalton (kDa) isoform of GAD65 encompass diverse autoimmune disorders such as T1D and rare neurologic disorders including LE, temporal lobe epilepsy (TLE), cerebellar ataxia, and large and small fiber peripheral and autonomic neuropathy [35].

Epidemiology

A review of adult-onset SPS showed a prevalence estimate of 1 in 1,250,000 [36] with a predominance of women, and average age of onset of 40 years. The frequency of high titers of anti-GAD antibodies defined an RIA value >1000 IU/ml in TLE of unknown origin is 21% [37] of cases, with the highest titers related to TLE. Affected patients are typically women with T1D, early-onset epilepsy, and concomitant hypothyroidism, psoriatic arthritis and Celiac disease, a third of whom reported onset of LE as the predominant feature, with supportive findings of amygdala and hippocampus signal intensities on brain MRI, and medial temporal hypometabolism on FDG brain PET. The levels of anti-GAD ranged from 1207 to 87 510 IU/ml, with absent OCB, and a ratio of serum/CSF GAD antibody levels >1 suggesting intrathecal synthesis. Malter [38] estimated the prevalence of GAD antibodies in LE to be 17%, noting a subgroup of patients with TLE who had very high titers equivalent to those with SPS, medial temporal inflammation on MRI, and concomitant LE. In the TLE cohort, GAD antibody encephalitis proved to be equally common to VGKC-complex antibodies but differed in younger age, female sex, and presentation of first seizure, CSF oligoclonal bands, and intrathecal autoantibody synthesis. Patients with high levels of GAD antibodies, and classic or other neurological syndromes not typically associated with GAD antibodies, were at higher risk for an underlying cancer.

Clinical Aspects

Gagnon and Savard [39] reviewed the clinical experience of 58 cases of GAD65-antibody LE beginning with the first reported case [40] inclusively through 2016, in 7 observational studies, 3 case series, and 21 published case reports providing a useful summary of the literature of anti-GAD65-associated LE. Among the 58 cases, there were 21 children and 37 adults, 59% of whom were female, with a median pediatric age of 10 years (range 1-17 years) and mean adult age of 39 years (range 19-70 years). Diabetes alone, generally T1D, was noted in 50% of cases, in association with thyroiditis, diabetes, Celiac disease, psoriasis, and common variable immune deficiency (CVID) respectively in 73%, 18%, 9%, and 9%. Cancer was noted in 6 (10%) cases, including 4 SCLC and 2 malignant thymomas, generally in men of mean age 61 years (range 38-70 years). The commonest presenting clinical features were seizures in 56 (97%) cases, most commonly refractory status epilepticus; cognitive impairment in 38 (59%) mainly affecting memory, language, executive function, and attention; psychiatric symptoms in 16 (28%) cases, most commonly depression, behavior, perception, and anxiety. Less common clinical manifestations included fever, dysautonomia, cerebellar incoordination and headache respectively in 8 (12%), 7 (12%), 4 (7%), and 3 (5%) cases. The most common seizure presentation was refractory status epilepticus.

Cellular and Synaptic Antibody Effects

Low titers of anti-GAD65 antibodies, generally <20 nmol/L occur in T1D and in the general population, while cases of anti-GAD65-associated neurological disorders including LE are seen in the hundreds of nmol/L. Two GAD isoforms with distinct localizations and functions, GAD65 and GAD67, are expressed in presynaptic CNS GABAergic neurons, and in pancreatic β cells. Glutamic acid decarboxylase converts L-glutamate to GABA using pridoxal-5'-phosphate (PLP) as a cofactor. GABA is the commonest inhibitory neurotransmitter in the CNS and the ligand for the inhibitory voltage-gated chloride channel $GABA_A$, and G-protein coupled $GABA_B$ receptors. GAD67 commonly coexists with GAD65 antibodies in patients with neurologic autoimmunity. However GAD67 is rarely an autoantigen in isolation, found predominantly in the cytoplasm where it produces basal levels of GABA; whereas GAD65 is located predominantly in nerve terminals anchored to the cytoplasm-facing side of synaptic vesicles where it believed to synthesize GABA for neurotransmission supplementary to basal levels. The classification of high titers of anti-GAD65 autoantibodies has bene problematic in being grouped with onconeural autoantibodies.

Laboratory Investigations

The dominant clinical phenotype of seizures, neurocognitive and neuropsychiatric disturbances in most patients with anti-GAD-autoantibody associated LE is explained by the frequent involvement of the medial temporal lobes; an inflammatory CSF with intrathecal secretion of the anti-GAD65 autoantibody, and oligoclonal bands. Bien and colleagues [41] described a 24-year-old women with frequent temporal lobe seizures, non-paraneoplastic LE, and a serum anti-GAD65 antibody titer of 1:32,000, in whom T_2/FLAIR MRI evolved over a period of 8 months, demonstrating right hippocampal swelling and signal increase to sclerosis and atrophy on MRI commensurate with clinical progression. Among 58 literature patients [39], 45/58 (78%) patient MRIs were abnormal with specific involvement of the temporal lobes in 34 (59%), and multifocal abnormalities in 9 (16%); and 7 patient MRIs were normal. The results of electroencephalography (EEG) available in 35 cases, showed epileptiform discharges in 27 (77%), and focal temporal involvement in 19 (70%). Lumbar CSF so studied in 41 cases, showed pleocytosis in 11 (27%) with white blood cell (WBC) counts ranging from 7 to 114 cells/ul; and present oligoclonal bands (OCB) in one-half of cases. Hyponatremia was identified in 3 cases. There were significantly elevated titers of anti-GAD65 antibodies in both serum and CSF in 35 patients; and in either serum (in 18) or CSF alone in 3. Concurrent antibodies were reported in 11 cases, including those to $GABA_A$ in 5 cases, and VGKC-complex or $GABA_B$ in 3 cases. Antibodies to NMDAR, AMPAR, and onconeural antibodies were all absent. FDG brain PET imaging and MRI were complementary in 50% of cases [49]. Combining both MRI and PET, all patients had temporal lobe abnormalities. EEG may be useful in classifying the seizure type and directing the use of anticonvulsants especially when clinical seizures lack motor convulsions.

Histopathologic Correlation

The clinicopathologic features of anti-GAD antibody LE were described in a woman [41] who presented with frequent complex temporal lobe seizures at age 23. Over 8 months there was an evolution of right hippocampal swelling and signal increase on T_2/FLAIR MRI to sclerosis and atrophy. At the time of epilepsy brain surgery CSF showed 10 WBC and

oligoclonal bands. Right-sided selective resection the sclerotic hippocampus showed strong encephalitic features. High-dose corticosteroid therapy administered over several months resulted in seizure-free status until weaning off 2.4 years later when she developed Cushing syndrome. She lapsed into a series of temporal lobe seizures and memory impairment accompanied by temporal left hippocampal swelling for which long-term corticosteroid and azathioprine therapy was started with slow clinical improvement. At follow-up 3.7 years later, she was still experiencing frequent partial temporal lobe seizures with memory deficits.

Bien and colleagues [23, 41] summarized the histopathologic features of selective resection of the sclerotic hippocampus in this patient that included neuronal loss and astrogliosis and a strong accumulation of inflammatory cells in the resected hippocampus. There was marked invasion of the hippocampus by lymphocytes that were mainly CD8+T-cells with the cytotoxic effector molecule GrB, in addition to CD20+ B-cells and CD138+ plasma cells. The pattern of pyramidal cell loss was severe in sectors CA4 and CA3, with selective sparing of CA1 and 2. Surviving neurons were positive for MHC class I, fulfilling the prerequisite for attack by CD8+ T-cells. The authors [23] quantitated the number of parenchymal T-, B-, and plasma cells, macrophages and glial cells in 3 cases of anti-GAD65 autoantibody LE that included a previously reported case [41] differentiating them from the IAg-onconeural (Ma2 in 3 cases; Hu in 4 cases); SAg types in associated with VGKC-complex (4 cases) and NMDA receptor (3 cases); and Rasmussen encephalitis (22 cases) and neurodegeneration controls (25 cases). The percentage of CD8 T-cells in the IAg-GAD cases was intermediate (54%) between the IAg-onconeural and SAg cases. The CD8+/CD3+ ratio of the SAg cases was significantly different from the Rasmussen encephalitis controls. That ratio was lower than in the parenchyma confirming that CD8+ T-cells migrated into the parenchyma more readily than CD4+ T cells. Apposition of multiple GrB+ lymphocytes to single neurons, consistent with a specific cytotoxic T-cell attack in case GAD/3. Bien and colleagues [23] noted diffuse cytoplasmic IgG detected by anti-human IgG in both neurons and astrocytes in all cases similar to that of controls which they attributed to leakiness of damaged neuronal membranes. Staining of C9neo indicative of complement activation was negative in the IAg GAD cases. CD68+ cells comprised 0.2% in the IAg-GAD cases.

The finding of a reduced CD8+/CD3+ ratio of the IAg-GAD cases, all without concomitant tumor, was lower than the IAg-onconeural group. It was also within the highest ratios of the SAg group of NMDAR cases compatible with the hypothesis that T-cells were a necessary aspect for neuronal loss and hippocampal atrophy in the 2 GAD-associated LE (in GAD cases 2 and 3). Notwithstanding, the absence of an underlying malignancy could contribute to the long duration of disease and overall less intense inflammation. As noted by Bien and coworkers [23], the pathogenic role of GAD antibodies has not been certain because of the different associated clinical syndromes (SPS, cerebellar ataxia, TLE and LE). Multiple antibodies against IAg and SAg may explain the relatively low CD8+/CD3+ and GrB/CD3 ratios in the IAg-GAD cases.

Diagnosis and Treatment

The diagnosis of anti-GAD LE should be considered in patients with a clinical syndrome of temporal lobe seizures, and cognitive and psychiatric disturbances, brain MRI abnormalities on T_2FLAIR MRI implicating the medial temporal lobes; CSF pleocytosis and OCB; and EEG revealing temporal lobe epileptic or slow-wave activity, in association with high levels of anti-GAD65 autoantibodies on RIA. Most cases will fail to disclose an underlying malignancy. In

the series of 58 literature case summarized by Gagnon and Savard [39] follow-up was available in 53 cases. Full recovery was noted in 4 (8%) cases, 3 of whom received corticosteroids alone, with intravenous immune globulin (IVIg), or in combination with PE; a fourth case received no immunosuppressant therapy and recovered. Death occurred in 4 (8%) cases, 3 of whom had an associated cancer. Sustained improvement was noted in 23 (43%) cases with followup of 96 months. A favorable outcome was noted in 45% of cases with positive CSF GAD65 antibodies compared to 56% of those with antibodies only in serum.

Anti-NMDA Receptor Encephalitis

Background

In 2007, Dalmau and colleagues [42] identified a new CNS antigen as NR1/NR2B12 heteromers of the NMDAR with predominantly neuropsychiatric symptoms from a cohort of 526 cases of noninfectious LE with antibodies against CNS proteins. The anti-NMDA receptor antibody appears to play a critical role in synaptic plasticity and memory. Although anti-NMDA receptor encephalitis is not by definition associated with cancer, 59% of patients had a tumor, most commonly benign-appearing cystic mature or immature teratomas tumors of the ovary. All showed serum or CSF antibodies to the NMDA receptor. A year later, the same investigators [27] described a case series of 100 patients with antibodies against NR1-NR2 heteromers of the NMDA receptor as measured by enzyme-linked immunosorbant assay (ELISA), 91 of whom were women, all with psychiatric symptoms or memory complaints. In addition, seizures were seen in 76 patients; 88 were unresponsive or had altered consciousness, 86 had dyskinesia, 69 had autonomic instability, and 66 showed hypoventilation. Three-quarters presented initially to a psychiatric service.

Epidemiology

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [43] representing about 1% of all young patients' admissions to intensive care units (ICU). A French study [44] noted a frequency of anti-NMDA receptor encephalitis of 2% in febrile encephalitis that may be an underestimate because it excluded children. A multicenter, population-based, prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the United Kingdom (UK) making it the most common cause of AE after acute demyelinating encephalomyelitis (ADEM) in children [45].

Clinical Aspects

Clinically, anti-NMDA receptor encephalitis commences with nonspecific prodromal symptoms of headache, fever, nausea, or viral-infection like illness [46], but over days to weeks, seizures, neurocognitive and neurobehavioral complaints emerge including memory loss and frank neuropsychiatric manifestations of insomnia, mania, anxiety, depression, and paranoia [47, 48]. There can be movement disorders with oro-lingual-facial dyskinesia, autonomic manifestations, central hypoventilation, tachycardia and bradycardia. The eventual outcome of all patients was favorable in three-quarters who recovered or had mild deficits with immunotherapy, whereas one-quarter had severe persistent deficits or died. Relapses so noted

in 25% to 30% of cases [49], were partly attributed to lack of treatment, while 12% of treated cases relapsed in the first two years in one long-term outcome cohort analysis [50].

Cellular and Synaptic Antibody Effects

Human embryonic kidney cells 293 (HEK293) ectopically expressing single or assembled NR1-NR2 subunits have been used to determine the epitope targeted by the anti-NMDA receptor, the extracellular N-terminal domain of the NR1 subunit. By quantitative analysis of the NMDA receptor in neuronal cell culture, there was a decrease in the numbers of cell-surface NMDA receptor, and NMDA receptor clusters in postsynaptic dendrites. Most patients with anti-NMDA receptor encephalitis have intrathecal synthesis of antibodies and numerous CD 138+ antibody-secreting plasma cells in perivascular, interstitial, and Virchow-Robin spaces with complement fixing IgG and IgG3 subtypes, as well as B- and T-cells in perivascular regions. Complement-mediated mechanisms in anti-NMDA receptor encephalitis studied in cultured rat hippocampal neurons tested for complement fixation [51] showed complement binding *in vitro* and in neural tissue of teratoma tumors, although not in the brains of affected patients.

Laboratory Investigations

Testing for NMDA receptor antibodies is recommended in patients who manifest encephalitic signs, psychiatric symptoms, seizures, and CSF inflammation, after exclusion of viral and bacterial causes of infection regardless of neuroradiologic investigation since the disorder may be associated with normal MRI findings in up to 50% of cases. The remaining one-half may include non-specific changes and abnormal T_2/FLAIR MRI hyperintensities in the mesial temporal lobe, cerebral or cerebellar cortex, basal ganglia or brainstem. There is typically no abnormal enhancement or hemorrhage. FDG brain PET may show hyper- or hypometabolism in the affected regions [52]. Up to 25% of patients have electrographic seizures. CSF analysis can show moderate lymphocytic pleocytosis, increased protein content, elevated IgG index, and CSF-specific oligoclonal bands which were typically negative at first testing, but can become positive later with disease progression in up to one-half of cases.

Histopathologic Correlation

The histopathologic aspects of NMDA receptor encephalitis have been studied in 14 cases, including 9 at postmortem examination, and 5 in brain biopsy tissue. Dalmau and colleagues [53] described 12 women with prominent psychiatric symptoms, amnesia, seizures, dyskinesia, autonomic dysfunction and altered consciousness. All had serum/CSF antibodies that immunolabeled the neuropil of hippocampus/forebrain, in particular the cell surface of hippocampal neurons and reacted with NR2B, and to a lesser extent NR2A, subunits of the NMDA receptor. NR2B binds glutamate and forms heteromers (NR1/NR2B or NR1/NR2A/NR2B) that are preferentially expressed in the adult hippocampus/forebrain. Expression of functional heteromers, and not single subunits, was required for antibody binding. The CSF and serum of all 12 patients showed a distinctive pattern of reactivity with the neuropil of rat hippocampus, and the immunolabeling predominantly occurred with the cell membrane of neurons and was intense in the molecular layer of the hippocampus. Three patients age 14, 24 and 35 years of age (Cases 2, 6, 10) died, including one (Case 10) were previously reported [54], 3 to 6 months after symptom presentation. MRI showed T_2/FLAIR

hyperintensities in the medial temporal lobes (Case 2); hyperintensity of the parietal sulci and enhancement of overlying meninges (Case 6); and a third (Case 10) showed normal findings. CSF in all three showed pleocytosis varying from 115 (Case 10) to 219 WBC (Case 6) with minimally increased or normal protein content, and positive oligoclonal bands. Immunofluorescence microscopy experiments demonstrated co-localization of antigens reacting with patient antisera and antibodies against NR2B, and co-localization of these antibodies in patients' tumor samples and in brain. Postmortem examination showed extensive gliosis, rare T-cell infiltrates, and neuronal degeneration predominantly involving, but not restricted to the hippocampus in all three. Microglial nodules and neuronophagia were rarely seen. In all cases, these findings predominated in the hippocampus but also affected other areas of the brain, brainstem, and spinal cord. There was intense IgG immunostaining of the hippocampi resembling rodent-staining of NMDA receptor in brain sections without complement immunostaining. The main epitope targeted by the antibodies is the extracellular N-terminal domain of the NR1 subunit. Patients' antibodies decreased the numbers of cell-surface NMDA receptor and clusters in postsynaptic dendrites, an effect that reversed by antibody removal. Tüzün and coworkers [55] extended the immunopathological analysis of Cases 6 and 10 reported previously by Dalmau and [53] noting that lymphocytic infiltrates were uncommon, and were rarely noted in the perivascular and leptomeningeal regions or scarcely distributed in the brain parenchyma. CD20+ B-cells and CD79a plasma cells were identified in the perivascular space including 1% cytotoxic T-cells and absence of GrB+, Fas and Fas ligand-positive cells. IgG, including deposits were noted in all areas of the CNS but most intense in the hippocampus, basal forebrain, and cervical spinal cord. Using HEK293 cells expressing NR1/NR2B, the NMDA receptor IgG were mainly IgG_1, but included IgG_2 and IgG_3 types. Tumor samples exhibited NR1/NR2-expressing tumor cells in varying amounts.

Camdessanché and coworkers [56] reported the postmortem findings of a brain biopsy specimen from an 18-year-old woman with NMDA receptor encephalitis who presented with subacute mood changes and facial jerks. Brain MRI showed foci of T_2 hyperintensities in the right frontal lobe, and CSF showed 21 WBC and oligoclonal bands. A frontal lobe showed that showed perivascular cuffing of CD20+ B-cells and a few CD138+ plasma cells, with few CD3+ T-cells or CD68+ macrophages scattered throughout grey and white matter and in perivascular spaces. Retrospective screening for anti-NMDA receptor antibodies was performed on a CSF sample that was positive at a dilution of 1:10, both in the neuropil of the rat hippocampus and in transfected HEK293 cells.

Martinez-Hernandez and coworkers [51] described 2 men, age 7 and 59 years, and three women age 5, 24 and 35 years, the latter two with ovarian teratomas, and anti-NMDA receptor encephalitis who presented with subacute short-term memory deficits, psychiatric disturbances, seizures, movement disorders, and dysautonomia ranging from 22 days to 4 months. CSF showed protein elevation ranging from 94 to 219 mg/dL with oligoclonal bands; and brain MRI showed increased FLAIR signal in medial temporal lobes (Case 1), parietal cortex (Case 2), left temporal cortex (Case 3), and in the insula and anterior temporal lobes with atrophy in another (Case 5). Brain MRI was normal in Case 4. Treatment with combined immunotherapy in one patient who underwent a brain biopsy was effective, while the others died. One patient who died underwent earlier brain biopsy, and the remaining three patients were studied at postmortem examination. Patients' antibodies were able to fix complement on cultures of rat hippocampal neuron but were not detected in any of the brain regions of 3 patients, or in biopsies of 2 patients, all with anti-NMDAR encephalitis. The main histological findings were

an abundance of infiltrating CD138+ plasma cells and plasmablasts in perivascular regions cuffing blood vessels, Virchow-Robin spaces, and lining the meningeal-brain surface in proximity to the CSF. Using cultures of rat hippocampal neurons, the patients' antibodies were able to fix complement but deposits of IgG were absent, nor was there complement immunostaining at postmortem examination or in brain tissue biopsies. In contrast to brain, tumor neural tissue showed complement immunoreactivity.

Bien and colleagues [23] examined brain biopsy tissue from 2 women and 1 man, age 17 to 22 years with NMDAR encephalitis, all three with encephalopathy lasting 2 months to 12 months, none with an associated tumor. Two were treated with immunotherapy before frontal (2 patients) or temporal lobe cortical biopsy. Serial MRI in one patient did not show hippocampal atrophy. Histopathology of the tissue specimens showed low density of T-cells, in the range of neurodegeneration controls. The ratio of perivascular CD8+/CD3+ was slightly elevated, and there were cytotoxic granules in some parenchymal T-cells, but no apposition of CD8++ T-cells to single neurons. Diffuse cytoplasmic IgG was evident in both neurons and astrocytes and C9neo deposition was present in the cytoplasm and on the surface of hippocampal CA4, dentate, and cortical neurons. The neocortex of NMDA receptor antibody-positive patients showed almost no inflammation, and no clear signs of neuronal loss. Even though NMDA receptor antibodies appeared to be involved in the clinical disease process, there was no evidence to suggest a classical mechanism of cytotoxic T-cell or humoral immune-mediated neuronal cell death. The possibility that a more active inflammatory infiltrate or antibody deposition could be found at an earlier disease stage in both the hippocampus and cortex, could not be excluded, although it was striking that MRI evidence of inflammation in the hippocampus was rare.

Collectively, the histopathologic findings were consistent with a selective and reversible decrease in NMDA receptor surface density and synaptic localization that correlated with patients' antibody titers. The mechanism of this decrease was selective antibody-mediated capping and internalization of surface NMDA receptors. This was supported by the experimental finding of Hughes and colleagues [57] who studied Fab fragments prepared from patients' antibodies that did not decrease surface receptor density. Subsequent cross-linking with anti-Fab antibodies recapitulated the decrease caused by intact patient NMDA receptor antibodies. These cellular mechanisms appear to be the cause of the specific titer-dependent and reversible loss of NMDA receptors. The loss of the subtype of glutamate receptors that eliminates NMDA receptor-mediated synaptic function may underlie the learning, memory and other behavioral deficits observed in affected patients.

Diagnosis and Treatment

Suggested criteria for the definite diagnosis of anti-NMDA receptor encephalitis [3] includes the presence of IgG anti-GluN1 antibodies in a suspected patient with subacute onset of psychiatric behavior or cognitive disturbances, seizures, movement disorder, and autonomic dysfunction; and abnormal EEG that shows focal or diffuse slowing or epileptic activity; and CSF pleocytosis or oligoclonal bands. Prompt diagnosis of anti-NMDA receptor encephalitis leads to improvement typically after removal and treatment of an offending cancer, or in the absence thereof. The demonstration of copious infiltrates of antibody-secreting cells in the CNS of affected patients provides an explanation for the intrathecal synthesis of antibodies, and implications for treatment used to arrest and reverse the disorder employing intravenous immunoglobulin (IVIg), corticosteroids, cyclophosphamide, or rituximab.

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [43] representing about 1% of all young patients' admissions to ICU. A French study [44] noted a frequency of anti-NMDA receptor encephalitis in 2% in febrile encephalitis that could be an underestimate because of the exclusion of children. A multicenter population-based prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the UK, making it the most common cause of AE after ADEM in children [45].

Anti-VGKC-Complex Encephalitis

Background

About the same time that MoS was described, anti-VGKC-complex antibodies were determined using RIA in patients with noninfectious AE [19]. While the disorder was generally termed LE, the term limbic encephalopathy was also used as more patients were found to be seropositive without evidence of classical features of hyperintense signal intensities in the medial temporal lobes on brain MRI, and CSF inflammation [19].

Alteration of trans-synaptic scaffolding systems in AE that affects neuronal cell adhesion molecules are crucial for proper synapse formation and adhesion, plasticity, and function. In both developing and mature neurons, these molecules serve to recruit and anchor pre- and postsynaptic proteins to appropriate synaptic localizations, allowing for normal synaptic transmission. Autoantibodies against the VGKC-complex detected by RIA in the sera of patients with AE do not bind directly to VGKC-complex channel proteins proper, but instead to synaptic and axonal neuronal proteins that co-precipitate with detergent-solubilized VGKC [58, 59].

Attention has focused on identifying the principal autoantigens in the VGKC-complex and expanding the spectrum of corresponding phenotypes. Initial reports [60, 61] suggested that patients' antibodies were bound to the VGKCs Kv1.1 and Kv1.2. Subsequent studies showed that leucine-rich glioma-inactivated protein 1 (LGI1) LGI1, and contactin-associated protein-like2 (CASPR2) were the main autoantigens [58, 59] which associated with transiently expressed axonal glycoprotein (TAG1), post synaptic density protein-Drosophila disc large tumor suppressor-zonula occludens-1 protein (PDZ), and the ankyrin-spectrin protein in both the peripheral and CNS. Antibodies against contactin-2 usually occur in association with those targeting LGI1 or Caspr2 were identified in other disorders, raising doubts about their importance. There is a diversity and overlap of neurological phenotypes associated with VGKC-complex-IgG in the serum and CSF, and distinct Ig-subtype specificity. The commonest presentation of VGKC-complex autoantibodies is LE in the CNS, and neuromyotonia or MoS in the periphery.

Epidemiology

In the UK, where the incidence of encephalitis is estimated at 5.23 cases/100,000/year based upon admissions to the National Health Service between 2005 and 2009, Granerod and colleagues [62] estimated the incidence of encephalitis as 4.32 cases/100,000 population/year. A capture–recapture model estimated the incidence of encephalitis to be 8.66

cases/100,000/year. Two percent of patients (n = 216) had >1 encephalitis admission during the study period; and the incidence did not change (4.20 cases/100,000/year) when subsequent admissions of these patients were excluded from the analysis. By using data restricted to the primary diagnostic field, the overall mean incidence was 2.75 cases/100,000/year (95% CI 2.39 cases–3.10/100,000/year). The results of multivariable analyses showed that compared with 2005–2006, incidence in all subsequent years was slightly higher but with little evidence of a trend (p = 0.19). The incidence rate was highest among patients <1 year of age, and in those >65 years of age. A retrospective study that reviewed antibodies to VGKC, LGI1 and CASPR2 in 46 children with severe acute encephalitis identified only one affected child (2.2%) among 46 children [63].

Clinical Aspects

Among 64 patients with VGKC-complex encephalitis [64] the clinical features overall included neuropsychiatric features, disorientation, confusion, or amnesia in 100% of patients; tonic-clonic seizures in 92%, delusions in 21%,, hallucinations in 17%, agitation in 6%, pain in 4.7%, and peripheral neuropathy in 1.6% of cases. Neurocognitive complaints, psychiatric symptoms and seizures typical evolve over days to weeks, occasionally acutely, but more often insidiously over months before coming to medical attention. The finding of an apparent dementia in 72 affected patients was studied by Flanagan and colleagues [65]. Responsiveness to immunosuppressant and immunomodulatory therapy was predicted by seropositivity for neuronal VGKC-complex antibody more than calcium channel or neuronal acetylcholine receptor (P = .01). Up to 40% of patients may also manifest frontal lobe and frank psychiatric features. Parthasarathi and colleagues [66] described a 58-year-old man with panic attacks and psychogenic non-epileptic seizures who later developed delusions and hallucinations followed by confusion. He was found to have VGKC-complex antibodies and treated with immuno-modulatory therapy leading to near complete recovery. Bettcher and coworkers [67] delineated cognitive strengths and weaknesses among 12 subjects with VGKC-complex encephalitis noting mild to moderate impairment in memory and executive functions, with variable impairments in language and sparing of visuospatial skills that correlated with MRI findings of T_2/FLAIR hyperintensities in medial temporal lobe (10/10) and basal ganglia (2/10). Serial cognitive examination revealed heterogeneity in cognitive function.

Seizures occur in up to 90% of cases and are most commonly focal in nature, with infrequent generalization, manifesting typical medial temporal lobe signature with hand and orofacial automatisms. Three seizure semiologies, ictal bradycardia, piloerection, and fasciobrachial dystonic seizures (FBDS), show a strong associations to LE associated with LGI1 antibodies. FBDS consist of brief frequent episodes abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face, and more rarely the leg. Video electroencephalography shows an epileptic origin of these myoclonic-like movements however regular EEG with scalp electrodes often misses an interictal focus. If FBDS are recognized early, and serum LGI1 antibodies are detected, immunotherapy prevents progression to frank LE, which in one study arose after a median delay of 36 days. Kalachikov and colleagues [68] described autosomal dominant lateral temporal epilepsy (ADLTE) characterized by partial seizures and preceding auditory signs in the LGI1/*epitempin* gene expressed on chromosome 10q24. Mutations in this gene introduce premature stop codons and prevents production of full-length protein from the affected allele. Although LGI1 haploinsufficiency causes ADLT, the underlying molecular mechanism that results in abnormal

brain excitability has instead been attributed to dysregulation of synaptic AMPA receptors in hippocampal neurons in the epileptic LGI1 knock-out mouse [69]. Fukata and colleagues [70] proposed that extracellularly secreted LGI1 linking two epilepsy-related brain receptors, a disintegrin and metalloproteinase domain 22 (ADAM22) and ADAM23, organize a transsynaptic protein complex that includes presynaptic potassium channels and postsynaptic AMPA receptor scaffolds. The lack of LGI1 disrupts this synaptic protein connection and selectively reduces AMPA receptor-mediated synaptic transmission in the hippocampus.

Younger [71] described new-onset FBDS and memory disturbances in association with distal large and painful small fiber peripheral neuropathy, dysautonomia without systemic malignancy in a patient with extrathecal VGKC-complex antibody production. Epidermal nerve fiber studies confirmed small fiber neuropathy in association with abnormal autonomic laboratory testing.

Neuropathic pain as a manifestation of VGKC-complex autoimmunity was noted in 316 (4%) of 1,992 patients evaluated neurologically at a tertiary referral center [72] that was typically subacute in onset, nociceptive, regional, or diffuse. In those suspected of peripheral neuropathy with mild subjective loss of temperature and pain attributed to small fiber dysfunction, electrodiagnostic studies show variable minor reduction of sural sensory nerve action potential amplitudes with motor hyperexcitability. The VGKC-complex antibody titers were often low (0.02-0.1 nM) and antibodies to GLI1 or CASPR2 were present in 28% overall, with the latter most common (7%).

Autonomic involvement was noted in 29% of the cohort studied by Klein and colleagues [72], and in 3 (60%) of the patients described by Lahoria and coworkers [73]. Hypothermia was described in association with VGKC-complex antibody-associated LE in 4 patients [22], Patient 1 of whom had concomitant neuropathic patient, and in the absence thereof in the others who were conjectured to have otherwise disturbed hypothalamic thermoregulatory mechanisms as the cause for dysautonomia.

Cellular and Synaptic Antibody Effects

LGI1 is a secreted synaptic protein that associates with, and regulates Kv1.1 and Kv1.2, as well as AMPA (128). Caspr2 is a transmembrane axonal protein of the neurexin IV superfamily that localizes to the juxtaparanode of myelinated axons, and its extracellular domain interacts with contactin-2, where it connects with the cytoskeleton via protein 4.1B. Caspr2, contactin-2 and protein 4.1B, all of which are necessary to concentrate Kv1.1 and Kv1.2 channels in the juxtaparanode. Lai and colleagues [58] studied proteins associated with Kv1.1 and Kv1.2, noting that VGKCs themselves were the autoantibody targets, explaining the diversity of symptoms among patients with these antibodies. LGI1 is primarily a CNS protein, and LGI1 antibodies are associated with LE, seizures, and hyponatremia. LGI1 antibodies cause reversible CNS synaptic dysfunction by several mechanisms. The antibodies may prevent binding of LGI1 to the receptors that it regulates, or they might act on the LGI1–ADAM protein complex. Alternatively, LGI1 antibodies could disrupt currents mediated by Kv1.1 and Kv1.2, and/or impair AMPAR function, either indirectly by blocking LGI1-mediated regulation of these proteins or directly by disrupting the entire protein complex. The identification of LGI1 as a major target of so-called VGKC antibodies clarifies several aspects of the associated disorder.

Caspr2 antibodies are associated with autoimmune encephalitis, peripheral nerve hyperexcitability, and MoS. Peripheral nervous system manifestations may precede or follow

those of the CNS by up to several years. Some affected patients may have an associated thymic tumor, but most do not. Mutations in the human gene encoding Caspr2 (*CNTNAP2*) are associated with autism, epilepsy, Tourette syndrome, cortical dysplasia, obsessive–compulsive disorder, Pitt–Hopkins syndrome, and other mental disabilities. Mice with a c*aspr2* deletion show analogous behavioral defects and symptoms [74]. Interestingly, common variants of the *CNTNAP2* gene in healthy individuals are associated with abnormal language processing and are a risk factor for autism [75]. Caspr2 antibodies act by disrupting axonal potassium currents. Factors such as differences in time to establishment of intrathecal antibody synthesis, or in the structure of tight, septate-like junctions of myelinating cells around the axons may explain this variability. The VGKC–complex antibody levels also broadly differ between the different syndromes, with highest levels in LE and FBDS, moderate levels in MoS, and lowest levels (often <400 pM) in PNH.

Laboratory Investigation

The high proportion of VGKC-complex IgG-seropositive patients whose serum samples lack LGI1 IgG and CASPR2 IgG specificities, suggests that other VGKC-complex molecular targets remain to be discovered. Only about 4% to 5.5% of unselected cases were seropositive by RIA with confirmatory retesting using 125I-α-dendrotoxin alone (radioligand for Kv1.1, Kv1.2, and Kv1.6 channels) [76, 77], making the test unreliable as a screen for LE without further subtyping for LGI1 and CASPR2-IgG. So selected, 26% to 28% of seropositive VGKC sera revealed reactivity with LGI1 and/or CASPR2-IgG, with a significant association between LGI1-IgG-positivity and cognitive impairment and seizures ($P < .05$), and CASPR2-IgG-positivity and peripheral motor excitability ($P = .004$), however neither autoantibody was pathognomonic for a specific neurologic presentation. There has been concern for screening of unselected sera for VGKC-complex antibodies by RIA. It can be argued that VGKC-complex RIA antibody test should be used as initial screening to select positive samples that could then be confirmed by LGI1 or CASPR2-IgG antibody subtyping, however the latter may also be positive in selected VGKC-complex antibody-negative sera by RIA. Paterson and colleagues [78] noted positive VGKC-complex antibody values (>400 pm; >0.4 nM) that were likely to be relevant in LE and related syndromes, as well as low-positive values (<400 pm; 0.1-0.4 nM) in 32/44 cases considered to be non-autoimmune, 4 (13%) cases of which were found to have a definite or probable paraneoplastic neurologic disorder, neuromyotonia or MoS. Ances and colleagues [30] noted that the RIA used in the clinical analysis of VGKC-complex antibodies identified a limited number of subunits (Kv1.1, Kv1.2 and Kv1.6) but that it was reasonable to speculate that antibodies to other subunits, K (+) channel families and VGKC ion channels might also associate with LE.

Cerebral imaging studies in VGKC-complex antibody associated LE show highly variable results. Both mesial temporal lobe hypometabolism on FDG brain PET, and hypermetabolism have been described [79, 80, 81]. In a patient with VGKC-complex LE [80] who did not definitively demonstrate structure abnormalities on serial brain MRI over time despite ongoing temporal lobe seizures captured on video-EEG, FDG brain PET fused with gadolinium-enhanced MRI later showed bitemporal hypometabolism. Baumgartner and colleagues [81] identified 9/18 (50%) patients positive for non-paraneoplastic antibodies against neuronal surface antigens (VGKC or NMDA-R), 2 of whom displayed mesiotemporal hypermetabolism on FDG brain PET, with 4 others were rated normal, and 3 displayed hypermetabolism outside

the mesiotemporal region. The fraction of abnormal scans employing MRI was lower (10/16; 62.3%) than FDG brain PET (14/18; 77.7%).

CSF results were equally variable in VGKC-complex autoimmunity. Jarius and colleagues [82] performed 29 lumbar punctures in 17 patients with VGKC-complex LE noting normal findings in up to 53% of CSF specimens. There were no significant differences between the CSF findings and the titers of serum VGKC-complex autoantibodies. Slight pleocytosis, mainly consisting of lymphocytes and monocytes, and elevated total protein concentrations were present in 41% and 47%, respectively. A disturbance of the integrity of BBB was found in 6 (35%) patients based upon an abnormal CSF/serum humoral immune response. Absence of CSF-specific OCB, considered a marker of autochthonous antibody synthesis within the CNS in all patients [82] suggested an extrathecal origin of VGKC-complex autoantibodies. Vincent and colleagues [19] reported the CSF findings in 10 patients, all with VGKC-complex antibody-associated LE, noting mild lymphocytosis and mild or moderately raised protein content in one-half. OCB were noted in 1 patient, while 6 other OCB were identical to serum. VGKC-complex antibody assays on matched serum and CSF showed antibodies levels of the latter present in 4 patients that varied between <1 and 10% of the serum, and beneath 10% in one patient with the lowest serum value. These findings were consistent with extrathecal synthesis of VGKC-complex antibodies.

Irani and Vincent [64] estimated features of peripheral neuropathy in 1.6% of VGKC-complex antibody-positive LE cases. Lahoria and coworkers [73] described 5 patients with painful polyneuropathy, all positive for VGKC-complex autoantibodies (range 0.08 to 1.18 nM), two of whom had antigens positive for CASPR2 and LGI1-IgG, both at low VGKC-complex antibody titers (respectively 0.08 and 0.16 nM/L). Electrodiagnostic studies showed length-dependent sensorimotor polyneuropathy that was concordant with abnormal indices of axonal degeneration or demyelination in 4 nerves, and the latter with quantitative analysis of semithin sections in 2. All 5 showed absence of inflammatory cell infiltration. By comparison, the symptoms of small fiber neuropathy, which arise from dysfunction in nociception, temperature and autonomic modalities are most adequately assessed by epidermal nerve fiber density in a 3 mm punch biopsy of skin from the later calf and thigh, and a combination of cardiovagal, sudomotor and adrenergic functions tests with comparison to controls.

Histopathologic Correlation

Eight patients with VGKC-complex LE were studied histopathologically, including stereotactic brain biopsy in 3 [19, 23] at epilepsy surgery in 1 case [23], and at postmortem examination in 4 patients [23, 83, 84, 85]. Vincent and colleagues [19] described a 56-year-old man with 7 month history of confusion and memory impairment who developed partial focal seizures, anxiety and delusions. CSF showed mild pleocytosis and brain MRI showed unilateral left medial temporal lobe signal change with focal slow activity on EEG. The serum VGKC antibody titer was 2224 pM (normal 0-100pM; >400 pM highly elevated). Histopathology of a stereotactic biopsy of the left amygdala showed positive staining for perivascular and parenchymal CD45+ lymphocyte infiltrates, astrogliosis, and CD68+ microgial activation. He was received a course of intravenous dexamethasone with a slight beneficial response with persistent memory deficits. Follow-up brain MRI showed evolution of bilateral hippocampus atrophy and signal changes.

Dunstan and colleagues [83] reported a 78-year-old man with a 2 week history of confusion, cognitive impairment and hyponatremia. Brain MRI showed increased signal in the

right medial temporal lobe with subcortical white matter changes. Cerebrospinal fluid was normal. Assay for VGKC antibodies were 1637 pM by RIA. He received anticonvulsants but deteriorated due to sepsis and died. Postmortem examination showed no evidence of a malignancy. The brain showed severe neuronal loss with multiple reactive astrocytes, macrophages, and scattered T-cells in the right amygdala nucleus and adjacent hippocampus.

Park and coworkers [84] described a 65-year-old woman with a 3 month history of amnesia, disorientation, memory loss, and partial complex seizures. Brain MRI was normal and CSF showed 17 WBC. EEG showed mild diffuse slowing. She later developed hyponatremia and serum VGKC-complex antibodies were 1.73 nmol/L (normal < 0.02 nmol/L) by RIA. Whole body FDG-PET showed mediastinal adenopathy. She was treated with intravenous corticosteroids for 5 weeks without improvement and later died. General autopsy limited to the chest showed no malignancy. Postmortem examination of the brain showed mild focal perivascular T-cell lymphocyte cuffing and infiltrates of overlying meninges and parenchyma of the cingulate gyrus, hippocampus, and amygdala and midbrain.

Khan and coworkers [85] reported a 56-year old man with a 4 month history of confusion, disorientation and seizures. A serum VGKC antibody titer was 3,327 pM by RIA and there was hyponatremia. Brain MRI showed left hippocampal atrophy on T_2/FLAIR images. General postmortem examination showed no malignancy. Examination of the brain showed pathological changes in both hippocampi and right amygdala regions comprised of pyramidal neuronal cell loss in the CA4 region, marked activation of CD68+ microglia and reactive GFAP+ astrocytosis extending to the subiculum, less so near the joining of the parahippocampus gyrus. There were perivascular infiltrates of CD20+ B-cells and a few CD4+ T-cells especially in the right hippocampus.

Bien and colleagues [23] summarized the histopathologic findings in the brain of 4 cases, 3 men and 1 woman, age 33 to 68 years, with LE (3 patients) and multifocal encephalitis in another, ranging from 5 to 9 months. Serum VGKC antibody titers were 167, 288, 958 and 2224 Pm respectively. Serial MRI showed an evolution from hippocampal swelling with T_2/FLAIR signal increase to frank hippocampal atrophy and increased signal intensities. Histopathologic examination including quantitative immunocytochemical studies showed variably intense inflammation and overall lower CD8/CD3 ratios, although there were GrB)+ T-cells present in the lesions without opposition to neurons or release of FrB, therefore T-cell cytotoxicity was not a major contributor. Immunoglobulin and complement deposition on neurons was a prominent finding, and terminal deoxynucleotidyl transferase dUTP nick and labelling (TUNEL) reaction in the same area demonstrated acute neuron cell death suggesting antibody and complement mediated neuronal cell damage in these patients. The authors [23] noted that IgG4 rather than IgG1 antibodies dominated in the sera of those with VGKC-complex LE.

Diagnosis and Treatment

Suspected patients with new-onset and rapid progression of memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system; bilateral medial temporal lobe abnormalities on T2/FLAIR MRI, and CSF pleocytosis combined with TLE or slow-wave activity on EEG should be screened for VGKC-complex antibodies, with detection of LGI1 and CSFPR2 by RIA. The diagnosis of VGKC-complex LE can be established in suspected cases when serological studies are combined with clinical, neuroradiologic and CSF inflammatory parameters, and a reasonable exclusion of alternative diagnoses. If so,

immunomodulatory and immunosuppressive therapy should begin. Less than one-half of affected patients fail to improve with first-line therapy employing IVIg, PE, or corticosteroids, needing to advance to second-line agents including cyclophosphamide and rituximab.

Bataller and colleagues [86] noted that treatment-responsiveness of LE was especially favorable among patients with antibodies to the VGKC-complex with overall improvement in two-thirds or more of patients. However, a favorable response to therapy was not limited to patients with VGKC-complex antibodies but extended to novel-cell-membrane antigens (nCMAg) expressed in the hippocampus. If the autoantigens were unknown but found to be highly enriched in neuronal cells membranes of the hippocampus, these antibodies were likewise associated with a favorable outcome emphasizing the usefulness of immunohistochemistry with PFA-fixed tissue and cultures of live hippocampus rat neurons in the analysis of highly-suspected patients with LE. The salutary effect of immunotherapy in the management of seizures in VGKC-complex antibody-associated LE is well supported by the autoimmune basis of FBDS [87].

HASHIMOTO ENCEPHALOPATHY

For nearly half a decade, investigators have been pursuing an associated rare encephalopathy associated with Hashimoto thyroiditis (HT). In 1966, the British neurologist, Lord Brain and colleagues [88] first described the entity of Hashimoto encephalopathy (HE) in a 40-year-old man with 12 ictal and stroke-like episodes of confusion and agitation one year after onset of treated hypothyroidism. The cerebral disorder remitted completely after 19 months commensurate with a decline in high serum thyroid- antibody levels. Treatment with prednisone and an anticoagulant for 3 months was ineffective. His neurologic symptoms remitted while he was taking only levothyroxine. The authors concluded that the likeliest explanation for this protracted and stuttering brain disorder was localized cerebral edema due to antibody-mediated autoimmunity, and that antibody studies in future cases of unexplained encephalopathy would show whether their findings constituted a syndrome or coincidence. Jellinek and Ball [89] extended the results of Brain and colleagues [88], describing the original patient, who at age 62, later died 12 years later of an unrelated cause. Postmortem examination showed virtually no remaining thyroid tissue and atheromatous cerebrovascular changes with splenic atrophy. The authors postulated that underlying autoimmunity was the cause Hashimoto's thyroiditis and encephalopathy, and splenic atrophy. Almost one half decade later, Rowland and colleagues [90] characterized the clinicopathologic aspects of HE beginning with the patient described by Lord Brain and coworkers [88] and ending in 2002, adding a case of their own. The diagnosis of HE, as described by Rowland and coworkers [90], which rests on the presence of HT with measurably high titers of TPO or Tg antibodies, clinical encephalopathy, and absence of cerebrospinal fluid evidence of bacterial or viral infection, serves as the standard for case selection. However then as now, it is unknown whether anti-thyroid antibodies and concomitant thyroid dysfunction contribute to the pathogenesis of HE.

Clinical Presentation

In the series of Rowland and coworkers [90] the mean age at onset of symptoms of Hashimoto's encephalopathy was 44 years (range, 9-78 years); 19 of whom were boys or girls, age 18 years or younger. Among the adults, there were 53 women and 13 men. In addition to encephalopathy as required, stroke-like signs presented in 23 (27%) case, seizure in 56 (66%), myoclonus in 32 (38%), and visual hallucination or paranoid delusion in 31 (36%). The course was relapsing and remitting in 51 (60%) of cases.

Laboratory Findings

Also in the series of Rowland and colleagues [90], both Tg and microsomal or TPO antibodies were found together in 60 (71%) cases with one antibody of the two normal in 20 (24%) cases. There was no relationship between the neurologic symptoms and signs and the type or serum concentration of anti-thyroid antibodies. Altogether, 30 (35%) cases were sub-clinically hypothyroid, 19 (22%) were euthyroid, and 17 (20%) were overtly hypothyroid. Fourteen (16%) cases had an elevated erythrocyte sedimentation rate or antinuclear antibody, and three had a concomitant connective tissue disease (psoriatic arthritis, Sjogren's syndrome, and sarcoidosis).

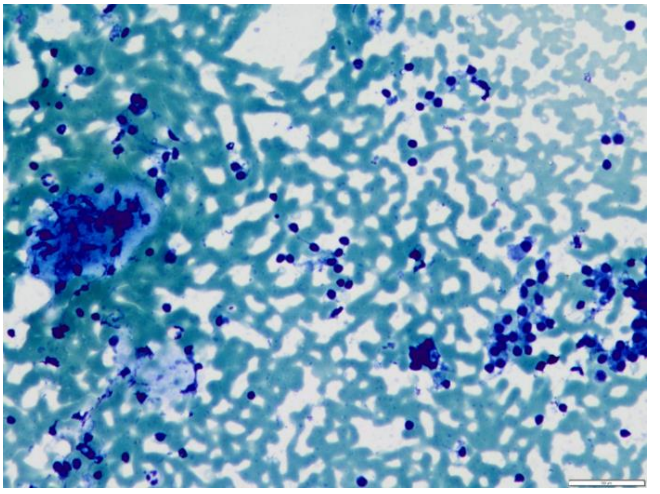


Figure 1. Hashimoto's thyroiditis. Fine needle aspiration in a Diff-Quik® staining of a goiter in a background of lymphocytic thyroiditis. There is a thin background of purple colloid in between grey staining red blood cells amid follicular cells and dark blue staining nucleated lymphocytes recognized by crush or stringing effects (Magnification 200X).

A 19 year-old male with HE and subacute neuropsychiatric complaints and HT recently seen at New York University Langone Health by this author, had HT demonstrated by ultrasound and fine needle aspiration (Figure 1). ^{18}Fluorodeoxyglucose positron emission tomography (PET) of the brain fused with MRI demonstrated the typical features of autoimmune encephalitis. There was signal abnormality in the left hippocampal tail and hypometabolism in the (mesial) temporal and parietal lobes (Figure 2). Nuclear medicine

cerebral perfusion (brain) single photon emission computed tomography (SPECT) showed bilateral temporal and right parietal lobe hypoperfusion.

Cerebrospinal fluid was normal without evidence of infection or another pathogenic autoantibody, apart from TPO. An elevated CSF protein level was noted in 66 (78%) patients, with abnormal findings in neuroimaging in 40/82 (49%) or electroencephalography in 80/82 (98%) patients. A goiter was detected in 24/39 (62%) patients, with a serum microsomal antibodies in 55/58 (95%), TPO antibodies in 26/26 (100%), and Tg antibodies in 45/62 (73%) patients.

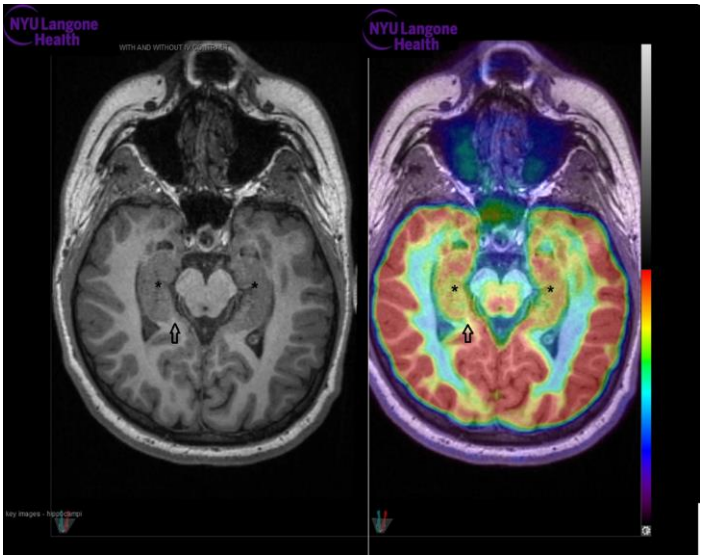


Figure 2. Hashimoto encephalopathy. Positron emission tomographic imaging (right panel) from the vertex to foramen magnum following injection of 10-mCi 18fluoro-D-glucose is fused with gadolinium-enhanced magnetic resonance imaging (left panel). There is hypometabolism of the medial temporal lobes (asterisks), and signal change in the tail of the hippocampus (arrows).

Immunopathogenic Mechanisms

Unlike the close relation between anti-thyroid antibodies and thyroiditis in HE, neither high titers of anti-thyroid antibodies nor the presence of subclinical or overt hypothyroidism accounted for the observed encephalopathy in the series of Rowland and coworkers [90]. The neurological findings in patients that were euthyroid were similar to those with subclinical or overt hypothyroidism. Given the lack of a well-defined pathophysiologic link between anti-thyroid antibodies or HT or HE, the term encephalopathy may be a misleading, as the disorder may be one of a larger group of autoimmune encephalopathies. Ochi and colleagues [91] provided a link between HT autoimmunity and the CNS. Using a human brain proteome map and two-dimensional electrophoresis to screen brain proteins reactive to serum antithyroid antibodies, the authors [91] identified α-enolase, a candidate marker for HE-related pathology, encoded on 1p36.23. Kishitani and coworkers [92] extended the findings of Ochi and colleagues [91] noting anti-NH2-terminal of α-enolase antibodies in 24% of HE patient sera and limbic abnormalities on MRI demonstrating abnormal signal in unilateral or bilateral

medial temporal lobes, and diffuse slow wave activity with epileptogenic discharges. These findings suggested that LE-associated with anti-NH_2-terminal of α-enolase antibodies could be a possible manifestation of HE in some cases. Graus and colleagues [3] proposed Hashimoto encephalopathy as an autoimmune encephalopathy or encephalitis after exclusion of other syndromes associated with well-defined autoantibodies. At present, it is unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathy or are truly associated with pathogenic mechanisms of the disorder.

According to Rowland and colleagues [90], one subgroup of patients with HE present with stroke-like episodes. Inoue and colleagues [93] described a patient with progressive Parkinsonism and normal cognitive and intellectual performance. Slow background activity on electroencephalography was the only sign of encephalopathy, which normalized after treatment with corticosteroids. Younger [94] described a patient with hemi-parkinsonism in a stroke-like onset. ^{18}Fluoro-D-glucose- positron emission tomography metabolic imaging showed severe hypometabolism within the posterior aspect of the left putamen suggesting focal vascular injury, with superimposed left temporal and left parietal hypometabolism and mild volume loss relative to the rest of the brain (Figure 3).

A vasculitic pathogenesis appears to be equally likely in some cases of HE based upon the tendency for increased autoimmunity in HT. In addition, the available histopathology in HE also supports an inflammatory vasculopathy, so noted in one postmortem case that showed lymphocytic infiltration of brainstem veins [95], and in brain biopsy tissue from another case categorized as isolated angiitis due to lymphocytic infiltration of the walls of arterioles and veins [96]. Brain biopsy tissue of second living patient showed perivascular cuffs of lymphocytic cells [90]. It is noteworthy that patients with HE and circulating α-enolase antibodies are at risk for heightened autoimmune activity, and a tendency for systemic and invasive autoimmune disorders including systemic vasculitis [97, 98].

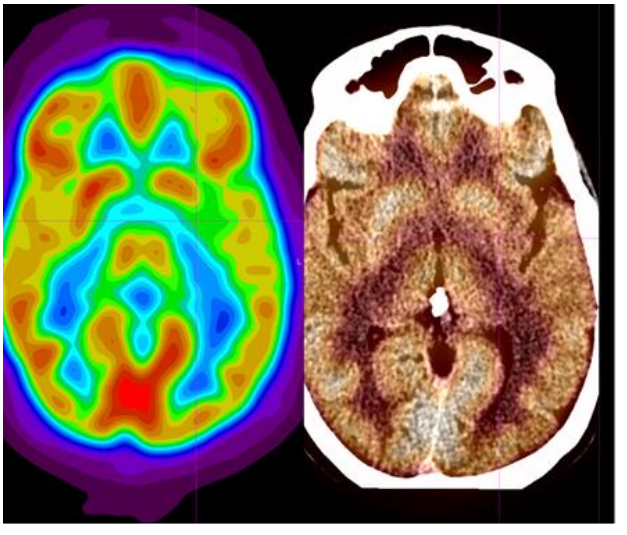


Figure 3. Hashimoto's encephalopathy. Positron emission tomographic (PET) imaging from the vertex to foramen magnum following injection of 10 mCi 18Fluoro-D-glucose (left image) shows severely reduced metabolic activity in the posterior half of the left putamen on standard PET imaging, and with fusion to gadolinium-enhanced magnetic resonance imaging (MRI) (right image).

Treatment

The significance of corticosteroid sensitivity in HE is widely accepted as a criterion for the diagnosis. However, as Rowland and colleagues suggested [90], it would be unwise to define any condition by response to any particular therapy especially if not replacing a specific deficit or directing it at a particular target. Patients with HE improve in association with, but not necessarily due to corticosteroid therapy. Moreover, those that respond to corticosteroids have no distinguishing clinical characteristics nor receive treatment in other fashions for a meaningful comparison.

CONCLUSION

There has been a rapid expansion in knowledge of autoimmune encephalitis neurological and neuropsychiatric disorders. Three well-describe disorders targeting antigens on the surface or in the cells of the temporal lobe neuropil manifest limbic and extra-limbic dysfunction. Patients with HT may develop a rare autoimmune encephalopathy. Recognition of these cases have shifted clinical paradigms and led to new insights into the mechanisms of autoimmune encephalitis. Those with available histopathology show variable humoral and cell-mediated autoimmune, with cytotoxic T-cell inflammation targeting neuropil antigens, making them more similar than not, to primary CNS vasculitis. One important difference however is the more favorable outcome in autoimmune encephalopathy and HE compared to primary CNS vasculitis, making their recognition essential in choosing appropriate immunotherapy to achieve long-lasting remission.

CONFLICT OF INTEREST

None.

REFERENCES

[1] Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: The 2016 Cotzias Lecture. *Neurology* 2016; 87:2471-2482.

[2] Lancaster E, Dalmau J, Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol* 2012; 8:380-390.

[3] Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15:391-404.

[4] Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis. *IMAJ* 2017; 19:448-453.

[5] Elbers J, Benseler SM. Central nervous system vasculitis in children. *Curr Opin Rheumatol* 2008; 20:47-54.

[6] Matar RK, Alshamsan B, Alsaleh S, et al. New onset refractory status epilepticus due to primary angiitis of the central nervous system. *Epilepsy & Behavior Care Reports* 2017; 8:100-104.

[7] Torres J, Loomis C, Cucchiara B, et al. Diagnostic yield and safety of brain biopsy for suspected primary central nervous system angiiits. *Stroke* 2016; 47:2127-2129.

[8] Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. *Brain* 1968; 91:481-496.

[9] Dalmau J, Graus F, Rosenblum MK, et al. Anti-Hu associated paraneoplastic encephalomyelitis/sensory neuronopathy: a clinical study of 71 patients. *Medicine* 1991; 71:59-72.

[10] Budde-Steffen C, Anderson NE, Rosenblum MK, et al. An antineuronal autoantibody in paraneoplastic opsoclonus. *Ann Neurol* 1988; 23:528-531.

[11] Younger DS, Graber J, Hayakawa-Yano Y, Parveen S, Mayu F, Darnell RB. Ri/Nova gene- associated paraneoplastic subacute motor neuronopathy. *Muscle Nerve* 2013; 47:617-618.

[12] Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. *Ann Neurol* 1983; 14:609–613.

[13] Dalmau J, Gultekin SH, Voltz R, et al. Ma1, a novel neuron- and testis-specific protein, is recognized by the serum of patients with paraneoplastic neurological disorders. *Brain* 1999; 122:27-39.

[14] Voltz R, Gultekin SH, Rosenfeld MR, et al. A serological marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. *N Engl J Med* 1999; 340:1788-1795.

[15] Bernal F, Graus F, Pifarre A, et al. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. *Acta Neuropathol* 2002; 103:509-515.

[16] Bien CG, Schulze-Bonhage A, Deckert M, et al. Limbic encephalitis not associated with neoplasm as a cause of temporal lobe epilepsy. *Neurology* 2000; 55:1823-1828.

[17] Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type 1 diabetes. *N Engl J Med* 1988; 318:1012-1020.

[18] Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: distinctive features of a rare disease. *Neurology* 2008; 71:1955-1958.

[19] Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127:701-712.

[20] Irani SR, Gelfand JM, Al-Diwani A, et al. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. *Ann Neurol* 2014; 76:168-184.

[21] Buckley C, Oger J, Clover L, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001; 50:73-78.

[22] Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *J Neurol* 2010; 257:509-517.
[23] Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain* 2012; 135:1622-1638.
[24] Bauer J, Bien CG. Neurpathology of autoimmune encephalitides. *Handb Clin Neurol* 2016; 133:107-120.
[25] Bataller L, Dalmau J. Paraneoplastic disorders of the central nervous system: update on diagnostic criteria and treatment. *Semin Neurol* 2004; 24:461-471.
[26] *Personal communication*, Professor Josep Dalmau.
[27] Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7:1091-1098.
[28] Turner MR, Irani SR, Leite MI, et al. Progressive encephalomyelitis with rigidity and myclonus: glycine and NMDA receptor antibodies. *Neurology* 2011; 77:439-443.
[29] Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann NY Acad Sci* 2015; 1338:94-114.
[30] Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005; 128:1764-1777.
[31] Goldsmith CA, Rogers DP. The case for autoimmunity in the etiology of schizophrenia. *Pharmacotherapy* 2008; 28:730-741.
[32] Nemeroff CB, Simon JS, Haggerty JJ Jr, et al. Antithyroid antibodies in depressed patients. *Am J Psychiatry* 1985; 142:840-843.
[33] Ching KH, Burbelo PD, Carlson PJ, et al. High levels of anti-GAD65 and anti-Ro52 autoantibodies in a patient with major depressive disorder showing psychomotor disturbance. *J Neuroimmunol* 2010; 222:87-89.
[34] Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. *J Neuropsychiatry Clin Neurosci* 2011; 23:90-97.
[35] McKeon A, Tracy JA. GAD65 neurological autoimmunity. *Muscle Nerve* 2017; 56:15-27.
[36] Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff person syndrome. *Muscle Nerve* 2006; 34:677-690.
[37] Falip M, Carreño M, Miró J, et al. Prevalence and immunologic spectrum of temporal lobe epilepsy with glutamic acid decarboxylase antibodies. *Eur J Neurol* 2012; 19:827-833.
[38] Malter M, Helmstaedter C, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. *Ann Neurol* 2010; 67:470-478.
[39] Gagnon M-M, Savard M. Limbic encephalitis: Associated with GAD65 antibodies: Brief review of the relevant literature. *Can J Neurol Sci* 2016; 43:486-493.
[40] Giometto B, Nicolao P, Macucci M, et al. Temporal lobe epilepsy associated with glutamic-acid-decarboxylase autoantibodies. *Lancet* 1998; 352-457.
[41] Bien CG, Urbach H, Schramm J, et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. *Neurology* 2007; 69:1236-1244.

[42] Dalmau J, Bataller L. Limbic encephalitis: the new cell membrane antigens and a proposal of clinical-immunological classification with therapeutic implications. *Neurologia* 2007; 22:526-537.

[43] Prüss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology* 2010; 75:1735-1739.

[44] Thomas L, Mailles A, Desestret V, et al. Autoimmune N-methyl-D-aspartate glutamate receptor antibodies in patient with an initial diagnosis of schizophrenia: specific relevance of IgG NR 1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. *J Infect* 2014; 68:419-425.

[45] Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicenter, population-based prospective study. *Lancet Infect Dis* 2010; 10:835-844.

[46] Izuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology* 2008; 70:504-511.

[47] Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; 10:63-74.

[48] Sansing LH, Tuzun E, Ko MW, et al. A patient with encephalitis associated with NMDA receptor antibodies. *Nat Clin Pract Neurol* 2007; 3:291-296.

[49] Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly nonparaneoplastic disorder of both sexes. *Brain* 2010; 133:1655-1667.

[50] Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factor for long-term outcome in a patient with N-methyl-D-aspartate (NMDA) receptor encephalitis: a cohort study. *Lancet Neurol* 2013; 12:157-165.

[51] Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, et al. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. *Neurology* 2011; 77:589-593.

[52] Kelley BP, Patel SC, Marin HL, et al. Autoimmune encephalitis: Pathophysiology and imaging review of an overlooked diagnosis. *AJNR Am J Neuroradiol* 2017; 38:1070-1078.

[53] Dalmau J, Tuzun E, Hai-yan W, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61:25-36.

[54] Stein-Wexler R, Wootton-Gorges SL, Greco CM, et al. Paraneoplastic limbic encephalitis in a teenage girl with an immature ovarian tetratoma. *Pediatr Radiol* 2005; 35:694-697.

[55] Tüzün E, Zhou L, Baehring JM, et al. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol* 2009; 118:737-743.

[56] Camdessanche JP, Streichenberger N, Cavillon G, et al. Brain immunohistopathological study in a patient with anti-NMDAR encephalitis. *Eur J Neurol* 2011; 18:929-931.

[57] Hughes EG, Peng X, Gleichman AJ, et al. Celllular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010; 30:5866-5875.

[58] Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010; 9:776–785.

[59] Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* 2010; 133:2734–2748.

[60] Hart IK, Waters C, Vincent A, et al. Autoantibodies detected to expressed K+ channels are implicated in neuromyotonia. *Ann Neurol* 1997; 41:238–246.

[61] Kleopa KA, Elman LB, Lang B, et al. Neuromyotonia and limbic encephalitis sera target mature Shaker-type K+ channels: subunit specificity correlates with clinical manifestations. *Brain* 2006; 129:1570–1584.

[62] Granerod J, Cousens S, Davies NW, et al. New estimates of incidence of encephalitis in England. *Emerg Infect Dis* 2013; 19:1455-1462.

[63] Lin JJ, Lin KL, Wang HS, et al. VGKG complex antibodies in pediatric severe acute encephalitis: a study and literature review. *Brain Dev* 2013; 35:630-635.

[64] Irani SR, Vincent A. Voltage-gated potassium channel-complex autoimmunity and associated clinical syndromes. *Handb Clin Neurol* 2016; 133:185-217.

[65] Flanagan EP, McKeon A, Lennon VA, et al. Autoimmune dementia: clinical course and predictors of immunotherapy response. *Mayo Clin Proc* 2010; 85:881-897.

[66] Parthasarathi UD, Harrower T, Tempest M, et al. Psychiatric presentation of voltage-gated potassium channel antibody-associated encephalopathy. *Case report. Br J Psychiatry* 2006; 189:182-183.

[67] Bettcher BM, Gelfand JM, Irani SR, et al. More than memory impairment in voltage-gated potassium channel complex encephalopathy. *Eur J Neurol* 2014; 21:1301-1310.

[68] Kalachikov S, Evgrafov O, Ross B, et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. *Nat Genet* 2002; 30:335-341.

[69] Ohkawa T, Fukata Y, Yamasaki M, et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptor. *The Journal of Neuroscience* 2013; 33:18161-18174.

[70] Fukata Y, Lovero KL, Iwanaga T, et al. Disruption of LGI1-linked synaptic complex causes synaptic transmission and epilepsy. *Proc Natl Acad Sci US* 2010; 107:3799-3804.

[71] Younger DS. Limbic Encephalitis Associated with Voltage-Gated Potassium Channel-Complex Antibodies: Patient Report and Literature Review. *World Journal of Neuroscience* 2017; 7:19-31.

[72] Klein CJ, Lennon VA, Aston PA, et al. Chronic pain as a manifestation of potassium channel-complex autoimmunity. *Neurology* 2012; 79:1136-1144.

[73] Lahoria R, Pittock SJ, Gadoth A, et al. Clinical-pathologic correlations in VGKC-subtyped autoimmune painful polyneuropathy. *Muscle Nerve* 2016 Aug 11. doi: 10.1002/mus.25371. [Epub ahead of print].

[74] Peñagarikano O1, Abrahams BS, Herman EI. CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* 2011; 147:235-246.

[75] Whalley HC, O'Connell G, Sussmann JE, Genetic variation in CNTNAP2 alters brain function during linguistic processing in healthy individuals. *Am J Med Genet B Neuropsychiatr Genet* 2011; 156B: 941–948.

[76] Apiwattanakul M, McKeon A, Pittock SJ, et al. Eliminating false-positive results in serum tests for neuromuscular autoimmunity. *Muscle Nerve*. 2010; 41:702–704.

[77] van Sonderen A, Schreurs MW, de Bruijn MA, et al. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. *Neurology* 2016; 86:1692-1693.

[78] Paterson RW, Zandi MS, Armstrong R, et al. Clinical relevance of positive voltage-gated potassium channel (VGKC)-complex antibodies: experience from a tertiary referral centre. *J Neurol Neurosurg Psychiatry* 2014; 85:625-630.

[79] Gast H, Schindler K, Z'Graggen WJ, et al. Improvement of non-paraneoplastic voltage-gated potassium channel antibody-associated limbic encephalitis without immunosuppressive therapy. *Epilepsy Behav* 2010; 17:555-557.

[80] Day BK, Eisenman L, Black J, et al. A case study of voltage-gated potassium channel antibody-related limbic encephalitis with PET/MRI findings. *Epilepsy & Behavior Case Reports* 2015; 4:23-26.

[81] Baumbartner A, Rauer S, Mader I, et al. Cerebral FDG-PET and MRI findings in autoimmune limbic encephalitis: correlation with autoantibody types. *J Neurol* 2013; 260:2744-2753.

[82] Jarius S, Hoffman L, Clover L, et al. CSF findings in patients with voltage gated potassium channel antibody associated limbic encephalitis. *J Neurol Sci* 2008; 268:74-77.

[83] Dunstan EJ, Winer JB. Autoimmune limbic encephalitis causing fits, rapidly progressive confusion and hyponatremia. *Age and Aging* 2006; 35:536-537.

[84] Park DC, Murman DL, Perry KD, et al. An autopsy case of limbic encephalitis with voltage-gated potassium channel antibodies. *Eur J Neurol* 2007; 14:e5-e6.

[85] Khan NL, Jeffree MA, Good C, et al. Histopathology of VGKC antibody-associated limbic encephalitis. *Neurology* 2009; 72:1703-1705.

[86] Bataller L, Kleopa KA, Wu GF, et al. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 2007; 78:381-385.

[87] Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol S, et al. Mutations in the LGI1/Epitemprin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. *Hum Mol Genet* 2002; 11:1119-1128.

[88] Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet* 1966; 2:512-514.

[89] Jellinek EH, Ball K. Hashimoto's disease, encephalopathy, and splenic atrophy. *Lancet* 1976; 1:1248.

[90] Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy. Syndrome or myth? *Arch Neurol* 2003; 60:164-171.

[91] Ochi H, Horiuchi I, Araki N, et al. Proteomic analysis of human brain identifies α-enolase as a novel autoantigen in Hashimoto's encephalopathy. *FEBS Lett* 2002; 528:197-202.

[92] Kishitani T, Matsunaga A, Masamichi I, et al. Limbic encephalitis associated with anti-NH2-terminal of a-enolase antibodies. A clinical subtype of Hashimoto encephalopathy. *Medicine* 2017; 96:10:e6181.

[93] Inoue K, Kitamura J, Yoneda M, et al. Hashimoto's encephalopathy presenting with micrographia as a typical feature of parkinsonism. *Neurol Sci* 2012; 33:395-397.

[94] Younger DS. Hashimoto's Thyroiditis and Encephalopathy. *World Journal of Neuroscience* 2017; 7, 307-326.

[95] Nolte KW, Unbehaun A, Sieker H, et al. Hashimoto encephalopathy: A brainstem encephalitis? *Neurology* 2000; 54:769-770.

[96] Shibata N, Yamamoto Y, Sunami N, et al. Isolated angiitis of the CNS associated with Hashimoto's disease. *Rinsho Shinkeigaku* 1992; 32:191-198.

[97] Li M, Li J, Li Y, et al. Serum levels of anti-a-enolase activity in untreated systemic lupus erythematosus patients correlates with 24-hour protein and D-dimer. *Lupus* 2017; Jan 1:961203317721752 [Epub ahead of print].

[98] Pancholi V. Multifunctional alpha-enolase: its role in diseases. *Cell Mol Life Sci* 2001; 58:902-920.

II. TREATMENT

In: The Vasculitides. Volume 2
Editor: David S. Younger
ISBN: 978-1-53615-135-0

Chapter 14

OVERVIEW OF THE TREATMENT OF PRIMARY SYSTEMIC VASCULITIS

Antoine Sreih, MD and Peter A. Merkel, MD, MPH*
Division of Rheumatology,
University of Pennsylvania, Philadelphia, PA, US

ABSTRACT

Vasculitis is a group of heterogeneous diseases that often involve organ- and life-threatening manifestations. Prior to effective therapy vasculitis had an extremely high mortality. However, the last 3 decades have seen continuous progress and substantial improvements in establishing early diagnosis and effective treatment for these diseases. These major advances are largely due to enhancement in the description and classification of vasculitis, the implementation of standardized outcomes, and the availability of large cohorts and randomized clinical trials due to ongoing collaborative efforts. This chapter will provide an overview of the general concepts of therapy for vasculitis, highlight the importance of randomized trials in establishing standard treatment algorithms for some forms of vasculitis, outline recent advances in the treatment of primary systemic vasculitis, and describe novel approaches being considered to treat the vasculitides.

Keywords: vasculitis, treatment, overview

* Corresponding Author's Email: pmerkel@upenn.edu.

INTRODUCTION

Primary systemic vasculitides are highly heterogeneous diseases in which inflammation of blood vessels, especially arteries, is the hallmark of the pathophysiology and usually the major source of morbidity for patients. The different forms of vasculitis affect different sized vessels and vary in the processes leading to inflammation, for example immune complex deposition or granulomatous pathology. These diseases can differ markedly in the predominant organ affected, the clinical manifestations, and the nature of the disease-related damage. Vasculitis ranges from a single-episode of mild annoyance to recurrent life- and organ-threatening disease. Approaches to the treatment of vasculitis can differ greatly and must take into account the great variation in disease type and extent.

Treatment of the primary systemic vasculitides has evolved over the past twenty years from a one-size-fits-all approach to more individualized therapy based on the type and severity of vasculitis. For some cases of vasculitis biomarkers or other prognostic factors affect treatment decisions. The great progress made in treatment of vasculitis is due to several advances that have occurred in parallel, including an increased understanding of disease pathogenesis, establishment of international clinical research networks, increased research funding, development of new drugs to treat autoimmune diseases, and conduct of high-quality, multinational randomized clinical trials (RCTs).

This chapter will describe the underlying concepts guiding treatment of vasculitis, clinical trial standards and individualization of therapy, and outline treatment of several types of vasculitis. Where possible the data presented will be based on clinical trials and other sources of good evidence. Details of treatment can be found in the chapters in this textbook dedicated to specific forms of vasculitis.

GENERAL APPROACH TO TREATMENT OF VASCULITIS

The treatment of primary systemic vasculitis largely depends on the specific type of vasculitis and the extent of organ involvement. Therefore, confirmation of the diagnosis and a comprehensive assessment of disease severity are necessary prior to initiating therapy. It is imperative to know the full extent of disease to both be sure that the level of treatment matches the most severe manifestations present, and to stage the extent of specific manifestations present at the start to therapy to allow for proper reassessment later in the treatment course.

Treatment of systemic vasculitis generally consists of a period of remission induction followed by remission maintenance, and long-term follow-up. The duration of therapy usually depends on the type and severity of vasculitis. Treatment also includes management of specific organ damage, prophylaxis against, and treatment of, medication-related toxicities.

Remission-Induction

Remission-induction is the period lasting from the initiation of treatment to the achievement of remission. The duration of this period is usually 3 to 6 months but may vary based on the severity and type of vasculitis. Some patients never achieve remission but most will achieve either remission or a state of low disease activity. Induction of remission almost always includes treatment with moderate-high doses of glucocorticoids alone or in conjunction with another form of immunosuppression. The most common immunosuppressive agents used for remission-induction of severe forms of vasculitis are cyclophosphamide and rituximab; however, several other agents are also used for induction. Adjunctive therapies such as plasma exchange, renal replacement therapy, respiratory support, infection prophylaxis, and other interventions may be used during this period depending on the specific type of vasculitis and the presence of organ failure.

Remission-Maintenance

Remission-maintenance is the period that follows induction and is aimed at consolidating remission and preventing relapses. During this period glucocorticoids are tapered off or lowered to the minimum dose possible. If cyclophosphamide is used for remission-induction then during the maintenance phase, cyclophosphamide is replaced by a less toxic immunosuppressive agent. However, when rituximab is used for remission-induction then additional doses are often given for remission-maintenance. The concept of remission-maintenance was initially introduced and demonstrated to be effective in clinical trials of small-vessel vasculitides, notably anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). A similar approach is now frequently applied to medium-vessel vasculitis such as polyarteritis nodosa (PAN) and Kawasaki disease (KD), and the large-vessel vasculitides including giant cell arteritis (GCA) and Takayasu arteritis (TAK), and other types of vasculitis. The duration of the remission-induction period varies among the vasculitides. For some diseases with a lower probability of relapse, such as PAN, this period may be 12 months while for a disease with frequent relapses, such as granulomatosis with polyangiitis (GPA), remission-maintenance may be much longer. Cogan's syndrome and Behçet's disease are examples of variable-vessel vasculitides and are considered in greater depth elsewhere in this textbook.

Post-Treatment

Even after the remission-maintenance phase of treatment has ended and all immunosuppressive drugs are discontinued, it is imperative that patients are followed regularly for the possibility of disease relapse and to monitor for the occurrence of late-onset medication side effects and cardiovascular events.

RANDOMIZED CLINICAL TRIALS IN THE VASCULITIDES

Since the first curative randomized clinical trial in the history of medicine was conducted in 1946 to study the use of streptomycin in tuberculosis [1] the design and complexity of RCTs steadily evolved to include various study designs, often large number of study subjects, and an emphasis on multicenter studies. The regular conduct of clinical trials to study treatment of vasculitis is only a relatively recent development. The rarity of primary systemic vasculitis, the lack of adequate research funding, the challenges of studying complex heterogeneous disorders, and the small number of academic centers with expertise in these diseases meant clinical research in vasculitis initially consisted of single-center case series and cohort studies, small single-arm and open label trials in a small set of diseases.

The past twenty years has witnessed tremendous progress in the conduct of clinical trials in vasculitis. This progress has occurred due to several factors. First, the widespread adoption of standardized definitions [2, 3] and classification criteria [4, 5] for the vasculitides, leading to greater standardization of eligibility criteria.

Second, the use of validated outcome measures for vasculitis [6-8], although many forms of vasculitis still lack well-validated measures of disease activity or state for use in clinical trials. The Vasculitis Working Group of the Outcome Measures in Rheumatology (OMERACT) initiative is actively pursuing a variety of projects to advance development of valid measures in multiple forms of vasculitis [7, 9-12].

Third, the establishment of national and international research networks including the Vasculitis Clinical Research Consortium (VCRC) (www.RareDiseasesNetwork.org/vcrc*), the* European Vasculitis Society (EUVAS) (www.vasculitis.org), and the French Vasculitis Study Group (FVSG) (www.vascularites.org). These networks facilitate collaborations between academic institutions with expertise in clinical care and research in vasculitis. Many of the key multicenter trials in vasculitis have been conducted by these groups or the core personnel within the groups. The VCRC and the EUVAS are now conducting several large RCTs together, indicative of the growing international cooperative spirit within the vasculitis research community.

Fourth, the increased funding for clinical trials in vasculitis by governmental agencies, private foundations, and the biopharmaceutical industry, singly or in combination.

Fifth, the rapid growth of patient engagement and patients as research-partners, the close collaboration between various stakeholders, and the use of the Internet as a means of communication, recruitment, and dissemination have revolutionized the way some clinical research is done.

Advances in standardized approaches to conducting clinical trials was demonstrated by the publication in 2007 by a group that included leaders of these networks and other international experts in vasculitis of recommendations for conducting clinical trials in systemic vasculitis [13].

OVERVIEW OF THE TREATMENT OF VASCULITIDES

The treatment of primary systemic vasculitis substantially evolved over the years from extended courses of monotherapy with glucocorticoids to more complex, multi-stage regimens that combine glucocorticoids with additional immunosuppressive drugs. These progressions in therapeutic approach are due to several factors, including the implementation of successful larger randomized clinical trials as outlined above, the availability of targeted therapy with so-called "biologic" therapies, and incorporation of specific disease subtypes and prognostic factors that allow for greater individualization of treatment.

Prognostic Factors

A major advance in the field of vasculitis has been the recognition and data supporting the concept that certain clinical factors are associated with disease course in some forms of vasculitis and can assist in the choice and duration of therapy. The clinical pattern, disease phenotype, and history of relapse in patients with GPA and microscopic polyangiitis (MPA) are each predictive of prognosis with treatment. Patients seropositive for anti-proteinase 3 ANCA are at substantially higher risk of relapse than patients with anti-myeloperoxidase ANCA [14, 15], while patients with GPA are more likely to relapse than patients with MPA, a finding not surprising given the much higher prevalence of anti-proteinase 3 ANCA among patients with GPA [15]. A history of relapse in AAV is highly predictive of future relapse. Thus, these prognostic factors are taken into consideration when developing a treatment regimen for patients with AAV, including duration of therapy.

The five factor score (FFS), a prognostic tool created by the FVSG [16-18], is another example of how severity and specific organ involvement may serve not only as a prognostic tool, but also help direct the therapeutic choice in systemic necrotizing vasculitis [19, 20]. The FFS is based on the presence of five clinical items: renal insufficiency, proteinuria, central nervous system involvement, cardiomyopathy, and gastrointestinal involvement. Each clinical item is assigned one point with a total maximum of five points. Patients with systemic vasculitis such as PAN, MPA, and eosinophilic granulomatosis with polyangiitis (EGPA) have a 5-year survival of 88% if FFS = 0, 74% if FFS = 1, and 54% if FFS $\geq$ 2 [16]. The FFS, which has only been substantively tested in PAN, MPA, and EGPA, is calculated at the initial presentation, and has been used to help decide among different treatment courses and whether to add another immunosuppressive agent to glucocorticoids for initial treatment of vasculitis [19, 21, 22]. The FFS was revised in 2011 to include GPA. The presence of ear, nose, and throat (ENT) involvement in GPA and EGPA was associated with a reduction in mortality. The revised FFS currently comprises: age $\geq$65 years, cardiac involvement, gastrointestinal involvement, renal insufficiency (stabilized peak creatinine $\geq$150 μmol/L), and absence of ENT involvement [17].

The type of vasculitis can also dictate the treatment of primary systemic vasculitis. Some vasculitides, such as PAN and anti-glomerular basement membrane disease are more likely to

have a single course of disease without relapse, while other diseases, such as GPA or GCA commonly relapse. Additionally, the severity or type of manifestations may change over time. All of these factors plus individual patient-specific variables are important when considering the treatment options for patients with vasculitis.

TREATMENT OF SPECIFIC VASCULITIDES

The following section will provide outlines on the treatment of specific forms of vasculitis with an emphasis on data derived from controlled clinical trials and will highlight some of the differences in the approach to treatment with the different forms of vasculitis. Many individual patient characteristics and disease variables will impact the decision to adopt and implement any of the treatment regimens described below. The treatment of affected patients with vasculitis should always be directed by physicians with experience in the treatment of vasculitides and the use of immunosuppressive medications. By far the most and highest quality data on treatment of vasculitis is available for GPA and MPA since AAV has been the focus of several large randomized controlled trials. The treatment recommendations and drug dosages provided below pertain mainly to adults should be appropriately adjusted for use in children.

Glucocorticoids

The treatment of nearly all forms of vasculitis involves the use of glucocorticoids and these agents remain a mainstay of treatment, either as single therapy or as part of combination therapy. For severe disease intravenous pulses are usually given for 1 to 3 days followed by high-dose oral glucocorticoids, for example prednisone 1 mg/kg/day followed by a steadily tapering dose. Less severe disease may be treated initially with lower doses of glucocorticoids and mild flares may be treated with only a small increase in their dose. More recently, a large multinational clinical trial called “Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis (PEXIVAS)” demonstrated that a reduced cumulative dose of glucocorticoids was as effective for induction of remission and long-term outcomes as the standard higher-dose regimen, with lower rates of infection seen in the lower-dose glucocorticoid arm [43]. Glucocorticoids are usually given for at least 6 months or more after the initial presentation or after a moderate-severe flare. The total duration of therapy with glucocorticoids for vasculitis is controversial with some experts advocating for attempting to get patients fully off glucocorticoids in the first year of treatment and others promoting the extended use of low-dose glucocorticoids in the first 12 to 18 months of treatment [23, 24].

SMALL-VESSEL VASCULITIS

ANCA-Associated Vasculitis: Granulomatosis with Polyangiitis and Microscopic Polyangiitis

The treatment of GPA and MPA has evolved over the last four decades from glucocorticoids alone to extended use of cyclophosphamide [25] to several different treatment protocols based on disease severity, disease stage, and including substantially reduced cumulative doses of cyclophosphamide or the avoidance of this medication altogether [26]. For purposes of treatment, severe disease flare in AAV is generally defined as the presence of active disease manifestations that are organ- and/or life-threatening.

Remission-induction therapy for severe initial presentations or flares and relapses of disease in AAV currently involves the use of glucocorticoids in combination with a choice of cyclophosphamide or rituximab. Two clinical trials compared cyclophosphamide to rituximab for remission-induction and found these two treatments to have similar efficacy in inducing remission when used in combination with glucocorticoids [27, 28]. The standard dose of oral cyclophosphamide for remission-induction of AAV is 2 mg/kg/day for 3 to 6 months. Pulse intravenous cyclophosphamide therapy is a reasonable alternative to oral administration. A randomized trial (the "CYCLOPS" study) demonstrated equivalence of the two routes of administration of cyclophosphamide for remission-induction [29] and the use of intravenous cyclophosphamide is supported by other studies [30]. However, it is important to note that the dosing of cyclophosphamide per the "CYCLOPS" regimen is 15 mg/kg every 2 weeks for 3 infusions then once every 3 weeks. The duration of cyclophosphamide use in the major trials was 4 to 6 months prior to transition to another agent. The dose of oral or intravenous cyclophosphamide should be adjusted down among patients with renal insufficiency, in response to leukopenia, and in older patients [31].

Remission-maintenance treatment in AAV following achievement of remission with cyclophosphamide involves the use of intravenous rituximab 500 mg every 6 months [32]. Azathioprine at the dose of 2 mg/kg/day or methotrexate at doses of 20 to 25 mg/week can also be used for at least 1-2 years after cyclophosphamide and often much longer or indefinitely for patients at high risk of relapse [33-35]; one RCT found no difference in the efficacy of azathioprine and methotrexate for maintaining remission [36]. The choice between these two agents depends on individual patient factors and preferences; methotrexate should not be used by patients with renal insufficiency. The IMPROVE trial in AAV [37] showed that following induction of remission with cyclophosphamide, azathioprine was superior to mycophenolate mofetil for remission-maintenance making the latter a third choice for this indication, after azathioprine and methotrexate.

Rituximab was found to be as effective as cyclophosphamide at inducing remission in AAV [27, 28]. The induction regimen used in the trials was 375 mg/m2 given intravenously weekly

for 4 consecutive weeks. Rituximab is a reasonable alternative to cyclophosphamide for treatment of severe AAV. However, the high cost of this drug has resulted in wide variation internationally in the use of rituximab. In some countries it is a first-line treatment option, especially to treat younger patients seeking to preserve their fertility. In many countries use of rituximab is restricted to patients with relapsing disease, especially those who have had prior courses of cyclophosphamide who comprise a subset of patients for whom rituximab was found superior to cyclophosphamide in the RAVE trial [15]. In other countries rituximab is an unavailable as a treatment option.

The appropriate choice of treatment for remission-maintenance following induction of remission with rituximab remains uncertain. In the RAVE trial [15] one course of rituximab was equally efficacious in maintaining remission as 18 months of cyclophosphamide and azathioprine. Single-center retrospective cohort studies provided evidence that repeated doses of rituximab helped maintain remission in many patients [38, 39]. However, due to the expense of rituximab and concerns about the impact of repeated dosing and hypogammaglobinemia, consideration has since been given to using more standard immunosuppressive agents such as azathioprine or methotrexate following rituximab. Different treatment strategies for maintenance of remission in AAV after induction with rituximab are currently being studied in a multinational clinical trial (RITAZAREM) (ClinicalTrials.gov Identifiers: NCT01697267) [40].

The role of plasma exchange in the treatment of AAV has been highly controversial. In one RCT of patients with AAV and severe rapidly-progressive renal impairment at diagnosis, the addition of plasma exchange reduced the frequency of progression to end-stage renal disease but not overall mortality [41]. Other studies did not clearly demonstrated the benefit of plasma exchange in AAV [42], including for the treatment of alveolar hemorrhage. A recent large multinational, randomized clinical trial involving 704 patients with GPA and MPA (the PEXIVAS trial), treatment of severe AAV in a large m [43] plasma exchange did not reduce the rate of end-stage renal disease or death.

Adjunctive therapy with high-dose intravenous immunoglobulin therapy has been used in patients who fail to achieve remission with standard approaches [44].

The data is mixed on the efficacy of trimethoprim-sulfamethoxazole as treatment for upper respiratory manifestations of AAV or in the maintenance phase of treatment [45-47]. This drug is routinely use for prophylaxis against *pneumocystis jirovecii* pneumonia for patients with AAV receiving immunosuppressive agents.

Two other immunomodulating drugs have shown promise in phase II clinical trials for the treatment of GPA and MPA including abatacept (CTLA4-Ig) for the treatment of non-severe relapsing GPA and an oral inhibitor of C5a (CCX168) for the treatment of GPA and MPA [48, 49]. The results of a phase III clinical trial are expected to provide more definitive data on the utility of the oral inhibitor of C5a (CCX168) for the remission and maintenance of GPA and MPA (ClinicalTrials.gov Identifier: NCT02994927).

The optimal duration of therapy for remission maintenance in GPA and MPA remains unknown. However, the trend has been towards longer courses of therapy with the remission-maintenance agent often continued for at least 12 to 18 months for treatment of new-onset disease and even longer or indefinitely for relapsing disease [50]. Affected patients that demonstrate ANCA with specificity to proteinase 3 have substantially higher rates of relapse than those patients positive for antibodies to myeloperoxidase; relapse in AAV is itself predictive of future relapse [15].

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

The approach to treatment of EGPA differs somewhat from the other AAV due to several factors including recognition that many patients may have a monocyclic course, identification of clinical prognostic factors influencing the choice of treatment, and the impact of recurrent asthma on clinical course.

A recent randomized trial demonstrated that blockade of IL-5 by a monoclonal antibody (mepolizumab) resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thus allowing for reduced glucocorticoid use in patients with EGPA [51]. This clinical trial led to the first FDA approval for a drug for the treatment of EGPA.

Several other clinical trials conducted in EGPA by the FVSG have provided guidance to treatment of this form of vasculitis; however, these studies have often included a mixture of patients with EGPA, MPA, and PAN making interpretation of results complicated. Glucocorticoids are the mainstay of therapy for EGPA and are included in all treatment regimens and are often the sole treatment for cases without poor-prognosis factors (FFS = 0) [19], or in combination with intravenous cyclophosphamide when the FFS $\geq$ 1. In a trial of superiority of six versus twelve pulses of cyclophosphamide (600 mg/m2 per pulse) in patients with a poor prognosis, defined as a FFS $\geq$ 1, the longer duration of treatment was superior to shorter treatment for control of disease [20]. Patients treated with glucocorticoids alone had more frequent relapses suggesting the need for a revision in this treatment approach. A RCT of azathioprine and glucocorticoids as first-line treatment in EGPA without factors mitigating poor-prognosis demonstrated no additional benefits for remission rates, relapse risk, sparing of glucocorticoids, or diminishing the EGPA asthma/rhinosinusitis exacerbation rate over glucocorticoids alone [52]. Although the trials of EGPA mainly involve use of intravenous cyclophosphamide, many centers will apply the treatment regimens used for GPA and MPA for patients with severe EGPA and prescribe oral cyclophosphamide for several months, transitioning afterward to azathioprine or methotrexate for remission maintenance. Methotrexate combined with glucocorticoids is another regularly used remission-induction regimens to treat non-severe EGPA [47].

It remains intriguing yet controversial to consider the ANCA status when treating patients with EGPA, include for example, whether patients positive for ANCA should be treated according to strategies for GPA and MPA or whether patients negative for ANCA be treated in a different manner.

Newer agents such as other IL-5 inhibitors (reslizumab [ClinicalTrials.gov Identifier: NCT02947945] and benralizumab [ClinicalTrials.gov Identifier: NCT03010436]) are under investigation for the treatment of EGPA. While rituximab use has been limited to a few case series [54, 55], there is enthusiasm for using rituximab to treat EGPA based on experience with GPA and MPA, especially for patients who test positive for ANCA (ClinicalTrials.gov Identifier: NCT02947945).

The treatment of EGPA is complicated by the presence of asthma in the vast majority of patients. It is controversial whether to consider asthma as a manifestation of vasculitis or a separate aspect of the disease. Asthma is the most common disease manifestation of EGPA and may drive the clinical decision to treat with glucocorticoids, whether prescribed at chronic low maintenance doses or periodically at high-doses to control exacerbations of asthma.

IMMUNE COMPLEX-MEDIATED VASCULITIS

Cryoglobulinemic Vasculitis

The treatment of cryoglobulinemic vasculitis (CV) depends upon the etiology and the severity of associated organ involvement. While antiviral therapies remain the cornerstone of the treatment of hepatitis C virus (HCV)-related CV, glucocorticoids, immunosuppressive drugs, and plasma exchange can all be used for the acute treatment of HCV-associated CV. Two RCTs demonstrated the efficacy of rituximab to treat HCV-related CV with recurrent disease despite anti-viral therapy and standard immunosuppression [56-58]. Rituximab is prescribed in non-HCV-associated CV but data from clinical trials for this indication are lacking. Less severe cases of CV, such as mild skin disease and arthritis, can be treated with a short course of glucocorticoids. Persistent disease with idiopathic CV may necessitate treatment aimed at whatever is presumed to be the underlying plasma cell dyscrasia.

IgA-Vasculitis (Henoch-Schönlein)

IgA-vasculitis (IgAV) is a disease for which the course and treatment may be different between children and adults. The data for treatment of IgAV is derived from a few clinical trials in children and mostly case series for adults. There is neither consensus for the treatment of IgAV, nor agreement as to whether available therapies change the course of the disease.

MEDIUM-VESSEL VASCULITIS

Polyarteritis Nodosa

In comparison to AAV, there are limited data from clinical trials to support the choice of treatment in PAN [59-61] and the often monocyclic nature of the disease may complicate the determination of risks and benefits any given immunosuppressant regimen. The practice of pooling patients with PAN, MPA, and EGPA within a single clinical trial can make study results difficult to interpret. The treatment of PAN generally follows a type- and severity-based strategy, including utilization of the FFS. Results from uncontrolled studies and expert opinion suggest that the primary treatment of hepatitis B virus (HBV)-associated PAN can be treated with antiviral therapies; however, a short course of glucocorticoids may be appropriate treatment of acute vasculitis-related complications. The role of plasma exchange in HBV-associated PAN remains controversial [62, 63].

The treatment of idiopathic PAN without HBV infection relies on immunosuppressive therapy. For limited cutaneous and mild systemic PAN (FFS = 0) prednisone in doses up to 1 mg/kg/day alone is often sufficient treatment; when the disease is controlled then the glucocorticoid dose is tapered slowly.

The treatment of patients with severe systemic PAN (FFS $\geq$ 1) associated with involvement of the kidney, heart, gastrointestinal tract, and the central nervous system (CNS) includes combination of high-dose glucocorticoids and another immunosuppressive agent. Pulse intravenous methylprednisolone at the dose of 1000 mg/day for 3 days followed by prednisone 1 mg/kg/day tapered over 6 months is the recommended glucocorticoid regimen. In addition, cyclophosphamide is given orally at a dose of 2 mg/kg/day or intravenously in doses of 600 to 750 mg/m^2 every 2 to 4 weeks for 6 months with subsequent transition to azathioprine at a dose of 2 mg/kg/day or methotrexate at doses of 20 to 25 mg weekly for remission maintenance [26]. Some centers treat systemic PAN by prescribing glucocorticoids at the outset in combination with azathioprine or methotrexate but without cyclophosphamide.

Kawasaki Disease

Kawasaki disease occurs almost exclusively in young children. Randomized trials have established the standard of treatment that includes aspirin, intravenous immune globulin, and comprehensive cardiac monitoring through centers experienced in the management of this disease [64-66].

LARGE-VESSEL VASCULITIS

There is ongoing controversy and interest in the question as to whether GCA and TAK constitute a single spectrum of large-vessel vasculitis and thus whether their respective treatments should be the same [67-69]. Glucocorticoids remain the mainstay of remission-induction and generally remission-maintenance therapy in both diseases. However, several recent clinical trials have provided evidence of the benefit of other immunosuppressive agents (anti-IL6R and anti-CTLA4) on disease remission and reducing glucocorticoids cumulative dose. Endovascular and surgical interventions may be required to manage the vascular damage leading to stenosis and aneurysm formation that may occur.

Giant Cell Arteritis

The usual starting dose of prednisone for the treatment of GCA ranges from 40 to 60 mg/day for four weeks with a subsequent gradual taper over many months [70]. The exact timing of glucocorticoid withdrawal is controversial with some centers seeking to attempt to withdraw them at six months and others advocating a longer course of low-dose daily prednisone for the first year of treatment. Intravenous pulse glucocorticoids for three consecutive days may be considered initially in cases of acute visual loss [71].

The benefit of tocilizumab, a monoclonal antibody directed against the IL-6 receptor, in combination with prednisone, was demonstrated in two randomized trials to effectively reduce the risk of relapse among patients with GCA compared to treatment with prednisone along. Based on the results of these trials, tocilizuamb was subsequently approved drug by the FDA and EMA for GCA [72; 73]. Abatacept, a CTLA4-IgG1 fusion protein that binds to the CD80/86 molecule and prevents the activation of T-cells, has also been shown in a double-blind RCT to reduce relapse rates in patients with GCA [74].

Weekly oral methotrexate can be used as a maintenance agent. The role of methotrexate as a glucocorticoid-sparing agent was studied in three RCTs [75-77] demonstrating conflicting results. However, an individual patient-level meta-analysis demonstrated that methotrexate was efficacious in preventing relapses and reducing total glucocorticoid usage [78]. While the overall efficacy of methotrexate in GCA appears to be modest, it is nonetheless frequently used to help avoid excess glucocorticoid use and to treat relapsing disease.

The use of anti-TNF alpha agents for treatment of GCA was studied in three RCTs, each of which failed to demonstrate efficacy for these agents [79-81]. A trial of infliximab also failed to demonstrate efficacy in polymyalgia rheumatic (PMR) [82].

Several other drugs have been proposed for use as glucocorticoid-sparing agents in GCA, including azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, and leflunomide but there is no evidence large clinical studies or RCTs to support the use of these agents [83-86].

The results from an analysis of two large retrospective patient series supported the use of low-dose aspirin as adjunctive therapy in GCA to prevent ischemic complications [87, 88]; however, the routine use of aspiring in GCA remains an ongoing controversy.

Among the challenges of conducting RCTs in GCA are the lack of a clear definition of disease activity, the accepted efficacy and low cost of glucocorticoids, the acute nature of the clinical presentation necessitating immediate treatment, and the difficulty older individuals may have in participating in research studies. Nonetheless, there remains an unmet need to find alternative therapies to high-dose or recurrent courses of glucocorticoids in GCA.

Takayasu Arteritis

Only two RCTs have been conducted in TAK. The first was a trial of abatacept plus glucocorticoids vs. glucocorticoids alone for the treatment of TAK that did not demonstrate efficacy of this biologic agent [89]. The second trial tested tocilizumab plus glucocorticoids vs. glucocorticoids alone and this trial had equivocal results but with some data that tocilizumab may help reduce the time to relapse [90]. Treatment approaches for this rare disorder continue to be based instead on case series, expert opinion, and extrapolation from studies in GCA, which may not be an ideal approach. Glucocorticoids are the foundation of therapy for induction or remission in TAK and the dosing regimen is similar to GCA and other vasculitides with initial high-dose oral glucocorticoids followed by a slow taper over several months. Other immunosuppressive therapies, including azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil are routinely prescribed in patients with severe disease or in those with recurrent or refractory disease [91]. Although initial case series reported high efficacy from use of anti-TNF-alpha agents, subsequent series demonstrated that these agents, while possibly helpful in some patients, were associated with substantial rates of disease relapse or incomplete remission-induction [92-95]. Initial patient reports of rituximab [96] to treat TAK have been promising, however, larger series with longer follow-up and RCTs are required to evaluate any agent in this chronic relapsing disease.

Surgical Intervention

Both GCA and TAK are associated with a variety of fixed vascular stenosis and aneurysm formation of the aorta and its main branches. Such lesions occur as a result of scarring after inflammation, even when the disease is seemingly well controlled. Aneurysms, once formed, tend to enlarge just as do aneurysms resulting from other etiologies such as hypertension. Patients with large-vessel vasculitis should be considered for surgical intervention to treat severe or functionally-limiting limb ischemia, cerebrovascular insufficiency, renal artery stenosis with associated severe hypertension, expanding aortic aneurysms, and severe cardiac valvular disease. There remains uncertainty regarding the relative efficacy and advisability of angioplasty, stents, and surgical repair for these vascular lesions. Regardless of which form of

repair may be considered, the consensus is that particular attention should be given to controlling disease activity in the peri-procedure period [98-100]. Endovascular procedures in patients with vasculitis should be performed in specialized centers with experience with both the procedures and the management of vasculitis [26].

VARIABLE VESSEL VASCULITIS

Cogan's Syndrome

Most patients with Cogan's syndrome are treated with glucocorticoids with a favorable response for both vestibule-auditory and ophthalmologic manifestations. Other therapies, all based on small case series or expert opinion, included methotrexate, cyclophosphamide, azathioprine, anti-TNF alpha agents, hydroxychloroquine, and intravenous immunoglobulin. Surgical cochlear implantation can lead to objective and subjective benefits with improved hearing recognition in the majority of patients.

Behçet's Disease

Behçet's disease is a complex multisystem disorder in which several clinical trials have been conducted using a variety of different outcome measures. However, unlike most trials in other forms of vasculitis where overall disease activity is the outcome of interest, those in Behçet's disease have often focused on specific manifestation such as mucocutaneous lesions and uveitis [101]. A RCT of apremilast for the treatment of oral ulcers in Behçet's disease showed promising results [11] and a larger Phase III has been completed (ClinicalTrials.gov Identifier: NCT02307513). Thus, treatment recommendations are complex and depend upon the stage of disease, sex of the patient, and disease manifestations of greatest concern.

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

There are no RCTs to guide treatment of primary centeral nervous system vasculitis (CNSV) also known as primary angiitis of the CNS. Treatment is based upon the clinical experience from case series, cohort studies, and expert opinion [102]. The initial treatment of CNSV includes prednisone 1 mg/kg/day often in combination with cyclophosphamide administered in monthly intravenous pulses with later transition to azathioprine, methotrexate, or mycophenolate mofetil for an additional period of 12 to 18 months as remission maintenance. TNF-alpha blocking drugs have been used to treat CNSV refractory to glucocorticoids and

other immunosuppressive drugs [103, 104]. The treatment of childhood CNSV is reviewed elsewhere [105].

OTHER SYSTEMIC VASCULITIDES

There are several other types of vasculitis for which treatment is based on small case series and expert opinion when RCTs are unavailable. These vasculitides include anti-GBM disease, relapsing polychondritis, single-organ vasculitis (SOV), drug-induced vasculitis, and other unclassifiable vasculitides.

TREATMENT-RELATED TOXICITY

Much of the morbidity incurred by primary systemic vasculitis results from the treatment, rather than the disease itself. It is essential for physicians and patients to constantly monitor for side effects of drugs and use appropriate measures to minimize or prevent treatment-related complications. A detailed discussion of the proper use of immunosuppressive medications is beyond the scope of this chapter.

LONG-TERM COMPLICATIONS OF VASCULITIDES

Disease-related problems in vasculitis go beyond the acute organ damage that occurs due to active vasculitis. Long-term complications of both the underlying vasculitis and the treatments are increasingly recognized as contributing to the overall morbidity of patients with vasculitis. In addition to the direct damage caused by vasculitis such as renal failure, visual loss, aneurysm, lung impairment, and other problems, it is important to monitor and treat other long-term complications that may be more common with vasculitis but overlooked. These complications include, hypertension from renal insufficiency and renal artery stenosis, accelerated cardiovascular disease thought secondary to chronic inflammation, obesity from often repeated courses of glucocorticoids, malignancy associated with treatment and possible increased incidence of cancer associated with vasculitis, depression and other mood disorders common among patients with serious chronic illnesses, and physical disabilities that impair daily function and work productivity.

CONCLUSION

Despite the substantial progress made in the therapy of primary systemic vasculitis, the treatment of many vasculitides remains a challenge. Dividing therapy into an induction phase

and maintenance phase to improve disease control and minimize side effects as well as individualizing medical management based on the severity, type, and prognostic factors have revolutionized the therapy of vasculitis. Multicenter RCTs have answered critical questions regarding the management of several primary systemic vasculitides but data from trials are still lacking for the majority of vasculitides and for treatment of children with vasculitis. The development of research networks including the VCRC, EUVAS, and FVSG, have all greatly facilitated RCTs in vasculitides and fostered collaboration among these networks to produce major new studies. Newer medications and novel approaches are constantly being tested to refine therapy and improve care in vasculitis. The rapid development of targeted immunomodulatory therapies will likely have a substantial positive impact on the treatment of vasculitis. Similarly, discovery and refinement of reliable biomarkers of disease activity, prognosis, and response to treatment, should usher in an era of individualized or personalized therapy for vasculitis.

REFERENCES

[1] British Medical Research Council. Streptomycin treatment of pulmonary tuberculosis: A Medical Research Council investigation. *BMJ* 1948; 2:769-783.

[2] Jeannette J, Falk R, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-192

[3] Jennette J, Falk R, Bacon P, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65:1-11.

[4] Hunder G, Arend W, Bloch D, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis Rheum* 1990; 33:1065-1067.

[5] Watts R & Scott D. Recent developments in the classification and assessment of vasculitis. *Best Pract Res Clin Rheumatol* 2009; 23:429-443.

[6] Luqmani R, Bacon P, Moots R, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994; 87:671-678.

[7] Direskeneli H, Aydin SZ, Kermani TA, et al. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. *J Rheumatol* 2011; 38:1471-1479.

[8] Stone J, Hoffman G, Merkel P et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. *Arthritis Rheum* 2001; 44:912-920.

[9] Merkel P, Aydin S, Boers M et al. Current status of outcome measure development in vasculitis. *J Rheumatol* 2014; 41:593-598.

[10] Merkel PA, Aydin SZ, Boers M, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. *J Rheumatol* 2011; 38:1480-1486.

[11] Hatemi G, Merkel PA, Hamuryudan V, et al. Outcome measures used in clinical trials for Behçet syndrome: a systematic review. *J Rheumatol* 2014; 41:599-612.

[12] Sreih AG, Alibaz-Oner F, Kermani TA et al. Development of a Core Set of Outcome Measures for Large-vessel Vasculitis: Report from OMERACT 2016. *J Rheumatol*. 2017 44:1933-1937

[13] Hellmich, Flossmann O, Gross W et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007; 66:605-617.

[14] Hogan S, Falk R, Chin H, et al. Predictors of relapse and treatment resistance in patients with antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005; 143:621-631.

[15] Specks U, Merkel PA, Seo P, et al, for RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369:417-427.

[16] Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996; 75:17-28.

[17] Guillevin L, Pagnoux C, Seror R, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90:19-27.

[18] Gayraud M, Guillevin L, le Toumelin P, et al. Long term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis and Rheum* 2001; 44:666-675.

[19] Ribi C, Cohen P, Pagnoux C, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum* 2008; 58:586-594.

[20] Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognostic factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum* 2007; 57:686-693.

[21] Guillevin L, Cohen P, Mahr A, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognoses factors: A prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in six-five patients. *Arthritis Rheum* 2003; 49:93-100.

[22] Ribi C, Cohen P, Pagnoux C, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognostic factors: A prospective randomized study of one hundred twenty-four patients. *Arthritis Rheum* 2010; 62:1186-1197.

[23] Walsh M, Merkel PA, Mahr A, Jayne D, Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res* 2010; 62:1166-1173.

[24] McGregor JG1, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH; Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. *Clin J Am Soc Nephrol* 2012; 7:240-247.

[25] Fauci AS, Wolff SM. Wegener's granulomatosis: Studies in eighteen patients and a review of the literature. *Medicine* (Baltimore) 1973; 52:535-561.

[26] Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; 68:310-317.

[27] Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363:221-232.

[28] Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363:211-220.

[29] De Groot K, Harper L, Jayne DRW, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis. *Ann Int Med* 2009; 150:670-680.

[30] De Groot K, Adu D, Savage CO; et al. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant* 2001; 16:2018-2027.

[31] Pagnoux C, Quéméneur T, Ninet J, et al; French Vasculitis Study Group. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis Rheumatol* 2015 67:1117-1127

[32] Guillevin L, Pagnoux C, Karras A, et al; French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014 371:1771-1780

[33] Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349:36-44.

[34] De Groot K, Rasmussen N, Bacon PA,, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Rheum* 2005; 52: 2461–2469.

[35] Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005 Jan 27; 352:351-361.

[36] Pagnoux C1, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008 25; 359:2790-2803.

[37] Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis. *JAMA* 2010; 304:2381-2388.

[38] Cartin-Ceba R1, Golbin JM, Keogh KA, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. *Arthritis Rheum* 2012; 64:3770-3778.

[39] Smith RM1, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; 64:3760-769.

[40] Gopaluni S, Smith RM, Lewin M, et al; RITAZAREM Investigators. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. *Trials.* 2017 18:112

[41] Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18:2180-2188.

[42] Walsh M, Catapano F, Szpirt W, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *Am J Kidney Dis* 2011; 57:566-574.

[43] Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 2013;14:73.

[44] Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 2000; 93:433-439.

[45] Israel HL. Sulfamethoxazole-trimethoprim therapy for Wegener's granulomatosis. *Arch Intern Med* 1988; 148:2293-2295.

[46] Stegeman CA, Tervaert JW, Sluiter WJ, et al. Association of chronic nasal carriage of Staphylococcus aureus and high relapse rates in Wegener granulomatosis. *Ann Intern Med* 1994; 120:12-17.

[47] De Groot K, Reinhold-Keller E, Tatsis E, et al. Therapy for maintenance of remission in sixty-five patients with trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; 39:2052-2061.

[48] Langford CA, Monach PA, Specks U, et al,; Vasculitis Clinical Research Consortium. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). *Ann Rheum Dis* 2014 731376-1379

[49] Jayne DRW, Bruchfeld AN, Harper L, et al; CLEAR Study Group. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephro*l. 2017 28:2756-2767

[50] de Joode AAE, Sanders JSF, Puéchal X, et al. Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data. *Rheumatology* (Oxford) 2017; 56:1894-1901

[51] Wechsler ME, Akuthota P, Jayne D, et al; EGPA Mepolizumab Study Team.Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; 376:1921-1932

[52] Puéchal X, Pagnoux C, Baron G, et al; French Vasculitis Study Group. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. *Arthritis Rheumatol* 2017; 69:2175-2186

[53] Meltzer C, Hellmich B, Gause A, et al. Churg Strauss syndrome-successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment. *Clin Exp Rheumatol* 2004; 22(Suppl 36):S52-S61.

[54] Clain JM, Specks U. Rituximab for ANCA-associated vasculitis: the experiences in the United States. *Presse Med* 2013; 42:530-532.

[55] Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option with Churg –Strauss syndrome. *J Allergy Clin Immunol* 2010; 125:1336-1343.

[56] De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64:843-853.

[57] Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64:835-842.

[58] Ferri C, Cacoub P, Mazzaro C, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. *Autoimmune Rev* 2011; 11:48-55.

[59] Guillevin L, Cohen P, Mahr A, et al. Treatment of polyarteritis and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003; 49:93-100.

[60] Gayraud M, Guillevin L, Cohen P, et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. *Br J Rheumatol* 1997; 36:1290-1297.

[61] Guillevin L, Jarrousee B, Lok C, et al. Longterm followup after treatment of polyarteritis and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. *J Rheumatol* 1991; 18:567-574.

[62] Guillevin L, Lhote F, Leon A, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. *J Rheumatol* 1993; 20:289-298.

[63] Guillevin L, Mahr A, Cohen P, et al. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum* 2004; 51:482-487.

[64] Harnden A, Takahashi M, Burgner D. Kawasaki disease. BMJ 2009; 338:b1514; Furukawa T, Kishiro M, Akimoto K, et al. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. *Arch Dis Child* 2008; 93:142-146.

[65] Durongpisitkul K, Gururaj VJ, Park JM, et al. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; 96:1057-1061.

[66] Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007; 356:663-675.

[67] Hoffman GS. Large-vessel vasculitis: unresolved issues. *Arthritis Rheum* 2003; 48:2406-2414.

[68] Maksimowizc-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? *Medicine* (Baltimore) 2009; 88:221-226.

[69] Grayson PC1, Tomasson G, Cuthbertson D, et al. Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis. *J Rheumatol* 2012; 39:303-309.

[70] Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *N Engl J Med* 2014; 371:50-57.

[71] Maziumzadeh M, Hunder GG, Easley KA, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum* 2006; 54:3310-3318.

[72] Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016; 387:1921-1927

[73] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med* 2017; 377:317-328

[74] Langford CA, Cuthbertson D, Ytterberg SR; Vasculitis Clinical Research Consortium. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. *Arthritis Rheumatol* 2017; 69:837-845

[75] Spiera RF, Mitnick HJ, Kupersmith M, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; 19:495-501.

[76] Jover JA, Hernández-García C, Morado IC et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; 134:106-114.

[77] Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46:1309-1318.

[78] Mahr AD, Jover JA, Spiera RF, et al. Adjuvant methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007; 56:2789-2797.

[79] Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticoid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007; 146:621-630.

[80] Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. *Ann Rheum Dis* 2008; 67:625-630.

[81] Seror R, Baron G, Hachulla E, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a muticentre randomised controlled trial. *Ann Rheum Dis* 2013 July 29 [Epub ahead of print].

[82] Salvarani C, Hunder GG. Tumor necrosis factor blocking agents in polymyalgia rheumatica and giant cell arteritis. *Ann Intern Med* 2008; 148:167-168.

[83] Loock J, Henes J, Kötter I, et al. Treatment of refractory giant cell arteritis with cyclophosphamide: a retrospective analysis of 35 patients from three centres. *Clin Exp Rheumatol* 2012; 30(Suppl 70):S70-S76.

[84] De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis* 1986; 45:136-138.

[85] Le Guennec P, Dromer C, Sixou L, et al. [Treatment of Horton disease. Value of synthetic antimalarials. Apropos of a retrospective study of 36 patients. *Rev Rheum Ed Fr* 1994; 61:485-490.

[86] Schaufelberger C, Möllby H, Uddhammar A, et al. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. *Scand J Rheumatol* 2006; 35:327-329.

[87] Nesher G, Berkun Y, Mates M, et al. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum* 2004; 50:1332-1337.

[88] Lee MS1, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 2006; 54:3306-3309.

[89] Langford CA, Cuthbertson D, Ytterberg SR, et al; Vasculitis Clinical Research Consortium. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis. *Arthritis Rheumatol* 2017; 69:846-853

[90] Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis* 2018; 77:348-354

[91] Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. *Curr Opin Rheumatol* 2005; 17:16-24.

[92] Hoffman GS, Merkel PA, Brasington RD, et al. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50:2296-2304.

[93] Molloy ES, Langford CA, Clark TM, et al. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis* 2008; 67:1567-1569.

[94] Mekinian A, Néel A, Sibilia J, et al. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. *Rheumatology* (Oxford) 2012; 51:882-886.

[95] Comarmond C, Plaisier E, Dahan K, et al. Anti TNF-α in refractory Takayasu arteritis: cases series and review of the literature. *Autoimmune Rev* 2012; 11:678-684.

[96] Hoyer BF, Mumtaz IM, Loddenkemper K, et al. Takayasu arteritis is characterized by disturbances of B cell homeostasis and responds to B cell depletion with rituximab. *Ann Rheum Dis* 2012; 71:75-79.

[97] Seitz M, Reichenbach S, Bonel HM, et al. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med Wkly* 2011 Jan 17; 141:w13156.

[98] Perera AH, Youngstein T, Gibbs RG, et al. Optimizing the outcome of vascular intervention for Takayasu arteritis. *Br J Surg* 2014; 101:43-50.

[99] Park HS, Do YS, Park KB, et al. Long term results of endovascular treatment in renal arterial stenosis from Takayasu arteritis: angioplasty versus stent placement. *Eur J Radiol* 2013; 82:1913-1918.

[100] Saadoun D, Lambert M, Mirault T, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicentre experience. *Circulation* 2012; 125:813-819.

[101] Hatemi G, Melikoglu M, Tunc R, et al. Apremilast for Behçet's syndrome--a phase 2, placebo-controlled study. *N Engl J Med*. 2015; 372:1510-1518

[102] Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62:442-451.

[103] Calabrese LH, Duna GF, JT Lie. Vasculitis in the central nervous system. *Arthritis Rheum* 1997; 40:1189-1201.

[104] Salvarani C, Brown RD Jr, Calamia KT, et al. Efficacy of tumor necrosis factor alpha blockade in primary central nervous system vasculitis resistant to immunosuppressive treatment. *Arthritis Rheum* 2008; 59:291-296.

[105] Cellucci T, Benseler SM. Central nervous system vasculitis in children. *Curr Opin Rheumatol* 2010; 22:590-597.

ABOUT THE EDITOR

David S. Younger, MD, MPH, MS
Department of Neurology, Division of Neuro-Epidemiology
New York University School of Medicine;

For the past three decades, the author, David S. Younger MD, MPH, MS has been a clinician, educator, and public health researcher. Dr. Younger is an authority in the use of immunotherapy to treat childhood and adult neuro-immunological disorders. He edits Motor Disorders 3rd Edition, The Vasculitides, Human Lyme Neuroborreliosis, Vasculitis of the Nervous System, and Global and Domestic Public Health and Neuroepidemiology; and the forthcoming book, The Autoimmune Brain. He has authored more than 250 peer-reviewed articles, book chapters, and abstracts. In addition to a clinical teaching and practice, he is a doctoral candidate in City University of New York School of Public Health, Department of Health Policy and Management.

Dr. Younger obtained his MD degree from Columbia College of Physicians and Surgeons P&S in 1981, afterward entering internship and residencies in Internal Medicine at Montefiore Hospital, and neurology at the Columbia University Neurological Institute. He continued his training in three postdoctoral fellowships: epilepsy and EEG, clinical neuromuscular disease, and clinical trials investigation at the Neurological Institute, mentored by "Bud" Rowland, Chairman of the Department. He laid the groundwork for his later academic career at his alma mater as an Assistant Professor until he moved to New York University becoming Clinical Associate Professor of Neurology, and the first Chief of the Division of Neuromuscular Disease.

Frustrated by the lack of connection with larger populations of disease risks and public health policy reform, he entered the New York University College of Global Public Health Master's degree program in Public Health, followed by s Master's degree program in Epidemiology at the Columbia Mailman School of Public Health. Urged further by colleagues and family, Dr. Younger embarked on a doctoral degree program in Health Policy and Management at City University of New York, School of Public Health focusing his thesis on the opioid epidemic and health and legislative policy reform of medical cannabis. He leaves New York University this year after 25 years of service, to join the Neuroscience teaching faculty of the City University of New York, School of Medicine.

Dr. Younger brings to the second edition of The Vasculitides, his typical editorial talent in assembling expert authors and cutting-edge chapters, notwithstanding in-depth topics of neurological vasculitis. His website: http://www.davidsyounger.com provides a useful toolbox of on-line resources.

LIST OF CONTRIBUTORS

Leonard H. Calabrese, DO
Department of Rheumatic and Immunologic Diseases
Cleveland Clinic
Cleveland, Ohio, USA
Adult Primary Angiitis of the Central Nervous System and Related Syndromes (Chapter 7)

Patrica K. Coyle, MD
Department of Neurology,
Comprehensive Multiple Sclerosis Center
Stony Brook University Medical Center, and the School of Medicine
Stony Brook, New York, US
Central Nervous System Vasculitis Due to Infection (Chapter 10)

Adam J. Davis, MD
Image Processing Lab, Department of Radiology
New York University School of Medicine
660 1st Avenue
New York, NY, USA
Neuroimaging of CNS Vasculitis (Chapter 6)

P. James B. Dyck, MD
The Peripheral Neuropathy Research Center
Mayo Clinic
Rochester, MN, USA
Peripheral Nerve Vasculitis: Classification and Disease Associations (Chapter 12)

Loïc Guillevin, MD
National Referral Center for Rare Autoimmune and Systemic Diseases
Department of Internal Medicine
University of Paris Descartes, Hôpital Cochin
Paris, France
Polyarteritis Nodosa (Chapter 2)

Kelly G. Gwathmey MD
Department of Neurology
University of Virginia
Charlottesville, VA, USA
Peripheral Nerve Vasculitis: Classification and Disease Associations (Chapter 12)

Rula A. Hajj-Ali, MD
Department of Rheumatology
Cleveland Clinic Lerner School of Medicine
Cleveland, Ohio, USA
Adult Primary Angiitis of the Central Nervous System and Related Syndromes (Chapter 7)

Gene G. Hunder, MD
Division of Rheumatology
Mayo Clinic
Rochester, MN, USA
Primary CNS Vasculitis: Pathophysiological Diversity (Chapter 8)

Peter A. Merkel, MD, MPH
Division of Rheumatology
Department of Biostatistics, Epidemiology, and Informatics
University of Pennsylvania
Philadelphia, PA, USA
Overview of the Treatment of Primary Systemic Vasculitis (Chapter 14)

Nicolò Pipitone, MD, PhD
Department of Rheumatology
Arcispedale Santa Maria Nuova
Reggio Emilia, Italy
Primary CNS Vasculitis: Pathophysiological Diversity (Chapter 8)

Charles D. Pusey, MD
Department of Medicine
Renal and Vascular Inflammation Section
Imperial College London
London, United Kingdom
Foreword

Loïc Raffray, MD, PhD
Department of Internal Medicine
Centre Hospitalier Universitaire Réunion
Réunion, France
Polyarteritis Nodosa (Chapter 2)

Eytan Raz, MD, PhD
Department of Radiology
Division of Interventional Neuroradiology
New York University School of Medicine, New York, NY, USA
Neuroimaging of CNS Vasculitis (Chapter 6)

Carlo Salvarani, MD
Azienda USL-IRCCS di Reggio Emilia
Università di Modena e Reggio Emilia
Reggio Emilia, Italy
Primary CNS Vasculitis: Pathophysiological Diversity (Chapter 8)

Antoine Sreih, MD
Division of Rheumatology
University of Pennsylvania
Philadelphia, PA, USA
Overview of the Treatment of Primary Systemic Vasculitis (Chapter 14)

Jennifer A. Tracy, MD
Department of Neurology
Mayo Clinic, Rochester, MN, USA
Peripheral Nerve Vasculitis: Classification and Disease Associations (Chapter 12)

Richard A. Watts, MD, MPH
Norwich Medical School, University of East Anglia,
Norwich, UK
Department of Rheumatology, Ipswich Hospital NHS Trust
Ipswich, UK
Foreword

David S. Younger, MD, MPH, MS
Department of Neurology, Division of Neuro-Epidemiology
New York University School of Medicine;
Doctoral Candidate, Department of Health Policy and Management
School of Public Health, City University of New York,
New York, New York, USA
Preface
The Clinical Approach to Patients with Vasculitis (Chapter 1)
Giant Cell Arteritis (Chapter 3)
Ophthalmologic and Neuro-Ophthalmologic Aspects of Vasculitides (Chapter 4)
The Blood-Brain Barrier (Chapter 5)
Neuroimaging of CNS Vasculitis (Chapter 6)
Stroke Due to Vasculitis in Adults (Chapter 9)
Central Nervous System Vasculitis Due to Infection (Chapter 10)
Central Nervous System Vasculitis Due to Drug Abuse (Chapter 11)
Autoimmune Encephalitides (Chapter 13)

INDEX

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

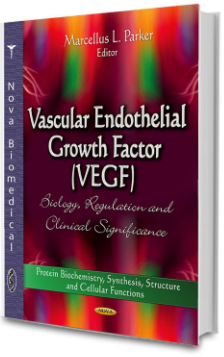
W

Y

Z

Vascular Endothelial Growth Factor (VEGF): Biology, Regulation and Clinical Significance

Editor: Marcellus L. Parker



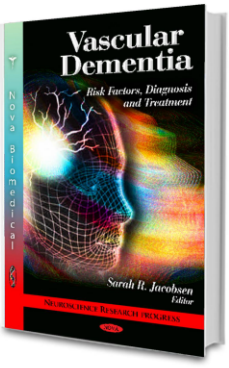
Series: Protein Biochemistry, Synthesis, Structure and

Book Description: Vascular endothelial growth factor (VEGF) is one of the most potent and specific angiogenic factors. In this book, the authors discuss the biology, regulation and clinical significance of VEGF.

Hardcover ISBN: 978-1-62618-655-2
Retail Price: $205

Vascular Dementia: Risk Factors, Diagnosis and Treatment

Editor: Sarah R. Jacobsen

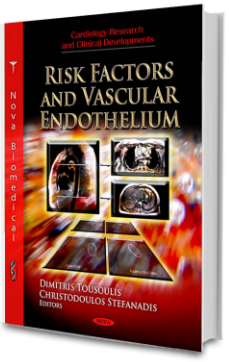


Series: Neuroscience Research Progress

Book Description: This book presents current research from across the globe in the study of vascular dementia, including GRK2 overexpression in the context of early Alzheimer disease pathogenesis; vitamin deficiencies and vascular dementia; biofluid markers as potential markers for vascular dementia; and the epidemiology of vascular dementia.

Hardcover ISBN: 978-1-61122-313-2
Retail Price: $245

Risk Factors and Vascular Endothelium



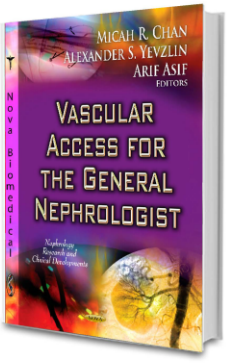
Editors: Dimitris Tousoulis and Christodoulos Stefanadis

Series: Cardiology Research and Clinical Developments

Book Description: This new book examines up-to-date research regarding the role of endothelial functions in terms of atherosclerosis and its clinical manifestations.

Hardcover ISBN: 978-1-61209-577-6
Retail Price: $280

Vascular Access for the General Nephrologist



Editors: Micah R. Chan, Alexander S. Yevzlin, and Arif Asif

Series: Nephrology Research and Clinical Developments

Book Description: This book is a compendium of vascular access insights designed to augment the knowledge base of the general nephrologist. This book provides up to date information for the clinical practice of general nephrology as it applies to the care of vascular access.

Hardcover ISBN: 978-1-62257-309-7
Retail Price: $175