14 Adult and Childhood Vasculitis of the Nervous System

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Introduction

Vasculitis results in a variety of clinical neurologic manifestations and neuropathologic changes in the central and peripheral nervous system (CNS and PNS). If unrecognized and therefore untreated, vasculitis leads to ischemia and injury of the involved tissues. Remarkable progress has been achieved in the pathogenesis, diagnosis, and treatment of vasculitis of the nervous system, making it an important topic for clinicians and researchers alike.

Classification and Nosology

Vasculitis is defined as inflammation of blood vessel walls for at least some time during the course of the disease and affects arteries and veins of varying caliber. Two Chapel Hill Consensus Conferences (CHCC), one in 1994 [1], and the other in 2012 [2], provided consensus on nosology and definitions for the commonest forms of vasculitis. The revised CHCC nomenclature serves as a guide for the categorization of diverse forms of vasculitis based upon the vessels involved, and provides a scheme for the neurologic aspects thereof (Table 14.1). Large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches, and analogous veins. Medium vessel vasculitis (MVV) inclusive of polyarteritis nodosa (PAN) and Kawasaki disease (KD) involves main visceral arteries and veins and initial branches. The category of small vessel vasculitis (SVV) recognizes the involvement of intraparenchymal arteries, arterioles, capillaries, veins, and venules, with a disease mechanism related to antineutrophil cytoplasmic antibody (ANCA) and immune complexes. The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) [Wegener granulomatosis (WG) type], eosinophilic granulomatosis with polyangiitis (EGPA) [Churg-Strauss syndrome (CSS)], and microscopic polyangiitis (MPA) (microscopic polyarteritis), while vasculitic disorders associated with immune complexes includes IgA vasculitis (IgAV) [Henoch-Schönlein purpura (HSP)], cryoglobulinemic vasculitis (CV), and hypocomplementemia 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 (CS). The

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Table 14.1 Childhood and adult vasculitides with nervous system involvement

Large vessel vasculitis
Giant cell arteritis
Takayasu arteritis
Idiopathic aortitis (IgG4)
Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
ANCA-associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Immune-complex vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis (IgA Vasculitis)
Variable vessel vasculitis
Behçet disease
Cogan syndrome
Primary CNS vasculitis
Vasculitis associated with collagen vascular disease
Systemic lupus erythematosus
Rheumatoid arthritis
Vasculitis due to substance abuse
Amphetamines
Cocaine
Opioids
Vasculitis and infection
Bacteria
Viruses
Neurosyphilis
Mycoses
Parasites
HIV/AIDS

category of vasculitis associated with systemic disease includes vasculitis associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) and other connective tissue disorders, wherein the vasculitic process is secondary to or associated with the underlying systemic disorder. There is a category of vasculitis associated with a probable specific etiology, such as substance abuse and infection designated by the specific vasculitic disorder with a prefix to denote the causative agent. The category of single-organ vasculitis (SOV) 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 characterized by primary CNS vasculitis, nonsystemic peripheral nerve vasculitis (PNV), and isolated aortitis.

Recognizing that certain forms of vasculitis are more common in childhood and that some vasculitides display different disease courses compared to adult forms [3], 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 [2]. In 2008, the EULAR, PRES, and the Pediatric Rheumatology International Trials Organization (PRINTO) reported their methodology and overall clinical, laboratory, and radiographic characteristics for several childhood systemic vasculitides [5] followed by a final validated classification [6].

A Century of Insights

The early history of vasculitis is debatable, but one fact is clear, the earliest patients with vasculitis appeared to have had neurologic involvement. According to Lamb [6], Kussmaul and Maier provided the first complete gross and microscopic description of a patient with leg pains, cramps, and tenderness so prominent that trichinosis was considered in an article entitled, "A hitherto undescribed peculiar disease of the arteries which is accompanied by Bright's disease and a rapidly progressive general paralysis of the muscles." At postmortem examination, there was widespread arteritis that resembled syphilitic periarteritis. The disorder was named periarteritis for the inflammation around blood vessels. In 1908, Langcope [7] described the first American patient with periarteritis, a 35-year-old man with constitutional symptoms and subacute leg pains. Postmortem examination showed widespread necrotizing arteritis and nodules along small and medium-sized vessels of the heart, liver, kidney, pancreas, testicles, brain, nerves and skeletal muscles, sparing the lungs and spleen. The histologic lesions consisted of mononuclear cell infiltration, necrosis of

internal and external elastic lamina of the media, fibrin deposition, aneurismal dilatation, perivascular inflammation of the adventitia, and intimal proliferation resulting in narrowing of arterial lumina. Kernohan and Woltman [8] summarized the clinical and neuropathologic aspects of adult PAN, and Krahulik and colleagues [9] reported the postmortem neurologic findings of fulminant childhood PAN (cPAN). The dominant neurologic picture of both adult and cPAN was a peripheral neuritis that occurred in one-half of patients early in the illness with a predilection for the legs. At postmortem examination, all had arteritic lesions along nutrient arteries of the peripheral nerves, and three-quarters had lesions in arteriae nervorum. The combination of acute and chronic lesions correlated with known exacerbations. Involvement of the CNS was estimated to occur in 8% of cases evident by clinically apparent brain infarcts resulting from occlusion of cerebral vessels, which was often insidious in its progression. In PAN, as in the other systemic necrotizing arteritis, the vasculitic lesion proceeded in a characteristic manner (Fig. 14.1) commencing with invasion of the intima, media, and adventitia by polymorphonuclear, plasma cells, eosinophils, and lymphocytes, leading to swelling of the media, and fibrinoid necrosis that clusters around the vasa vasorum, with fragmentation of the internal elastic lamina. There was focal deposition of perivascular connective tissue, vascular necrosis, and denuding of the endothelium, followed by vascular thrombosis, ischemia, aneurysm formation, rupture, and hemorrhage. Healed lesions coexisted with active lesions. Harry Lee Parker conceptualized nerve and muscle biopsy in a discussion of the paper by Kernohan and Woltman [8] commenting, "It occurs to me that in any case in which polyarteritis nodosa may be suspected, it is advisable to take a biopsy from a peripheral nerve, muscle or artery." There are no published series confirming the correlation of the extent of systemic necrotizing arteritis that may be predicted by the singular finding of vasculitis in a cutaneous nerve biopsy specimen. Only one reported series [10] reported neither systemic nor isolated PNV was found at postmortem after diagnostic cutaneous nerve biopsy evidencing necrotizing vasculitis in life. A variant of PAN was recognized in very young children with mucocutaneous lymph node syndrome [11, 12]. Although early publications used the term infantile PAN [13, 14], KD is the preferred term to describe this childhood syndrome with worldwide occurrence, affecting children of all ages and races. Both PAN and KD are prototypical examples of MVV.

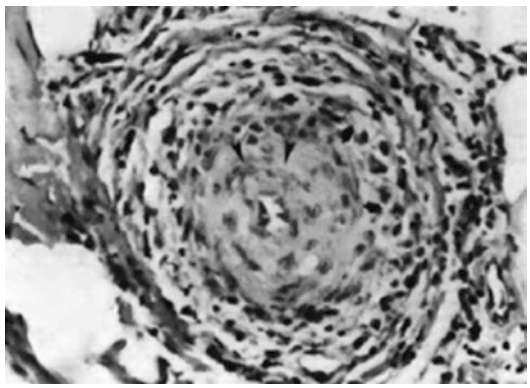

Fig. 14.1 This small muscular artery from muscle is from a patient with polyarteritis nodosa. In the third, or proliferative, phase illustrated here, chronic inflammatory cells replace the neutrophils of the second phase; there is evidence of necrosis of the media, early intimal proliferation (arrowheads), and fibrosis. The lumen is almost completely occluded. Ultimately, in the healing phase, this process is replaced by dense, organized connective tissue (stain, hematoxylin and eosin; original magnification, ×250)

Contemporaneously, SVV syndromes were recognized and differentiated from PAN. First described by Wohlwill in 1923 [15], Davson and colleagues [16] and Wainwright and Davson [17] described MPA among 34 patients who differed from PAN due to selective involvement of small microscopic arteries, arterioles, capillaries, and venules including glomerular and pulmonary alveolar capillaries. Fever, arthralgia, purpura, hemoptysis, pulmonary hemorrhage, abdominal pain, and gastrointestinal bleeding likewise preceded the explosive phase of systemic necrotizing vasculitis that affected the kidney and lungs, with rapidly progressive glomerulonephritis and pulmonary capillaritis. Two of five deaths were attributed to CNS involvement by vasculitis during periods of disease respectively at 4 and 8 months; however,

that could not be confirmed since postmortem examinations were not performed. The disorder was later reclassified by the CHCC [1, 2] as a necrotizing SVV with little or no immune-complex deposition that primarily affected the kidney and lungs. Medium-sized arteries might be involved even though the disease was predominantly considered to affect small-sized arteries, arterioles, capillaries, and venules of the two organs most affected, with variable systemic necrotizing vasculitis.

The first patient with EGPA was probably Case 1 of Lamb [18] reported in 1914 under the heading of PAN. That patient, a 26-year-old man with 2 years of worsening asthma, developed fever, palpable purpura, nodular skin lesions, hemoptysis, vomiting, urinary difficulty, and granular urinary casts. He died 1 month later and postmortem examination showed necrotizing arteritis of small arteries, with dense collections of extravascular eosinophils and tissue eosinophilia in the heart, stomach, and kidney. Decades later, Churg and Strauss [19] described the clinical and postmortem findings of 13 patients with asthma, fever, and hypereosinophilia, accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation that constituted the so-called allergic granuloma, found within vessel walls and in extravascular connective tissue of major organ systems, leading to cardiac, pulmonary, gastrointestinal, skin, PNS, and CNS manifestations. In 1977, Chumbley and coworkers [20] described 30 asthmatic patients from the Mayo Clinic over the period 1950–1974, with necrotizing vasculitis of small arteries and veins with extravascular granulomas and infiltration of vessels and perivascular tissue with eosinophilia. The lungs, peripheral nerves, and skin were most frequently involved, and renal failure was encountered in only one patient. Corticosteroids seemed to confer long-term survival. In 1984, Lanham and colleagues [21] emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas suggested by Churg and Strauss [19], occurred contemporaneously in only a minority of patients. Moreover, such histologic findings could be encountered in well as in other granulomatous, vasculitic, and eosinophilic disorders in the absence of clinical asthma, allergic rhinitis, sinusitis, pulmonary infiltrates, and cardiac involvement pathognomonic of EGPA. The authors described a phasic pattern of EGPA in which allergic disease preceded systemic vasculitis and eosinophilic tissue infiltrates might occur in the absence of peripheral blood eosinophilia. Pulmonary infiltrates, upper respiratory tract, and gastrointestinal disease often preceded the vasculitic component of the syndrome leading to cardiac, cutaneous, nervous system, renal, bone, and muscle involvement. In 1990, the American College of Rheumatology (ACR) [22] developed criteria for the classification of EGPA, that included ascertainment of four or more of the following: asthma, eosinophilia of >10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates on chest radiograph, paranasal sinus abnormality, and extravascular eosinophils on tissue biopsy that included an artery, arteriole, or venule. These criteria were inadequate in differentiating the various clinicopathologic expressions of SVV and a patient with asthma and paranasal sinusitis could fit the designation of EGPA. The 1994 CHCC [1] characterized EGPA as an eosinophil-rich and granulomatous inflammatory process that involved the respiratory tract, with necrotizing vasculitis that affected small to medium-sized vessels such as capillaries, venules, arterioles, and arteries, with associated asthma and eosinophilia.

In 1954, Godman and Churg [23] described the syndrome of GPA that included granuloma in the nasopharynx, sinuses, and lower respiratory tract with focal segmental glomerulonephritis and disseminated small vessel vasculitis (Fig. 14.2). Nervous system involvement in GPA was found in up to one-half of patients according to Drachman [24] who also described a patient with 1 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, not in peripheral nerves. Two decades later, Fauci and colleagues [25] and Hoffman and colleagues [26] at the National Institutes of Health (NIH)

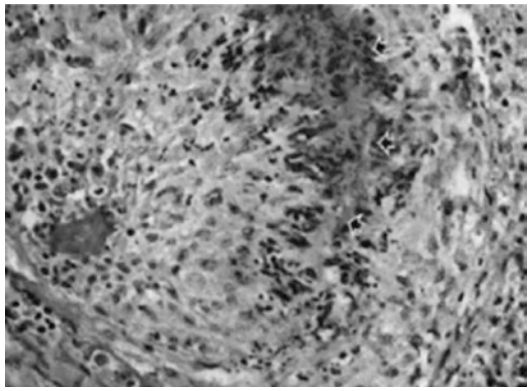

Fig. 14.2 Wegener's granulomatosis. This small muscular artery is destroyed. A large confluent area of fibrinoid degradation (arrows) is surrounded by neutrophils, palisading histiocytes, lymphocytes, plasma cells, and some giant cells (stain, hematoxylin and eosin; original magnification, ×250)

respectively reported a prospective series of 85 patients with GPA, and a retrospective assessment of 180 patients followed for 6 months to 24 years, describing nervous system involvement in up to 23% of patients. There was a preponderance of mononeuritis multiplex with CNS abnormalities in 8–10% of patients. CNS involvement included stroke, cranial nerve abnormalities, and diabetes insipidus. Fauci and colleagues [25] established the efficacy of cyclophosphamide and prednisone in achieving complete remissions in 93% of patients as well as the tendency of patients to relapse and accrue additive mortality from both disease and treatment; however, alternative immunosuppressant regimens were not equally effective [26]. In a landmark article, Godman and Churg [27] concluded that MPA, EGRA, and GPA were related to one another yet distinct from PAN. This astute conclusion was based mainly on pathologic features was later substantiated by their common association with ANCA, but not so for PAN [28].

There ensued a renaissance in the understanding of primary systemic vasculitis with convincing clinical evidence to support an important role for ANCA in the development of AAV. Early observations of ANCA were provided by van der Woude and colleagues in 1985 [29], and Falk and Jennette [30] and Goldschmeding and colleagues [31] in 1988, followed by progress in the differentiation of these subtypes and understanding of the eponymous manifestations [32]. Proteinase 3 (PR3) is a serine protease found in the azurophilic granules of neutrophils and peroxidase-positive lysosomes of monocytes. Myeloperoxidase (MPO), which constitutes about 5% of the total protein content of the neutrophilic cell, is localized to the same cellular compartment as PR3. However, PR3 in contrast to MPO is also found on the plasma membrane of resting neutrophils and monocytes in many patients. Autoantibodies directed against PR3 and MPO are directed against multiple epitopes. Although sera from different patients may recognize different epitopes, all ANCA recognized restricted epitopes of PR3 involving its catalytic site [33]. An AAV classification appears to better recognize ANCA disease and predict prognosis than other any existing clinical classification systems [34]. However, as with other autoimmune disorders, the etiology and pathogenesis appeared multifactorial, involving the interplay of initiating and predisposing environment and genetic factors. Important contributing factors to the mediation of vascular and extravascular inflammation included a loss of regulatory T- and B-cell function, acute neutrophilic cell injury with release of ANCA-antigens, cytokine priming of neutrophilic cells, and subsequent complement activation by Fc and Fab2 engagement, and enhancement of complement-dependent cytotoxicity with release of ANCA-antigens into the microenvironment [35–37]. The ANCA lesion typical of GPA includes both vasculitic and granulomatous features in lung, with focal segmental glomerulonephritis typified pathologically by lysis of glomerular tufts, basement membrane disruption, accumulation of fibrinoid material, thrombosis of glomerular capillary loops, acute tubular necrosis, and cant deposition of immunoglobulin (Ig) and complement. There are genetic distinctions between MPO and GPA suggested by the strong association of PR3-ANCA disease with antigenic specificity of HLA-DP and the genes encoding α1-antitrypsin (*SERPINA1*) and PR3 (*PRTN3*), and HLA-DQ for MPO-ANCA [38]. An immunofluorescence technique (IFT) has been the standard method for routine determination of ANCA

in vasculitis using ethanol-fixed human neutrophils as substrate. Two main immunofluorescence patterns are distinguished, a cytoplasmic (c-ANCA) and perinuclear (p-ANCA). The 1999 "International consensus statement on testing and reporting ANCA" [39] required laboratories to screen for ANCA by IFT and to confirm the specificity of fluorescent sera by enzyme-linked immunoassay (ELISA) for PR3 and MPO-ANCA. However, conventional ELISA using PR3 immobilized to the surface of the ELISA plate shows great variation in performance and often lack sensitivity. Capture ELISA is superior in overall diagnostic performance to direct ELISA [40], but the capturing antibodies hiding relevant epitopes may reduce the sensitivity of capture ELISA. High sensitivity PR3 (hsPR3)-ANCA ELISA, which immobilizes PR3 via a bridging molecule to the plastic plate and preserves nearly all epitopes for the binding of ANCA, was superior to direct and capture techniques in GPA [41].

Hypersensitivity vasculitis leading to cutaneous vasculitis was conceptualized as an immunologic response to antigenic material associated with clinically evident purpura, and small vessel inflammation affecting arterioles, capillaries, and postcapillary venules. Between 1948 and 1952, Zeek [42, 43] separated the hypersensitivity vasculitides from allergic granulomatous angiitis, rheumatic arthritis, PAN, and GCA. Hemorrhage into the skin or palpable purpura was noted in virtually all patients resulting from extravasation of erythrocytes, pronounced endothelial swelling, polymorphonuclear, and later mononuclear cell infiltration, followed by fibrosis, necrosis, fibrinoid deposits, and visible polymorphonuclear debris termed leukocytoclasia (Fig. 14.3). Zeek [44] likened hypersensitivity vasculitis to the anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits [45]. Osler [46] first appreciated the relation of purpuric attacks to cerebral manifestations in the report of a patient with transient hemiparesis, and three others with potentially fatal cerebral hemorrhages. Gairdner [47] described HSP among 12 patients with anaphylactoid purpura including one child who developed rash, colic, melanotic

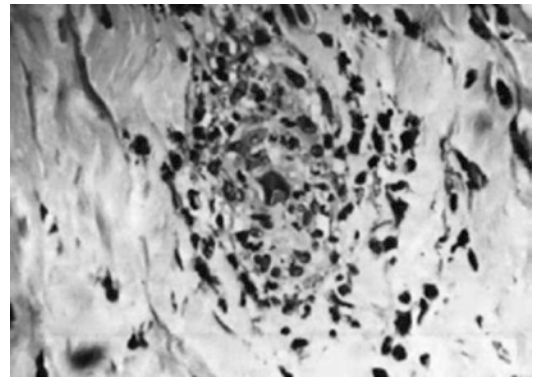

Fig. 14.3 This arteriole from muscle is from a patient with leukocytoclastic vasculitis. The entire vessel and perivascular tissue is infiltrated with polymorphonuclear leukocytes and some chronic inflammatory cells with necrosis and nuclear debris. The vascular lumen is nearly obliterated (stain, hematoxylin and eosin; original magnification, ×400)

stools, intussusception, and hematuria followed by a typical exanthema and convulsion. She died 3 months later and postmortem examination showed scattered cortical hemorrhages associated with cerebral necrotizing arteriolitis. Levitt and Burbank [48] described the clinicopathologic findings in two previously nonallergic patients with recurrent fatal attacks of HSP after injection of penicillin and ingestion of strawberries respectively that included glomerulonephritis alone or with systemic arteriolitis. The finding of IgA deposits in cutaneous blood vessel walls and in glomerular mesangial biopsies of patients with HSP and IgA nephropathy (IgAN) [49, 50] was circumstantially convincing enough to substitute the term IgAV for HSP.

Wintrobe and Buell [51] described cryoglobulinemia in a patient with progressive frontal headache, facial pain, Raynaud symptoms, recurrent nosebleeds, exertional dyspnea, palpitation, and changes in the eye grounds due to central vein thromboses. Postmortem examination showed infiltrating myeloma of the humerus and lumbar vertebra and splenic enlargement. A unique plasma protein was detected that spontaneously precipitated with cold temperature and solubilized at high temperature differed from Bence-Jones proteinuria of other myeloma patients. Lerner and Watson [52] noted the

association with purpura, and later, Lerner and Watson [53] described its occurrence in 10% of pathological sera. Gorevic and colleagues [54] described mixed CV in forty patients, the clinical features of which included palpable purpura in all patients, polyarthralgia in three-quarters, and kidney involvement in slightly more than one-half, and deposits of IgG, IgM, and complement, or renal arteritis in a third of patients.

Recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions that last 24 h at a time, associated with recurrent attacks of fever, joint swelling, abdominal distress, and depressed serum complement indicative of HUV, were described by McDuffie and colleagues in 1973 [55]. Small amounts of cryoglobulin were present at one time or another in the serum of each patient. When tested by immunodiffusion against purified preparations of rheumatoid factor (RF) and human C1q, two patients consistently produced bands against the former, and two others reacted strongly with purified C1q. Skin biopsies showed leukocytoclasia characteristic of necrotizing vasculitis in one patient; anaphylactoid purpura in two others; and mild nonspecific perivascular infiltration in another. Immunofluorescence of skin specimens performed in three patients showed fixation of Ig in the patient with necrotizing vasculitis, while in two others with a pathologic picture of anaphylactoid purpura or nonspecific dermal infiltrate, and immunofluorescence was negative. Renal biopsy in two patients showed mild to moderate glomerulonephritis indistinguishable for those seen in other forms of chronic membranoproliferative glomerulonephritis. The differences from SLE included more urticarial and purpuric skin lesions, with relatively mild renal or absent and other visceral involvement in the patients with HUV, that was atypical for SLE. Moreover, serum speckled antinuclear and anti-DNA antibodies, and basement membrane Ig deposits were absent in those with HUV, also atypical for SLE. An etiopathogenesis related to chronic vascular inflammation resulting from deposits of immune complexes in small vessel walls seemed likely. Zeiss and colleagues [56] characterized C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among four additional patients. Wisnieski and Naff [57] showed C1q-binding activity in IgG from HUV sera, which suggested a relation to LE, but that view was later amended.

The historical account of the category of LVV spanned more than a century with notable advances in the past several years. Hutchinson provided the first clinical description of temporal arteritis [58], followed by a pathologic description by Horton [59] more than 50 years after the description and designation of polymyalgia rheumatic (PMR) by Bruce [60] and Barber [61]. Temporal arteritis was named for the site of granulomatous giant cell inflammation and vessel involvement [62]. Those with biopsy-proven temporal arteritis and associated blindness due to vasculitic involvement of ophthalmic and posterior ciliary vessels were classified as cranial arteritis [63]. The occasional finding of giant cell lesions along the aorta, its branches, and in other medium- and large-sized arteries at autopsy in other patients warranted the additional diagnosis of generalized GCA [64]. The pathologic heterogeneity of temporal arteritis was further demonstrated by the finding of intracranial lesions in eight patients who also qualified for the diagnosis of granulomatous angiitis of the nervous system (GANS) [65–70]. PNS involvement in GCA was exceedingly uncommon [71]. The earliest lesions of GCA consisted of vacuolization of smooth muscle cells of the media, with enlargement of mitochondria, infiltration of lymphocytes, plasma cells, and histiocytes. With progression, there was extension of inflammation into the intima and adventitia leading to segmental fragmentation and necrosis of the elastic lamina, granuloma formation, and proliferation of connective tissue along the vessel wall. This eventuated in vascular thrombosis, intimal proliferation, and fibrosis (Fig. 14.4). One other LVV was described in the Japanese literature as unusual changes of the central vessels of the retina in the absence of peripheral arterial pulses in a woman [72]. This pulseless disease [73] and occlusive thromboaortopathy [74] or TAK disease [75], manifested constitutional complaints of malaise, fever, stiffness of the shoulders, nausea, vomiting, night sweats, anorexia, weight loss, and irregularity of menstrual periods weeks to months before the

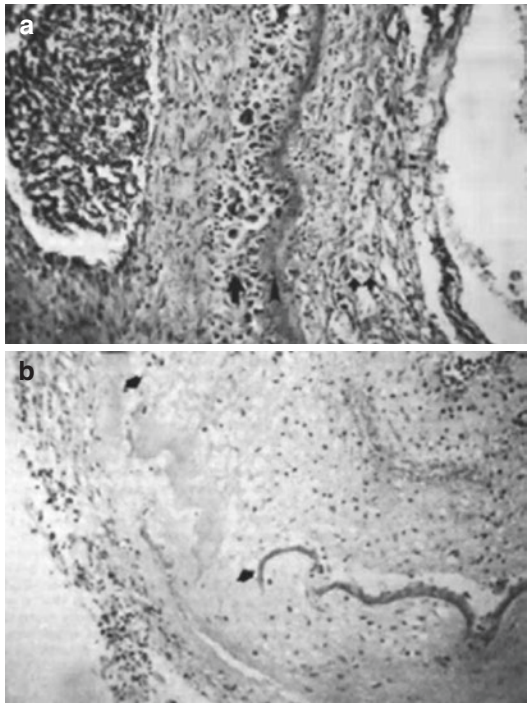

Fig. 14.4 Temporal arteritis. (**a**) In an early lesion of a large muscular artery, necrosis, inflammation, and giant cell formation (single arrow) can be seen immediately adjacent to the internal elastic lamina (arrowhead), which is undergoing degenerative changes, and there is some intimal proliferation (double arrows) (stain, hematoxylin and eosin; original magnification, ×100). (**b**) This more advanced lesion has complete segmental destruction of the internal elastic lamina and virtually the entire media (arrows). Marked intimal proliferation has nearly occluded the lumen, and few inflammatory cells remain (stain, hematoxylin and eosin; original magnification, ×50)

local signs of vasculitis were recognized in up to two-thirds of patients. It is the commonest large vessel vasculitis among Asian women.

One other form of inflammatory aortic disease, aortitis, surfaced in the surgical literature with equally broad and far-reaching implications for concepts of autoimmunity. In 1972, Walker and colleagues [76] noted that 10% of 217 patients presenting with abdominal aneurysms at Manchester Royal Infirmary between 1958 and 1969 for resection showed excessive thickening of aneurysm walls and perianeurysmal adhesions at operation. Subsequent histologic examination of the walls of the aneurysms showed extensive active chronic inflammatory changes including plasma cell infiltration. The clinical features of patients with inflammatory aneurysms differed from those with atherosclerotic disease due to generally younger age by a decade, lower incidence of rupture, lack of claudication of intermittent the limbs and presence of peripheral pulses, less likelihood of unusual presenting features, elevated ESR, and lack of calcification on preoperative abdominal radiographs. In 1985, Pennell and coworkers [77] reported inflammatory aortic or iliac aneurysms in 4.5% of 2816 patients undergoing repair for abdominal aortic aneurysm from 1955 to 1985. Ultrasound and CT imaging suggested the diagnosis respectively in 13.5% and 50% of patients, the former showing a sonolucent halo with clear definition of the aortic wall posterior to the thickened anterior and lateral aortic walls. In 2000, Rojo-Leyva and colleagues [78] noted idiopathic aortitis in 43% of 1204 aortic specimens gathered over a period of 20 years. In 96% of the patients with idiopathic aortitis, aneurysm formation and aortitis were present only in the thoracic aorta. In 2001, Hamano and colleagues [79] noted high concentrations of IgG4 associated with sclerosing pancreatitis characterized by obstructive jaundice, infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, sonolucent swelling of the parenchyma, lymphoplasmacytic infiltration, fibrosis, and a favorable response to corticosteroid treatment. One year later, Hamano and coworkers [80] noted the association of sclerosing pancreatitis with raised concentrations of IgG4 among those with concomitant hydronephrosis that caused ureteral masses, later diagnosed as retroperitoneal fibrosis (RPF). Histologic examination of ureteral and pancreatic tissues revealed abundant tissue infiltration by IgG4-bearing plasma cells. In the same year, 2008, three important observations were in this area. First, Sakata and colleagues [81] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues [82] concluded that IAAA was an IgG-related disease (IgG4-RD) together with RPF. Third, Ito and colleagues [83] described a patient with IAAA, hydronephrosis caused by RPF, and high levels of IgG4 I in whom treatment with corticosteroids led to clinical improvement and reduction in

IgG4 levels. Histologic inspection of the aortic wall specimen showed lymphocytoplasmacytic infiltration. Immunohistochemical analysis of the tissue showed IgG4-positive plasma cells. The findings suggested that IAAA had an etiopathogenesis similar to autoimmune pancreatitis and that some cases of IAAA and RPF may be aortic and periaortic lesions of an IgG4-RD. One year later, in 2009, Khosroshahi and colleagues [84] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels with progression to autoimmune pancreatitis, and Stone and coworkers [85] described IgG4-related thoracic aortitis with a media-predominant pattern of aortic wall infiltration and marked elevation of serum IgG4 levels, unequivocally linking IgG4-RD with thoracic lymphoplasmacytic aortitis.

Two forms of VVV, BD and CD, were recognized with very different clinical presentations and systemic involvement. Adamantiades [86] recognized the disorder of relapsing aphthous ulcers of the mouth, eye, and genitalia, and the clinicopathologic details of which were described in later detail by Behçet [87, 88] in two Turkish patients. Nervous system involvement of a 28-year-old Yemenite with relapsing oral, genital, and oral eruptions over 4 years, was accompanied by severe headache, memory loss, dizziness, lethargy, fatal seizures, and coma. Postmortem examination showed perivascular inflammatory cell infiltration of the meninges, brain, and central retinal artery and optic nerve with necrotic cerebral lesions. Encephalomyelopathy was detailed at postmortem examination in two Australian patients with BD [89] who presented with hemiparesis, while the other patient presented with pseudobulbar affect, vertical gaze palsy, nystagmus, and spastic paraplegias. Postmortem examination showed widespread lesions in cortical and brainstem white matter and hypothalamus, corresponding to small blood vessels including arterioles and veins that showed perivascular mononuclear cell infiltration. The first well-documented American patient with nervous system involvement of BD was described by Wolf and coworkers [90]. The patient was a 22-year-old woman with a 5-year history of recurrent oral and genital ulceration, and a 2-year course of progressive visual loss, headache, hemiparesis, ataxia, tremor, dysarthria, cranial nerve palsy, cerebellar and corticospinal tract disease, and mental deterioration, which responded to prednisone therapy.

Mogan and Baumgartner [91] 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. In retrospect, he was probably the first reported patient with CS of nonsyphilitic interstitial keratitis (IK) [91]. Cogan [92] later described vestibuloauditory symptoms. Haynes and colleagues [93] set forth the diagnostic criteria for typical CS according to the definitions established by In a review of 30 patients seen at the National Eye Institute of the NIH by Cogan [92, 94, 95], symptoms of IK developed abruptly and gradually resolved, associated with photophobia, lacrimation, and eye pain which may be unilateral or bilateral. 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 1–6 months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of 1–3 months, certainly no longer than 2 years. Cody and Williams [96] provided a description of atypical CS if another significant inflammatory eye lesion in addition to, or instead of IK such as scleritis, episcleritis, retinal artery occlusion, choroiditis, retinal hemorrhage, papilledema, exophthalmos, or tendonitis. Haynes and colleagues [93] defined acute CS as the presence of acute eye disease within 2 weeks of hearing loss, while inactive CS was applied to patients without active eye disease or vestibuloauditory dysfunction of greater than 2 weeks prior to study. With less than 100 reported patients with this rare childhood and young adult disorder, the majority of reported patients with typical CS

appeared as single case reports or patient series [93, 97–100], often without pathologic confirmation [92, 94, 100, 101] or evidence of systemic vasculitis in a biopsy or at postmortem examination [95, 96, 102, 103]. In contrast to Mogan and Baumgartner [91] and Cogan [92, 94], headache and other CNS manifestations occurred. Norton and Cogan [95] described a patient with atypical acute CS in whom headache instead preceded detection of superior central retinal artery branch occlusion and orbital edema.

The histopathologic appearance of vasculitis of the peripheral nerve is similar regardless of whether the process is primary or secondary to underlying systemic vasculitis. Historically, detailed neurovascular anatomy historically arose from the careful dissection of amputated limbs following injection of India ink to opacify peripheral nerve vessels in World War II veterans [104, 105]. Such studies indicated that proximal stretches of each of the major nerves were supplied both by a single arterial vessel, such as in the axilla-to-elbow and knee-to-elbow segments located peripherally in the nerve trunk, and abundantly along their distal course by a succession of microvessel. Their repeated division and anastomosis outlined an unbroken vascular net that assured continuous vascular supply. As there was no evidence for the presence of watershed zones of poor vascular supply along major nerves of the arm or leg, ischemic paralysis of a limb should rarely if ever occur in the absence of widespread arteritis, abrupt occlusion of large named vessels, or focal nerve compression. A quarter-century later, Dyck and coworkers [106] ascribed ischemic centrofascicular nerve fiber degeneration of named upper arm and thigh nerves in a patient with necrotizing angiopathic neuropathy to poor vascular perfusion along presumed watershed zones of the upper arm and thigh regions. However, the clinical details of the patient were not given, the centrofascicular fiber loss was only pronounced in the legs, and extraneural blood vessels of the arms were not studied. Two decades later, Moore and Fauci [107] ascribed progressive weakness and sensory loss in the arms and subsequently in the legs distally from the knees in Patient 8 with extensive mononeuritis multiplex due to infarction of specific peripheral nerves, culminating in ambulation with leg braces and good use of the hands. However, that patient was not studied pathologically. Vasculitis of the peripheral nerves leads to specific alterations in the arteriae nervorum with a caliber of 100 μm located in the epineurial compartment, as well as in peripheral nerve fascicles ensheathed by perineurium and endoneurium. The key elements of pathologically definite nonsystemic vasculitic neuropathy, generally regarded as a form of SOV, are intramural inflammation accompanied by pathologic evidence of vascular wall damage without evidence of systemic involvement [108].

Diverse syndromes of adult and childhood primary CNS vasculitis with very different clinical presentation, histopathology, and prognosis were described. Primary CNS vasculitis was first described by Harbitz in 1922 [109] in one patient with worsening headaches, mental change, and ataxia culminating in stupor, spastic paraparesis, coma and death in 2 years. A second patient presented with hallucination and confusion progressing to gait difficulty, stupor, coma, and death in 9 months. At postmortem examination, both had granulomatous vasculitis of the meninges comprised of lymphocytes, multinucleate 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 [110], giant cell arteritis [111], and sarcoidosis [112]. Cravioto and Fegin [113] delineated the clinicopathologic syndrome of noninfectious granulomatous angiitis, and for two more decades, rare affected patients were identified in life, but there was no effective treatment. Hinck and coworkers [114] in GCA and later by Cupps and Fauci [115] in other patients with first noted the identification of angiographic beading and a sausage-like appearance of cerebral vessels at sites of presumed arteritis (Fig. 14.5) so-called, isolated angiitis of the CNS (IACNS). The angiographic features of presumed vasculitis along with the judged efficacy of a combination immunosuppressive regimen of oral cyclophosphamide and alternate-day prednisone, including three patients with IACNS defined angiographically, and another with biopsy-

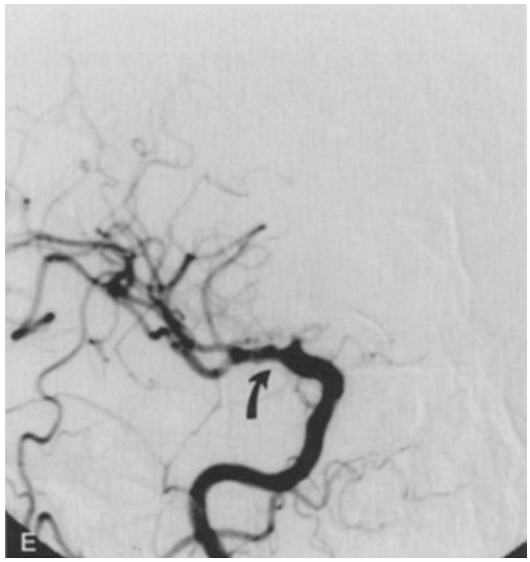

Fig. 14.5 Radiographic features of cerebral vasculitis. Ectasia and beading in the M1 segment and lack of flow in the A1 segment of the right anterior cerebral artery (arrow)

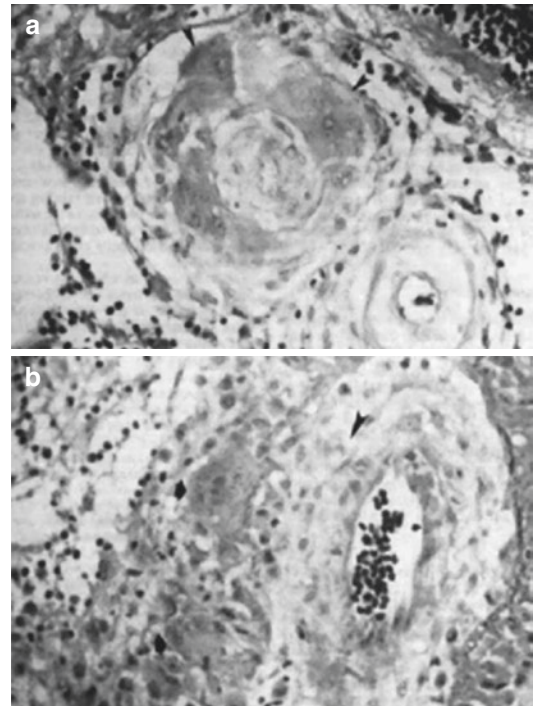

Fig. 14.6 Central nervous system vasculitis. (**a**) The media and adventitia of this small leptomeningeal artery have been almost completely replaced by multinucleated giant cells (arrowheads). There is intimal proliferation with obliteration of the vascular lumen, and a dense, perivascular, mononuclear inflammatory infiltrate can be seen (stain, hematoxylin and eosin; original magnification, ×250). (**b**) A somewhat larger leptomeningeal vessel shows necrosis of the media and internal elastic lamina with multinucleated giant cell formation (arrows), intimal proliferation (arrowhead), and lymphocytic infiltration of the adventitia and neighboring meninges (stain, hematoxylin and eosin; original magnification, ×250)

proven GANS of the filum terminale, led to prospective diagnostic and therapeutic recommendations [116]. At that time, investigators at the NIH regarded IACNS and GANS as equivalent entities with the former term emphasizing the restricted nature of the vasculitis and the latter the granulomatous histology. Giant cells and epithelioid cells, usually found at autopsy in GANS (Fig. 14.6), were an inconsistent finding in a meningeal and brain biopsy, and therefore considered unnecessary for antemortem diagnosis. In the same year of 1988, Calabrese and Mallek [117] proposed criteria for the diagnosis of PACNS, while Younger and colleagues [118] contemporaneously described the limits of granulomatous angiitis of the brain (GAB) and nervous system (GANS) [119]. The past quarter-century has witnessed an expansion in the present understanding of primary CNS vasculitis in children and adults.

Vasculitis due to drug abuse captured the interest of successive generations of investigators. The earliest reports of misuse of amphetamine sulfate occurred in 1937 when students used it to avoid sleep during examination periods [120]. This was followed by reports of death by those who ingested the drug repeatedly as a stimulant for the same purpose [121], in a suicide attempt that resulted in a fatal intracerebral hemorrhage [122], or accidentally, when dexamphetamine and phenelzine were fatally ingested together decades later [123]. During the Second World War, amphetamine and methamphetamine were used clinically and illicitly, but their abuse soared in San Francisco after 1962 wherein it was illegally produced and distributed [124]. By 2009, the United Nations Office on Drugs and Crime estimated that 16–51 million persons between the age of 15 and 64 years consumed amphetamine drugs, with more than half using methamphetamine [125], exceeding the combined consumption of all other drugs of abuse

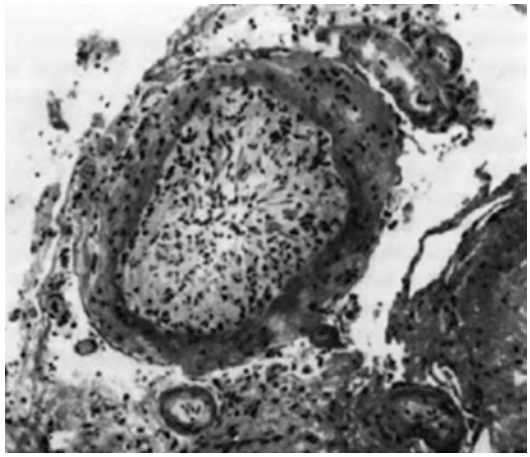

Fig. 14.7 Cerebral vasculopathy in a case of intracerebral hemorrhage associated with the use of phenylpropanolamine as an aid to weight loss. The profound intimal hyperplasia all but obliterates the vascular lumen. Polymorphonuclear leukocytes are in all three vascular layers but particularly the intima. The media are remarkably well preserved compared with cases of polyarteritis nodosa and leukocytoclastic vasculitis (stain, hematoxylin and eosin; original magnification, ×100)

except cannabis [126]. Such drug agents comprise a large spectrum of agents available in powder, capsule, tablet, and injectable fluid form that can be swallowed, snorted or taken intranasally, smoked or injected with highly variable purity and dosage equivalence. Histologically confirmed cerebral vasculitis (Fig. 14.7) due to amphetamine, methamphetamine, and related agents is exceedingly rare which is surprising given the number of substances that could cause this disorder if there was a true association.

Perhaps, the most interesting recent development in vasculitides has been the recognition of rare encephalopathies and autoimmune encephalitides with a possible relation to CNS inflammation [127–129]. For almost half a century, neurologists have been pursuing the rare encephalopathy associated with Hashimoto thyroiditis with recent recognition of its association with autoimmune encephalitis and CNS vasculitis. In 1966, the British neurologist, Lord Brain and colleagues [130] described the entity of Hashimoto encephalopathy in a 40-year-old man with 12 ictal and stroke-like episodes of confusion and agitation 1 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. Jellinek and Ball [131] extended the results of Brain and colleagues [130], describing the original patient, who at age 62, 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 of Hashimoto thyroiditis and encephalopathy, and splenic atrophy. In 2003, Rowland and colleagues [132] characterized the clinicopathologic findings of literature cases of Hashimoto encephalopathy beginning with the patient described by Lord Brain and coworkers [130] through 2002, and adding their own patient. The diagnosis of Hashimoto encephalopathy, as described by Rowland and coworkers [132] rested on the presence of thyroiditis with measurably high titers of thyroid peroxidase (TPO) or thyroglobulin (Tg) antibodies, clinical encephalopathy (clouding of consciousness with reduced wakefulness, attention, or cognitive function), and absence of cerebrospinal fluid (CSF) evidence of bacterial or viral infection. These criteria remain the standard for case selection; however, then as now, it is unknown whether antithyroid antibodies and concomitant thyroid dysfunction contribute to the pathogenesis of Hashimoto encephalopathy. Ochi and colleagues [133] provided a link between Hashimoto thyroiditis autoimmunity and the CNS. They developed a human brain proteome map using two-dimensional electrophoresis and applied it to the immunoscreening of brain proteins that reacted with serum antithyroid antibodies in Hashimoto's encephalopathy patients, identifying the novel antigen, α-enolase, encoded on 1p36.23, as a candidate and marker for Hashimoto encephalopathy-related pathology

and corticosteroid sensitivity. Kishitani and coworkers [134] extended the findings of Ochi and colleagues [133] noting anti-NH2-terminal of α-enolase antibodies in 24% of Hashimoto encephalopathy patient sera and limbic abnormalities on magnetic resonance imaging (MRI) demonstrating abnormal signal in unilateral or bilateral medial temporal lobes, and diffuse slow wave activity with epileptogenic discharges. These findings suggested that limbic encephalitis associated with anti-NH2-terminal of α-enolase antibodies could be a possible manifestation of Hashimoto encephalopathy in some cases. Vasculitic pathogenesis also appeared to be likely in some cases of Hashimoto encephalopathy based upon the tendency for increased autoimmunity in Hashimoto thyroiditis. In addition, the available histopathology in Hashimoto encephalopathy also supports an inflammatory vasculopathy, so noted in one postmortem case that showed lymphocytic infiltration of brainstem veins [135]; and in brain biopsy tissue from another case, categorized as isolated angiitis due to lymphocytic infiltration of the walls of arterioles and veins [136]. Brain biopsy tissue of second living patient showed perivascular cuffs of lymphocytic cells [132]. It is noteworthy that patients with Hashimoto encephalopathy and circulating α-enolase antibodies are at risk for heightened autoimmune activity, and a tendency for systemic and invasive autoimmune disorders including systemic vasculitis [137, 138]. Moreover, like Hashimoto encephalopathy, 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 have led to the identification of new syndromes and biologic 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. However, in those available, there are variable infiltrating inflammatory T cells with cytotoxic granules in close apposition to neurons, analogous to CNS vasculitis.

Clinical Presentation and Laboratory Evaluation

The clinical presentation of a patient with vasculitis of the nervous system depends on three factors: distribution of the involved neural vessels, spectrum of extraneurologic organ involvement, and severity and rate of progression of the underlying vasculitic process. Patients with systemic vasculitis will have other involved tissues besides peripheral nerve, brain and spinal cord, including the skin, joints, kidneys, lungs, and gastrointestinal tract, although the dysfunction may be extremely mild or subclinical and detectable only after extensive laboratory evaluation. Constitutional symptoms such as fever, weight loss, anorexia, myalgia, arthralgia, and nonspecific fatigue and weakness occur in about 80% of patients, but careful general examination and laboratory investigation is mandatory to look for systemic abnormalities that may suggest a more generalized process. Two exceptions are patients with isolated PNV and primary CNS vasculitis in which systemic organ involvement by definition is lacking. Since the ischemic process in PNS vasculitis does not have a predilection for motor or sensory fibers, both modalities are nearly always affected. Most patients complain of deep aching discomfort in the affected limb that later evolves into burning dysesthetic pain. There may be restricted involvement such as unilateral foot drop or intrinsic hand muscle weakness due to single nerve involvement. However, multifocal nerve involvement is more typical at the outset, with up to one-half of patients presenting with mononeuropathy multiplex and a quarter to a third of patients demonstrating overlapping bilateral involvement resulting in distal symmetrical and asymmetrical polyneuropathy

due to extensive confluent ischemic involvement at many levels of multiple nerve trunks [139]. The clinical manifestations of primary CNS vasculitis range from minor to severe life-threatening signs of ischemia, although specific symptoms and signs depend upon the associated underlying mechanism. Affected adult and children present with headache, cognitive impairment, mood impairment, seizures, and focal deficits. It generally evolves in a stepwise or insidious fashion with progressive deficits culminating in quadriparesis, lethargy, coma, and death due to additional ischemic lesions.

The clinical manifestations of primary and secondary CNS vasculitis range from minor to severe life-threatening signs of ischemia, although specific symptoms and signs depend upon the associated underlying mechanism.

There is general agreement on four principles in the diagnosis of vasculitis, especially applicable to the nervous system:

First, vasculitis is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction; recognition of the neurologic manifestations is important in developing a differential etiologic diagnosis.

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 never be considered a substitute for the absolute proof of the diagnosis of vasculitis.

Fourth, histopathologic confirmation of vasculitis is essential for accurate diagnosis, such as by brain and meninges where there is CNS involvement, and analysis of nerve and muscle biopsy tissue when PNS involvement is postulated.

Serologically specific studies should be obtained in all patients guided by the clinical presentation and postulated etiologic diagnosis to avoid excessive cost and spurious results.

Electrodiagnostic studies are useful in the initial investigation of systemic vasculitis because they can identify areas of asymptomatic involvement and sites for muscle and nerve biopsy and distinguish the various neuropathic syndromes associated with peripheral nerve and muscle involvement. A wide sampling of nerves and muscles should be examined, both distal and proximal, using standard recording and needle electrodes for the performance of nerve conduction studies (NCS) and needle electromyography (EMG), at skin temperatures of 34 °C, with comparison to normative data. Most patients with peripheral nerve vasculitis show evidence of active axonopathy acutely in a mononeuritis multiplex pattern and over time in a distal symmetric or asymmetric pattern. Quantitative motor unit potential (MUP) analysis can delineate whether proximal wasting and weakness are caused by myopathic or neurogenic disease. In clinically suspected patients, open biopsy of a cutaneous sensory nerve is indispensable in the evaluation of primary and secondary PNV. Collectively, the observed primary pathologic process is generally an axonopathy with correlative findings on light microscopy employing cryostat- and paraffin-stained hematoxylin and eosin (H&E) sections, and later by plastic embedded, 1-mm, semithin sections, and teased nerve fiber studies. Such studies show 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 identify components of the cell-mediated and humoral immune system that may be present in active or chronic vasculitis.

Cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and CNS neuroimaging studies are integral to the diagnostic evaluation of most CNS disorders including vasculitis. Properly performed lumbar puncture carries minimal risk and provides potentially useful information regarding possible underlying vasculitis as suggested by pleocytosis in excess of 5 cells/mm^3, protein elevation >100 mg/dL, and evidence of intrathecal synthesis of immunoglobulin (Ig) and oligoclonal bands. Molecular genetic, immunoassay, and

direct staining techniques to exclude spirochetal, fungal, mycobacterial and viral infections, as well as cytospin examination of CSF for possible malignant cells should be performed. There are no typical EEG findings in CNS vasculitis. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT), but both methods lack specificity in histologically confirmed cases. The most common MRI findings are multiple bilateral cortical and deep white matter signal abnormalities and enhancement of the meninges after gadolinium. High-resolution 3-Tesla (3-T) MRI, MR angiography (MRA), and CT angiography (CTA) and functional imaging of the brain provide complementary information (Fig. 14.8). The former is useful in the evaluation of medium and large vessel disease, but can miss fine vessel contours better seen on cut-film or digital subtraction angiography (DSA). The abnormal diffuse and focal perfusion patterns seen on single photon emission-CT (SPECT) do not always correlate with neurologic symptoms or distinguish vasculitic from nonvasculitic vasculopathy. Some authorities have claimed that cerebral angiography showed diagnostic features, but that assertion was later modified. Beading of vessels is found in only about a third of patients with histologically proven CNS vasculitis, as well as in CNS infection, atherosclerosis, cerebral embolism, and vasospasm of diverse cause. Multiple microaneurysms, often seen on visceral angiography in systemic vasculitis, are distinctly rare in CNS vessels. The synergy of integrating functional imaging of ^{18}2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography with the anatomical nature of CT (^{18}F-FDG PET/CT) offers substantial benefits in the diagnostic work-up of patients with the clinical suspicion of LVV. One important feature of ^{18}F-FDG PET imaging in this regard is its ability to reveal increased metabolism and functional vascular alterations that precede, or are concomitant with the morphologic changes of frank vasculitis.

Biopsy of the brain, spinal cord, and attached meningeal tissue are the gold standard for the diagnosis of CNS vasculitis, but false-negatives occur because of focal lesions and sampling errors. Radiographic studies that guide the biopsy site toward the areas of abnormality appear to improve its sensitivity. The risk of serious morbidity related to biopsy is less than 2.0% at most centers, which is probably less than the cumulative risk of an empiric course of long-term immunosuppressive therapy. Experts in childhood and adult CNS vasculitis disagree in the correlation between brain and leptomeningeal biopsy and other clinical or laboratory predictors. Torres and colleagues [140] identified histopathologic evidence of CNS inflammation in 9/79 (11%) adults of mean age 55 year, with suspected primary angiitis of the CNS (PACNS). The authors noted perivascular inflammation instead of vessel wall inflammation in 18% of cases, and an alternative diagnosis in 30%, including cerebral amyloid angiopathy, encephalitis, demyelination, and lymphoma. They concluded that brain biopsy was an important diagnostic tool; however, further studies were needed to establish the clinical variables associated with a positive yield. Cellucci and colleagues [141] identified three different clinical groups in children whose mean age was 8.8 years with PCNSV, noting paresis and speech deficits as the commonest presenting features in the stroke phenotype; behavior changes, cognitive dysfunction, and seizures in the encephalopathy phenotype; and ataxia, vision abnormalities, and seizures in an encephalopathy/impaired vision phenotype. Altogether, 93% of the patients with the encephalopathy phenotype showed signs of vascular inflammation in CNS biopsy specimens, compared to none of those with the stroke phenotype. Salvarani and colleagues [142] studied adults of mean age 47 years, noting granulomatous, lymphocytic, and acute necrotizing patterns of inflammation in 29 of 47 (62%) patients who underwent CNS biopsy specimens with suspected primary CNS vasculitis (PCNSV), noting the absence of a clear clinical relation among the three histologists. However, the patients with a granulomatous pattern were most often older in age and presented with altered cognition. Notwithstanding, the CNS tissue examination would certainly be warranted if there were no other explanation for the

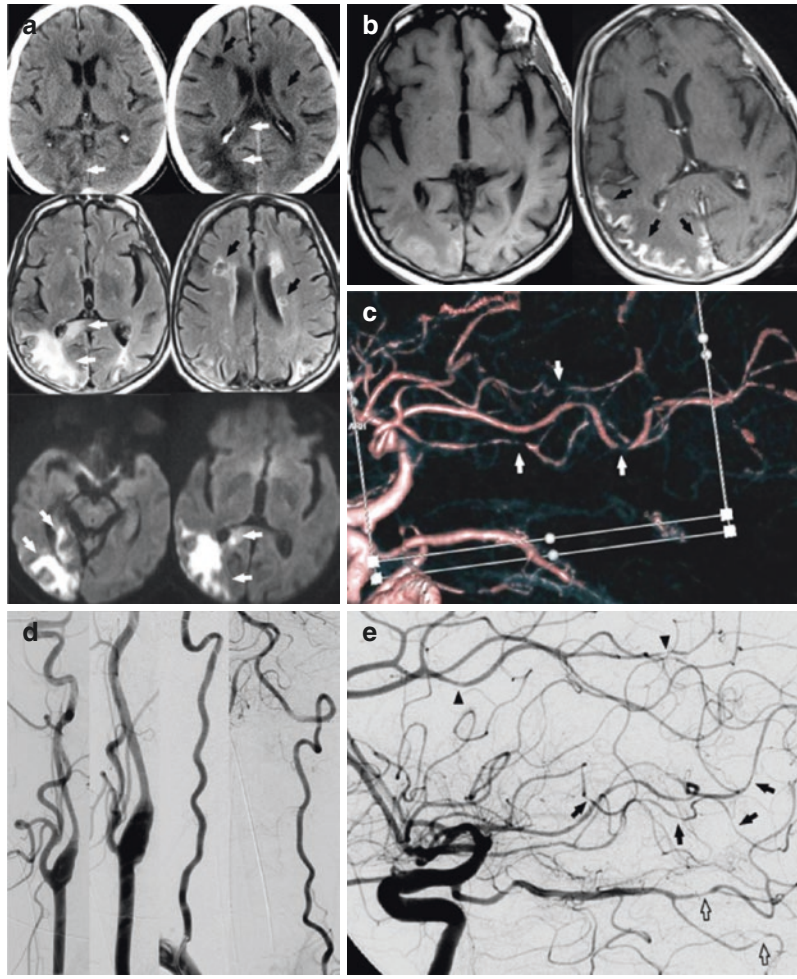

Fig. 14.8 (**a**–**e**) Primary angiitis of the central nervous system. (**a**) Noncontrast CT (top) demonstrates multifocal regions of low attenuation. Those in the right frontal subcortical white matter and left basal ganglia (black arrows) are sharply defined without mass effect and likely reflect 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**) T_1-weighted imaging pre- and postgadolinium 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, there is vascular narrowing within the posterior cerebral artery. (**d** and **e**) Angiogram reveals completely normal extracranial vasculature. The anterior cerebral (black arrowheads), middle cerebral (black arrows) and posterior cerebral artery (black outlined arrows) demonstrate mild to severe short segment stenosis. *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. (Reproduced from Ref. [164], with permission of the publisher)

progressive syndrome of fever, headache, encephalopathy, and focal cerebral signs, in association with CSF pleocytosis, and protein content elevation greater than 100 mg/dL [118].

Treatment

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 14.2.

The standard of care for the treatment of vasculitides, notably AAV, has been evolving in response to several factors [143]. One factor is the steady influx of multicenter, national, and international randomized clinical trials (RCT). A second factor has been large collaborative networks such as the French (FVSG), European (EUVAS), and Italian (IVSG) Vasculitis Study Groups, and the Vasculitis Clinical Research Consortium (VCRC) that share data. A third is the influence of gene-wide association studies (GWAS) that have elucidated risk gene loci, single nucleotide polymorphism (SNP) and human HLA in disease clusters and population cohorts [38]. Such inherited and environmental factors, gene-gene interactions, epigenetic factors, and other influences upon the immunopathogenesis of vasculitides have important theoretical importance for the performance of an RCT in vasculitides subtypes, as well as the relevance of screening studies and timing of therapy. The following section deals with the specific therapeutic agents employed in vasculitides.

The usefulness of corticosteroids in the treatment of systemic vasculitis has been appreciated for over 50 years; however, there has never been a randomized controlled trial conducted to support their use. The beneficial effects of corticosteroids are attributed to a multiplicity of effects on the cell and humoral immune system, including inhibition of activated T, and B cells, antigen-presenting cells (APC), and leukocytes at sites of inflammation, interferon (IFN)-γ, induced main histocompatibility class (MHC) class II expression, macrophage differentiation, pathogenic cytokine expression, complement interactions, and immunomodulation of cell adhesion molecules. Patients receiving long-term corticosteroid therapy for vasculitis should be monitored closely for hypertension, fluid retention, glucose

Table 14.2 Recommendations for the treatment of vasculitides

Large vessel vasculitis GCA, TAK: CS, AZA, RTX, infliximab, anti-TNF-α, anti-IL-6, 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 ribavirin 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, and MTX PACNS: Induction with CS, CS + CYC 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

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, *PACNS* primary angiitis of the central nervous system, *PAN* polyarteritis nodosa, *PE* plasma exchange, *RAV* rheumatoid arthritis vasculitis, *RTX* rituximab, *SLE* systemic lupus erythematosus, *TAK* Takayasu arteritis, *TNF* tumor necrosis factor

intolerance, cataracts, myopathy, avascular necrosis, infection, gastric and duodenal ulcers, and psychosis, and followed empirically for the need of short-acting insulin coverage as needed. The American College of Rheumatology (ACR) [144] addressed two serious complications of corticosteroid therapy, osteoporosis, and bone fracture. The guidelines, which assessed fracture risk by a Fracture Risk Assessment Tool (FRAX), categorized patients into low, medium, or high-risk categories depending on the estimated 10-year risk for major osteoporotic fracture. Patients at low risk should be offered bisphosphonate, whereas those at the highest risk of a major fracture should be treated with bisphosphonate therapy and teriparatide.

The effectiveness of a daily oral regimen of 2 mg/kg/day or oral cyclophosphamide with prednisone in GPA served as a template for the treatment of virtually all types of systemic vasculitis for decades [25], and together, they remained the standard treatment for inducing remission in virtually all forms of potentially fatal systemic vasculitis until 2010 when Stone [145], and Jones [146] and coinvestigators demonstrated the superiority and safety of rituximab. Although 75–90% of patients with GPA and other AAV achieve remission with oral or intravenous cyclophosphamide, few data are available on therapeutic strategies for patients with disease refractory to this first-line therapy. Its favorable effect on vasculitis derives from the preferential T-cell lysis resulting from the inhibition of hematopoietic precursors in the bone marrow, leaving stem cells unharmed. At high doses, this inhibition favors repopulation of the marrow and thus the cellular immune system. After an intravenous dose of cyclophosphamide, the nadir of peripheral leucopenia, which corresponded with peak marrow suppression, occurred in 7–18 days. Less than 20% of labeled cyclophosphamide is excreted unchanged in the urine. The toxic side effects include hemorrhagic cystitis, bladder cancer, bone marrow suppression, and the risk of fatal infection and gonadal toxicity. Bladder toxicity may be reduced by administration of the drug in a single daily oral morning dose followed by hydration; and administration of the drug intravenously as pulse therapy, adjusting the dose to renal function. Intravenous cyclophosphamide, which can be administered as pulses therapy based on body surface area, is as effective as and less toxic than oral cyclophosphamide. Premature ovarian failure occurs in 30–50% of premenopausal women following cyclophosphamide therapy that is cumulative and more pronounced with increasing age at administration. Accordingly, women with GPA so treated with daily oral cyclophosphamide for up to 6 months had significant loss of ovarian reserve as measured by the anti-Müllerian hormone level [147]. The administration of gonadotropin-releasing hormone (GRH) analog 10 days prior to an intravenous bolus of cyclophosphamide appears to preserve fertility [148]. Cryopreservation techniques to preserve ovarian tissue and stimulate oocytes can be offered to childbearing women before treatment of cyclophosphamide [149].

Rituximab is a chimeric monoclonal anti-CD20 antibody that selectively depletes B cells, but not plasma cells. The rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) [146] demonstrated nonsuperiority of rituximab to standard intravenous cyclophosphamide for severe AAV with highly sustained remission rates in both groups. Rituximab-based therapy was not associated with reductions in early adverse events. The rituximab in ANCA-associated vasculitis (RAVE) study [145] found that rituximab was not inferior to daily cyclophosphamide treatment for induction of remission in severe AAV and possibly superior in relapsing disease.

The bioavailable agents with activity against TNF-α, which include etanercept and infliximab have been well studied in AAV and other systemic vasculitides. In animal models, inhibition of TNF-α markedly decreases the development of bactericidal granulomas during Bacille de Calmette et Guérin (BCG) infection. Moreover, CD4+ T cells from patients with GPA are associated with HLA-DR+ CD4+ T cells that exhibit an unbalanced Th1-type cytokine pattern and elevated levels of TNF-α [150]. Serum levels of TNF-α receptor correlate with disease activity and TNF-α-positive cells infiltrate renal lesions

[151]. Treatment with the dimeric soluble TNF receptor etanercept was not effective for the maintenance of remission in patients with GPA and durable remissions were achieved in only a minority of patients, with a high rate of treatment-related complications including the development of solid cancers in six patients in the etanercept group as compared with none in the control group [152]. A pilot study of the anti-TNF-α antibody infliximab [153] were well tolerated during short-term follow-up and successfully induced prompt symptomatic responses in those with systemic vasculitis not responding to conventional treatments. Seven patients with GPA, two with RV, and one with CV of mean duration of 9, 21.5, and 17 years respectively, so treated had no major side effects.

Oral methotrexate at the dose of 20–25 mg/week with prednisolone was as effective as oral cyclophosphamide 2 mg/kg/day with prednisolone that was tapered and withdrawn over 12 months in the initial treatment of early nonsevere AAV [154]. However, the methotrexate regimen was less effective for induction of remission in those with extensive disease and pulmonary involvement, and associated with more relapses than with cyclophosphamide after the termination of treatment. The high relapse rates in both treatment groups supported the practice of continuing immunosuppressive treatment beyond 12 months. The adverse effects of methotrexate in that study [154] included infection, leukopenia, hypertension, liver dysfunction, nausea, and vomiting.

The purine analog azathioprine, which metabolizes to the cytotoxic derivative 6-mercaptopurine, exerts favorable action in vasculitis by the inhibition of T-cell activation and T-cell-dependent antibody-mediated responses. Azathioprine is generally considered a safe alternative although less effective agent to prednisone and cyclophosphamide in virtually all forms of vasculitis. However, there are three drawbacks to its use. First, idiosyncratic side effects, most often gastrointestinal and flu-like, occur in approximately 10% of patients and rarely necessitate permanent withdrawal of the medication. However, pancreatitis and gastritis severe enough to warrant hospitalization can occur. Second, bone marrow suppression occurs in nearly all patients, usually manifested by mild pancytopenia. Third, there is typically a long delay in the onset of the therapeutic effect of 3 months or more. Taking all of these factors into account, most clinicians concur with the slow advancement of the dose over weeks, commencing with 50 mg/day and achieving maintenance levels of 2–3 mg/kg/day with careful monitoring of liver and marrow function.

Mycophenolate mofetil is an inhibitor of purine synthesis. It has been traditionally employed to prevent organ transplant rejection. Initial enthusiasm for mycophenolate in refractory autoimmune disorders was tempered by recognition of its predisposition to systemic tumor formation as a rare side effect as well as the inability to demonstrate superiority over corticosteroids and other immunosuppressants. Nevertheless, most experts agree that patients with systemic vasculitides who are poor candidates for corticosteroids, cyclophosphamide, and are intolerant of azathioprine may be given effective, safe, and long-term treatment with mycophenolate [155, 156]. While azathioprine and methotrexate appeared to be equally effective in maintaining remission in GPA [157], mycophenolate mofetil was less effective than azathioprine [158], it can be used as an alternative to cyclophosphamide, azathioprine and methotrexate in patients AAV with renal impairment where it carries less risk [159].

Infection is an important risk of immunosuppressant therapy; therefore, every effort should be made to exclude infection prior to initiation of such therapy including prophylaxis and vaccination when appropriate. Two-thirds of patients receiving immunosuppressive medications were asymptomatic at the time of HBV reactivation [160]. The latter is preventable with preemptive antiviral therapy in appropriately selected patients, particularly those with HBs and core antigenemia, or present HBV DNA. Patients with suspected TB exposure should be screened with a tuberculin skin test and interferon-gamma release assay (IGRA) prior to initiation of corticosteroids and immunosuppressive therapy [161]. Corticosteroids and cyclophosphamide with prolonged lymphopenia are known risk

factors for Pneumocystis pneumonia. Unlike HIV, there are no guidelines for prophylaxis in vasculitides although trimethoprim-sulfamethoxazole (TMP-SMZ) should be considered for all AAV patients receiving cyclophosphamide with dose adjustment for renal function. The Centers for Disease Control and Prevention (CDC) Vaccination should be considered for immunosuppressed patients with a minimum interval between vaccination and initiation of immunosuppressive therapy of 2 weeks. The live varicella, measles/mumps/rubella, yellow fever, typhoid fever, polio, and intranasal attenuated influenza, should be avoided in patients receiving greater than 20 mg/day of prednisone or other immunosuppressive medications. All patients should be offered inactive influenza vaccination annually. The pneumococcal polysaccharide vaccination should be administered to all eligible adults.

High dose IVIg therapy is the most widely employed immunomodulating agent for autoimmune neurologic disorders [162]. It is an alternative therapy for CNS and PNS vasculitis and diverse connective tissue disorders. Among 22 patients with relapsing AAV including 19 with GPA and 3 MPA, IVIg was administered at the dose of 0.5 g/kg/day for 4 days as additional therapy monthly for 6 months in conjunction with corticosteroids and immunosuppressants (21 patients) [163]. IVIg induced complete remissions of relapsed AAV in 13 of 22 patients at 9 months. The immunomodulating and anti-inflammatory actions of IVIg are provided by monthly doses of 2000 mg/kg/body weight given 400–500 mg/kg/day respectively over 4–5 days each month at a slow drip with acetaminophen and diphenhydramine pretreatment to prevent the commonest side effects including headache, fever, chills, rash, erythema, flushing, nausea, myalgia, arthralgia, abdominal cramps, and chest and back pain. True anaphylactic reactions to IVIg can occur in recipients with documented prior allergies to immune globulins or antibodies, especially IgA type. Transient reversible renal insufficiency occurs in individuals with preexisting renal disease. Susceptible individuals can be identified by less than normal expected 24-h creatinine clearance rates for age and abnormal vascular perfusion on radionuclide scans. Aseptic meningitis rarely occurs several hours after treatment and resolves over several days with discontinuation of therapy.

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