Stroke due to Vasculitis in Children and Adults

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KEYWORDS

• Stroke • Vasculitis • Central nervous system

KEY POINTS

- The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in vessel walls.
- There is an increased propensity for ischemic stroke resulting from thrombosis and compromise of vascular lumina.
- This results in distal tissue ischemia with hemorrhagic or nonhemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity.
- Vascular inflammation is the leading cause of stroke in children but the pathophysiology of childhood vasculitis is poorly understood. Moreover, it is rarely proven histologically.
- Small-vessel or large-vessel arteriopathy as useful models of primary central nervous system vasculitides of childhood are based on predictive clinical, neuroradiographic, and histopathologic features.

INTRODUCTION

The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in vessel walls. There is an increased propensity for ischemic stroke because of the compromise of vessel lumina and distal tissue ischemia, and hemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity. The revised 2012 Chapel Hill Consensus Conference (CHCC)[1] provides a systematic nosology and categorization of primary and secondary vasculitides. Central nervous system (CNS) vasculitides leads to stroke as a result of a single-organ vasculitic syndrome, variably termed primary CNS vasculitis (PCNSV),[2] granulomatous angiitis of the brain,[3] and adult primary angiitis of the CNS (PACNS) or childhood PACNS (cPACNS)[4]; and as a secondary consequence of systemic vasculitides. Although applicable to pediatric patients, the CHCC nosology[1] was not specifically designed

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for this population. The European League Against Rheumatism and the Pediatric Rheumatology European Society[5] developed consensus criteria for the classification of the childhood forms of adult vasculitis disorders, including childhood polyarteritis nodosa (cPAN), granulomatosis with polyangiitis (GPA) as childhood GPA (cGPA), and microscopic polyangiitis (MPA) as childhood MPA (cMPA). Others are not specifically abbreviated with the childhood designation because of their common pediatric occurrence, including Takayasu arteritis (TAK) and Kawasaki disease (KD). The subtypes of childhood PACNS[6] are distinguished by vessel size, angiographic and pathologic findings, and the presence or absence of long-term progression.

Stroke Patterns and Classification

Patterns of stroke identified by the region of brain supplied by the affected vessel, and the size of the vessels and infarctions that ensue, are referred to as large-vessel or small-vessel (SV) lesions. Large-vessel infarcts typically result in wedge-shaped parenchymal lesions that occur secondary to occlusion of branches of the major arteries of the circle of Willis. SV diseases result in smaller, often multifocal or diffuse parenchymal infarcts with highly variable imaging appearances. Large-vessel infarcts present with sudden onset focal neurologic deficits, such as contralateral hemiparesis when the middle cerebral artery (MCA) is occluded. In contrast, strokes in SV territories present with subacute, nonlocalizing neurologic complaints, such as headache, behavioral changes, seizures, or cognitive decline.

Adult strokes classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[7] (into large-artery atherosclerotic, cardioembolic, SV lacunar, other, determined, and undetermined cause) have not been widely applicable to pediatric stroke patients owing to often underdetermined causes.[8] The International Pediatric Stroke Study (IPSS), applying standardized classification and diagnostic evaluations to childhood arterial ischemic stroke (AIS), developed the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria.[9] Vascular inflammatory mechanisms incorporated into the CASCADE system recognize SV arteriopathy of childhood, unilateral focal cerebral arteriopathy (FCA) of childhood, bilateral cerebral arteriopathy of childhood, aortic or cervical arteriopathy, cardioembolic, other, and multifactorial causes of AIS, making it a useful starting point with the potential for ongoing modification as new information about childhood AIS is learned. However, there were limitations to the CASCADE. First, it did not recognize all of risk factors potentially related to structural disease of the heart or blood vessels. Second, future modifications of the CASCADE criteria need to unify and elaborate classification of these factors in a secondary classification system. Third, additional revisions need to address the recurrences beyond the acute period of childhood AIS.[10]

The Vascular effects of Infection in Pediatric Stroke (VIPS)[11] study prospectively enrolled 355 children with AIS between 2010 and 2014 to diagnose childhood arteriopathy and classify subtypes, including arterial dissection, FCA-inflammatory type (FCA-i), which included transient cerebral arteriopathy, moyamoya, and diffuse or multifocal vasculitis. The most common childhood arteriopathies in the cohort of children presenting with acute AIS were moyamoya, arterial dissection (intracranial and extracranial), and FCA-i but not primary SV-PACNS, which typically presents only with headache or cognitive decline, and less so with focal signs or symptoms.

Primary Central Nervous System Vasculitis

Adults

With several proposed diagnostic schemes for PCNSV over the years,[12] the combination of clinical, neuroradiographic, and histopathological findings remains the

recommended method for reliable diagnosis and facilitates the identification of clinicopathologic subtypes, including those with persistent focal deficits, stroke, and intracranial hemorrhage. Persistent neurologic deficits, including stroke and headache, were the commonest initial symptoms affecting 68% of 101 studied subjects with PCNSV,[13] as defined by diagnostic criteria of Calabrese and Mallek[4] and modified by Birnbaum and Hellmann.[14] Infarctions were the commonest type of lesion noted with MRI of the brain, among 53% of 90 subjects so studied, and were multiple in appearances in 85% and bilateral in 83%, with cortical and subcortical involvement in 63% overall, suggesting larger artery, branch-artery, and small-artery distributions (**Fig. 1**). Intracranial hemorrhage was noted in 8% of subjects.

In a retrospective cohort of 163 patients with PCNSV from 1983 to 2011 at the Mayo Clinic,[2] 105 patients (64%) showed angiographic changes supporting the diagnosis of PCNSV (manifesting 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) and 58 patients (36%) showed CNS tissue changes of vasculitis (demonstrating transmural vascular inflammation involving leptomeningeal or parenchymal vessels). The histopathology was granulomatous in 35 (60.3%), lymphocytic in 13(22.4%), and necrotizing alone in 10 (17.2%). These histologic patterns seem to identify subsets of disease rather than different stages of the same process because no individual subject had histologic evidence of more than 1 pattern. Comparatively, among the 112 subjects reported by De Boysson and colleagues,[15] 68 (61%) and 11 (10%) had digital subtraction angiography or magnetic resonance angiography (MRA) consistent with PCNSV, respectively, whereas 33 (29%) subjects had CNS tissue diagnosis of vasculitis.

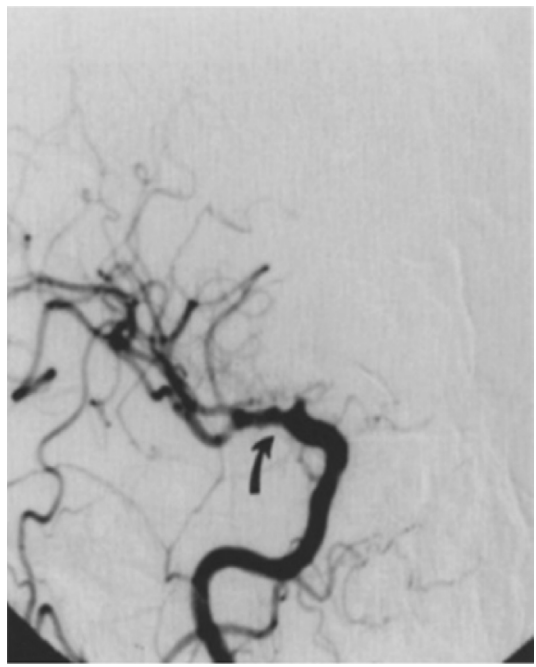

Fig. 1. Radiographic features of cerebral Vasculitis. Ectasia and beading in the M1 segment and lack of flow in the A1 segment of the right anterior cerebral artery (*arrow*). (*From* Younger DS. Adult and childhood vasculitis of the nervous system. In: Younger DS, editor. Motor Disorders. Third edition. Brookfield, CT: Rothstein Publishing; 2015. p. 242; with permission.)

Children

Advances in the understanding of childhood AIS occurred independent of pediatric inflammatory brain disease (IBrainD) and cPACNS,[6] with inconsistencies between the adult PACNS and cPACNS, making the latter problematic for several reasons.

First, unlike antemortem pediatric cases of cerebral vasculitis that show angiographic evidence of large named vessel involvement, children with SV-cPACNS can only be conclusively diagnosed by CNS biopsy tissues that show transmural inflammation of small meningeal and penetrating cortical vessels. Affected patients present with focal symptoms suggesting an association with stroke but are more likely to develop subacute, nonlocalizing, neurologic complaints, such as headache, behavioral changes, seizures, school failure, or cognitive decline. Moreover, childhood strokes may be highly variable in character and distribution.

Second, compared with their adult counterparts, the estimated incidence of hemorrhagic lesions in children is minimal, making up less than 10% of all strokes.[16]

Third, neuroimaging is far less specific in cPACNS. Noninvasive arterial imaging using computed tomography (CT) angiography and MRA show typically normal findings even when parenchymal MRI imaging ranges from normal to diffusely abnormal across a wide array of lesion characteristics.

Fourth, childhood AIS associated with conventional angiography that fails to show radiographic changes consistent with SV-cPACNS are placed in the category of angiography-negative SV-cPACNS,[17] typically with unsubstantiated histopathology, yet suggesting a corresponding caliber of vessel involvement.

Fifth, despite the similarities to adult forms of PACNS, recent cPACNS series[6] fail to mention prototypical granulomatous pathologic conditions, suggesting a bias of selection, making clinicopathological comparisons further problematic.

Sixth, while awaiting the results of the Pediatric Vasculitis Initiative, a Canadian and United Kingdom collaborative study of pediatric and adult cases of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) such as GPA and PACNS, the approach of cPACNS has been to lump them into the broader category of inflammatory brain disease (IBrainD)[18] and systematically exclude angiography-positive mimics of cPACNS and angiography-negative, brain biopsy–positive true SV-cPACNS.

Seventh, because the approach to management of SV-cPACNS is patterned after SV vasculitides (SVV), including antineutrophil AAV, it is difficult to reconcile the disappointing results of the PedVas Initiative,[19] which showed a remission status of 42%, and visceral organ damage in 63% of cases following treatment with corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission induction; plasma exchange in conjunction with cyclophosphamide and/or rituximab; and azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide for up to 12 months for remission maintenance.

LARGE-VESSEL SYSTEMIC VASCULITIDES

Giant cell arteritis (GCA) and TAK are prototypical large-vessel granulomatous vasculitides that involve the aorta and its major branches; however, any size artery can be affected. Kermani and colleagues[20] reported a population-based incident cohort of 204 patients with GCA seen between 1950 and 2004 at the Mayo Clinic, noting a mean age of diagnosis of 76 years, and a female to male ratio of 1.5:1. It is the most common vasculitis in populations with predominantly Northern European ancestry, with an annual incidence of 15 to 33 cases per 100,000 age 50 years and older.[21] GCA is a polygenic disease in which multiple environmental and genetic factors influence susceptibility and severity.[22]

Neuroimaging studies using ultrasonography, high-resolution MRI, and ^{18}flurodeoxyglucose (^{18}FDG) PET are useful imaging modalities to identify superficial cranial and extracranial, and large-vessel subclavian artery and aortic involvement in GCA and TAK.[23] CNS involvement in GCA results from thrombosis of the carotid and vertebral arteries rather than intracranial arteritis, affects vessels that contain elastin, more specifically the internal elastic lamina that is absent from intracranial vessels more than 5 mm beyond the point of dural perforation. Hollenhorst and colleagues[24] noted CNS events, including stroke in 7.4% of 175 subjects with confirmed GCA, including 1 with massive cerebral hemorrhage, 2 with stroke, and 6 with occlusive disease of the aortic arch. Caselli and colleagues[25] noted transient ischemic attacks or stroke in 7% of 166 subjects with biopsy-proven GCA, among whom 4 had events in the vertebrobasilar system and 8 were affected in the carotid arterial system. Approximately 30% of subjects manifested neurologic findings, the commonest of which were neuropathies of the arms and legs, according to Caselli and colleagues.[25] Salvarani and colleagues[22] observed that transient ischemic attacks or stroke in the territory of the carotid or vertebrobasilar arteries were less common neurologic findings. Gonzalez-Gay and colleagues[26] studied GCA among 239 patients in a multicenter retrospective, noting stroke occurrence in only 8 patients (3%), equally divided between the vertebrobasilar and carotid territories. Other symptoms of arteritis preceded ischemic events 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 a month despite aggressive corticosteroid therapy. Stepwise logistical regression analysis revealed visual loss and jaw claudication as the predictors of stroke.

The reported mean annual incidence of TAK was .4 per million in a population study in eastern Denmark between 1990 and 2009.[27] Stroke occurrence was noted in 17% of 230 reported children with TAK between 1994 and 2008.[28] There is risk of both focal AIS from thromboembolism, and hypoperfusion-induced brain infarction secondary to proximal arterial stenosis. Although the pediatric presentation of TAK includes hypertension similar to adults,[29] affected children more commonly manifest fever, weight loss, abdominal pain, and headaches.[28] Kerr and colleagues[30] summarized the clinical, laboratory, and treatment responses of 60 subjects with TAK based on the presence of symptoms and signs of ischemic, inflammatory large-vessel disease, as well as supportive arteriography findings, so noted in 10 (17%) subjects with either transient ischemic attacks or stroke, and carotid or vertebral artery disease. Riehl[31] and Riehl and Brown[32] reported the clinical and pathologic features of 6 cases of TAK, noting widespread arteritis that involved not only the aortic arch and its tributaries by clinical and angiographic, studies but also many other medium-size and large-size vessels, including the cerebral arteries, by granulomatous panarteritis in 1 patient studied at postmortem examination. 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 and thrombosis of an aortic arch graft, with nearly complete obstruction of all the great vessels. Vascular thromboses were noted along proximal portions of the left MCA, both posterior cerebral arteries, and the 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.

Although arterial biopsy is impractical given the restriction of lesions to the aorta and its branches, MRA and conventional angiography demonstrate vessel irregularities, stenosis, poststenotic dilatations, aneurysmal formation, occlusions, and increased collateralization. There are strong similarities and subtle differences in the distribution

of arterial disease on cerebral arteriography between GCA and TAK that suggest that the two disorders may nonetheless exist on a spectrum of a similar disease.[33] Ishikawa[34] reported the natural history of TAK among 54 Japanese subjects from 1957 to 1975, classified as uncomplicated (group I), monocomplicated (group II), and multicomplicated (group III). The 5-year survival rate after the established diagnosis in the 54 subjects was 83%. The major factors related to death among the 8 subjects so studied included fatal cerebral events in 3, cardiac events in 3, and events related to aortic reconstruction surgery or steroid withdrawal in another. Ohigashi and colleagues[35] ascertained an improved prognosis among 106 consecutive subjects with TAK in those with onset before 1999 compared with those diagnosed after 2000 (4.2% vs 0%, respectively). This was attributed to reduction in the time from onset to diagnosis; replacement of digital subtraction angiography (79% vs 9%) with ultrasound (6% vs 34%), CT angiography (24% vs 77%), MRA (21% vs 57%), and ^{18}FDG PET (0% vs 20%); less frequent complications of moderate or severe aortic regurgitation; increase in the use and maximal dose of corticosteroids (70% vs 97%); and the use of first-line and second-line immunosuppressant agents (7% vs 42%). Surgical treatment of TAK was similar between those with onset before 1999 and after 2000 (22.5% vs 22.8%, respectively).

MEDIUM-VESSEL SYSTEMIC VASCULITIDES

Watts and colleagues[36] used the 2012 revised CHCC[1] and American College of Rheumatology (ACR) criteria for PAN,[37] noting its incidence in the United Kingdom compared with Spain, varying from 9.7 versus 6.2 per million, respectively. KD is common in childhood, with the highest incidence in Japan where it exceeds 120 per 100,000, with 80% of these children younger than 5 years of age and a boy to girl ratio of 1.5:2.[38,39] Both are prototypical medium-vessel vasculitides, although arteries of any size may be affected. PAN is associated with necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Such are not features of AAV. By contrast, KD is an infantile or childhood disorder associated with the mucocutaneous lymph node syndrome, predominantly affecting medium and small arteries, occasionally coronary, the aorta, and other large arteries (1).

Kernohan and Woltman[40] summarized the clinicopathological aspects of adult PAN in 6 subjects studied at postmortem examination, estimating CNS involvement, including stroke, to be about 8% of cases, and noting a combination of acute and chronic lesions that correlated with known exacerbations. According to Guillevin and colleagues,[41] CNS involvement was uncommon but motor deficits, stroke, and brain hemorrhage occur, the cause of which was generally multifactorial. Cases with cognitive disturbances, such as abrupt memory loss in which MRI shows scattered T_2-weighted hyperintensities suggestive of brain vasculitis, have generally not been demonstrated as such histopathologically. CNS involvement, including stroke, was noted in 9.6% (26) of 115 subjects registered in the French Vasculitis Study Group (FVSG) with hepatitis B virus (HBV)-PAN. These cases were seen between 1972 and 2002, and had biopsy-proven PAN or demonstration of microaneurysms and multiple stenoses by abdominal or renal angiography. There were associated clinical symptoms of vasculitis with concomitant hepatitis B surface antigen (HBsAg) antigenemia and demonstration of viral replication supported by hepatitis B e antigen, viral DNA, or DNA polymerase. A retrospective study of 348 adult subjects registered in the FVSG[42] who satisfied criteria for the diagnosis of PAN between 1963 and 2005 noted CNS involvement, including stroke, in 4.6% of subjects overall, with relatively equivalent frequency in those with and without HBV-related illness.

cPAN is rare, and the classification criteria for cPAN requires histologic evidence of necrotizing vasculitis in medium-sized or small-sized arteries or angiographic abnormalities demonstrating aneurysm formation or vascular occlusions as a mandatory criterion, plus 2 of 5 features: myalgia, skin involvement, hypertension, neuropathy, or abnormal urinalysis, or impaired renal function.[43] Disease manifestations range from a benign cutaneous form with clinical, laboratory, and molecular characteristics of familial Mediterranean fever[44,45] to severe disseminated multisystemic disease. Ozen and colleagues[46] studied 110 children of mean age 9 years, from 21 pediatric centers worldwide, diagnosed with cPAN, dividing them into 4 groups, including systemic PAN (57%), cutaneous PAN (30%), and classic PAN with HBsAg (4.6%) as well as 8% manifesting ANCA seropositivity, so qualifying for MPA. Cutaneous cPAN was confined to the skin and musculoskeletal system. There are reported children with serologic and microbiologic evidence of preceding streptococcal infection.[47]

The diagnosis of KD requires the presence of fever for at least 5 days and 4 of the following criteria: desquamation of extremities or perineum, polymorphous exanthema, bilateral conjunctiva injection, injection of oral or pharyngeal mucosa, and cervical lymphadenopathy.[5] The disease affects the coronary arteries and stroke as a complication has only rarely been reported, predominantly large-vessel cardioembolic stroke but also cerebral microhemorrhages.[48–50] Evaluation of 24 subjects with KD using MRI revealed 1 cryptogenic cardioembolic posterior inferior cerebellar artery infarct.[51] Risk is potentially higher in patients with ventricular dysfunction secondary to myocardial infarction or arrhythmia. Stroke should be considered in children with signs or histories of medium-vessel vasculitis and neurologic symptoms, particularly acute focal neurologic deficits.

SMALL-VESSEL SYSTEMIC VASCULITIS

SVV predominantly affects SVs, defined as small intraparenchymal arteries, arterioles, capillaries, and venules; however, medium-sized vessels and veins may be affected. Two major categories of SVV include AAV characterized by necrotizing vasculitis with few or no immune deposits predominantly affecting small arteries, arterioles, capillaries, and venules associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3), whereas immune complex vasculitis is characterized by marked vessel wall deposits of immunoglobulin (Ig) and/or complement. GPA (Wegener granulomatosis type), eosinophilic GPA (EGPA; Churg-Strauss syndrome), and MPA (microscopic polyarteritis) are prototypical AAV, whereas cryoglobulinemic vasculitis (CV), IgA vasculitis, and hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies comprise the immune complex vasculitides.

The classification of AAV has been controversial,[52] with existing systems developed by the ACR,[53,54] the CHCC,[1] and the European Medicines Agency algorithm,[55] to provide a standardized method for their application in epidemiologic studies, each with separate deficiencies, especially when applied to unselected patients. These systems were developed as classification criteria and not as diagnostic criteria. Because there were no validated diagnostic criteria for AAV, the Diagnostic and Classification Criteria for Vasculitis Study (DCVAS), developed by Watts and colleagues,[55] led to the consensus development and validation of diagnostic criteria by an algorithm to avoid inclusion of patients with other conditions. In incident cases of primary systemic vasculitis identified in Seine-St. Denis County, Paris, France, Mahr and colleagues[56] estimated the prevalence of GPA at 23.7, MPA at 25.1, and EGPA at 10.7 per million adults in a population of 1,093,515, 28% of whom were of non-European ancestry, with an overall prevalence that was 2-fold higher for those of European ancestry

(104.7 5 per million) compared with others of non-European ancestry (52.5 per million). Mohammad and colleagues[57] estimated incident cases of GPA, MPA, and EGPA in southern Sweden 9.8, 10.1, and 0.9 per million, respectively, in a total population of 641,000 between 1997 and 2006, with a progressive increase in age-specific incidence rates over the study period.

Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

Granulomatosis and polyangiitis

GPA is characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tracts and necrotizing AAV affecting small to medium arteries, arterioles, capillaries, veins, and venules, together with glomerulonephritis. Drachman[58] 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. Based on his observations in a single postmortem case, cerebral involvement stroke resulted from a combination of 4 separate entities, including frank vasculitis of larger arterial branches, particularly over the surface of the brain as demonstrated in his patient report, with evidence of ischemia in portions of the territory supplied by the affected vessels; subarachnoid hemorrhage, hypertensive encephalopathy evidenced by microscopic infarcts in close relation to arteries with fibrinoid impregnation of their walls; and meningeal infiltration by mononuclear cells.

Nishino and colleagues[59] described neurologic involvement in 34% of 324 consecutive patients with GPA at the Mayo Clinic between 1973 and 1991, classified according to the ACR,[53] that included peripheral neuropathy in 16% compared with cerebrovascular events in 4% at some time in the course of illness, rarely, if ever, at presentation. Of 5 patients with presumed clinical vasculitis, cerebral angiography was negative in 2; and of 12 patients studied at postmortem examination, findings of vasculitis were detected in only 2 patients.

Fauci and colleagues[60] noted nervous system involvement in 22% of 85 subjects, 10 subjects (12%) of whom had CNS involvement, including strokes, at some point in the illness, although not ever specifically mentioned at presentation. Moore and Cupps[61] estimated the frequency of neurologic abnormalities of GPA to be 23% to 50%, with commonly encountered focal deficits due to CNS involvement, citing the mechanism of neural dysfunction to be inflammation from primary sites, remote granuloma formation, and vasculitis. The opinion of Drachman[58] was that contiguous extension of necrotizing granulomas might account for up to 24% of all neurologic complications, including those of the CNS. Extensive cerebral infarction in the territory of bilateral anterior cerebral arteries was ascertained in a 67-year-old man with frontal headache that preceded detection of a large midline frontal mass lesion on 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 ACAs, with occlusion of large-sized ACA vessels by organized mural thrombi, fibrinoid necrosis in the arterial branches, and 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[62] ascertained nervous system involvement in 23% of 110 subjects, with GPA noted in 15% of subjects and CNS involvement, including strokes, in 8% of subjects. de Groot and colleagues[63] performed a prospective analysis of 128 GPA subjects, noting CNS involvement, including stroke, in 7% of subjects. The latter included granulomatous infiltration of frontobasal cortex arising from adjacent

paranasal sinus granulomas, cerebral vasculitis, vascular myelopathy, and meningeal granulomatosis.

CNS involvement in cGPA is not common and often appears at a later stage in the disease. The criteria for cGPA requires the presence of 3 of the following 6 criteria: abnormal urinalysis; granulomatous inflammatory on tissue biopsy; nasal-sinus-oral inflammation; subglottic, tracheal, or endobronchial stenosis; abnormal chest radiograph or CT; and positive ANCA staining.[43] Single large or multifocal insults involving 1 or more lobes consistent with the distribution of cerebral arteries are typical childhood presentations and respond to high-dose corticosteroid and intravenous immune globulin therapy.[64]

Microscopic polyangiitis

MPA is a necrotizing AAV vasculitis with few or no immune complex deposits and is commonly associated glomerulonephritis without granulomatous inflammation. From 1934 to 1947, Davson and colleagues[65] separated 14 reported postmortem subjects with MPA into 2 groups based on the presence of severe widespread glomerular damage. Wainwright and Davson,[66] who described MPA among 6 studied postmortem subjects from 1947 to 1948, failed to note CNS or stroke-onset, or histopathologic changes in the brain. Savage and colleagues,[67] who studied 34 subjects with MPA, all of whom presented with clinical evidence of a systemic SVV predominantly affecting the skin and musculoskeletal system associated with focal necrotizing glomerulonephritis, cited CNS involvement at presentation in 18% of subjects without specific mention of stroke. Serra and colleagues,[68] who reported the presentation, histopathology, and long-term outcome of 53 subjects with MPO from 1965 to 1981, cited CNS involvement at presentation in 15% of subjects that included stroke, convulsions, headache, confusion, and drowsiness, providing further breakdown of the individual frequencies thereof. Guillevin and colleagues,[69] who reported the clinical and laboratory findings in 85 subjects from the FVSG with MPA from 1969 to 1995, noted CNS involvement in 11.8% of subjects at presentation and in 3% of 29 subjects who experienced a relapse; however, there was no specific mention of stroke. Gayraud and colleagues,[70] who analyzed 4 prospective trials that included 278 subjects with PAN, MPA, and EGPA from 1980 to 1993, reported stroke occurrence among 85 deaths. Villiger and Guillevin,[71] who reviewed several retrospective European subject cohorts, cited CNS involvement that was described in a few subjects that included subarachnoid hemorrhage, cerebrovascular disease, meningitis, and diffuse brain injury. Ben Sassi and colleagues[72] described intracerebral hemorrhage secondary to necrotizing vasculitis that similarly involved the nerves and muscles, and citing 3 additional subjects with hemorrhagic stroke due to MPA.[73–75] Ahn and colleagues,[76] who studied 55 subjects with MPA, 69% of whom demonstrated perinuclear ANCA by immunofluorescence or MPO ANCA-seropositivity, noted neurologic involvement at diagnosis in 43.6% of subjects, and CNS involvement in 5 (9.1%), none of whom developed end-stage renal disease and 1 of whom was dead at follow-up.

cMPA is uncommon and the criteria for diagnosis includes 3 of the following features to be present: abnormal urinalysis, granulomatous inflammation on tissue biopsy, nasal sinus inflammation, subglottic, tracheal, or endobronchial stenosis; abnormal chest radiograph or CT scan; and PR3 ANCA staining.[43] Those with cMPA accounted for 4 of the first 32 children in the United States-Canadian: A Registry for Childhood Vasculitis (ARChiVe) registry.[77] Treatment of cMPA does not significantly differ from that of adults or other forms of AAV. An analysis of 4 prospective trials of 278 subjects comparing PAN, MPA, and EGPA[70] observed excess deaths during follow-up of MPA subjects, with survival probability trends adjusted to the

Five-Factor Score[78] and the Birmingham Vasculitis Activity Score,[79] which suggested increased mortality in MPA subjects compared with the other forms of vasculitis. Of 53 subjects studied by Serra and colleagues,[68] all 10 oliguric and untreated subjects at presentation died. Among the remaining 43 subjects treated with varying immunosuppressive regimens, including corticosteroids, cyclophosphamide, and azathioprine, in varying combination, 33 (77%) survived the acute stage of disease, 30 of whom made up a long-term analysis that showed stable vasculitis in 12 (40%), smoldering disease in 16 (53%), and recurrent vasculitis in 2 (7%) subjects. Savage and colleagues[67] noted an overall survival rate of 65%, and an actuarial survival rate of 70% at 1 year and 65% at 5 years following treatment with prednisolone, azathioprine, and cyclophosphamide or plasma exchange in varying combinations.

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. Churg and Strauss[80] described the clinical and postmortem findings of 13 subjects 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%) subjects and in the cause of death in 3 subjects who sustained cerebral hemorrhage (2 subjects) or subarachnoid hemorrhage.

Chumbley and colleagues[81] described 30 asthmatic patients from the Mayo Clinic over the period 1950 to 1974 with necrotizing vasculitis of small arteries and veins, with extravascular granulomas and infiltration of vessels and perivascular tissue with eosinophilia. Neurologic involvement, so noted in 19 (63%) patients, was consistent with mononeuritis multiplex. Lanham and colleagues,[82] who emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils, and extravascular granulomas similar to Churg and Strauss,[80] found them contemporaneously in only a minority of subjects. Such histologic findings, which could be encountered in other granulomatous, vasculitic, and eosinophilic disorders, even in the absence of clinical asthma, allergic rhinitis, sinusitis, pulmonary infiltrates, and cardiac involvement (pathognomonic of EGPA), was accompanied by CNS involvement in up to 25% of cases. Moreover, cerebral hemorrhage or infarction as a consequence of vasculitis or hypertension was a major cause of morbidity and mortality, accounting for 16% of deaths in their series of 16 subjects combined with 34 subjects reported in the literature.

Sehgal and colleagues[83] noted neurologic involvement among 14 subjects with the clinical diagnosis of EGPA. Three subjects had cerebral infarction 2 to 15 years after initial diagnosis, including a 68-year-old woman with a stroke involving the territory of the MCA manifested as hemiparesis and aphasia. 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, as did a 62-year-old woman with a thalamic infarction, who developed hemibody sensory loss. Guillevin and colleagues[84] studied 96 subjects with EGPA between 1963 and 1995, noting ischemic stroke in 6 (6%) as assessed by brain CT at presentation and none during follow-up, 1 of whom had clinically asymptomatic brain lesions, another who had cognitive disturbances related to vasculitis that improved with corticosteroid therapy, and focal deficits in the other 4. Mouthon and colleagues[85] reported 38 subjects with EGPA from

1978 to 1998, citing CNS involvement in 3 (7.9%) elderly subjects that suggested CNS vasculitis on MRI of the brain in only 1 subject so studied. Among 383 subjects with EGPA enrolled in the French FVSG Cohort (58), CNS involvement was noted in 20 (5.2%) of subjects at onset, with 2-fold greater frequency with ANCA-seropositive status than ANCA-seronegative but no specific mention of stroke frequency.

Immune Complex Vasculitis

Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis (CryoVas) is typified by cryoglobulinemic immune complexes deposited along SVs, predominantly arterioles, capillaries, veins, and venules in association with serum cryoglobulins that typically have associated rheumatoid factor activity consisting of IgM and polyclonal IgG, so-called mixed cryoglobulinemia (MC) and hepatitis C virus (HCV) infection.[86] Purpura, among the commonest features of cryoglobulinemia, was noted in 24% of subjects at presentation[60] and in 15% to 33% during disease evolution, in whom skin biopsy typically showed leukocytoclastic vasculitis. Neurologic manifestations noted in 23% of cases included peripheral neuropathy in 17% and CNS involvement in 6%. HCV infection is a main etiologic factor noted overall in 75% of subjects; antibodies to HCV and human immunodeficiency virus are noted in 75% and 19%, respectively, followed by HBsAg in 3%. A concomitant autoimmune disorder was noted in 24%, with frank hematologic disease in 7%, and essential cryoglobulinemia in 11% of subjects.

Historically, the patient described by Lerner and Watson,[87] 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 and Malone[88] 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[89] described MC in a 55-year-old woman with anarthria, hyperreflexia, bilateral Babinski signs, and progressively fatal coma, who was later found to have multiple thrombotic occlusions of small intracerebral blood vessels with adjacent foci of ischemia and marked demyelination at postmortem examination. A second patient, a 50-year-old woman, who presented with a Wallenberg syndrome, had MC and angiographically demonstrable occlusion of the left posterior inferior artery. A third patient, a 50-year-old woman who presented with right hemiparesis and pyramidal signs, had a cryoprecipitate with occlusion of the left MCA.

Gorevic and colleagues[90] summarized the clinical aspects of long-term follow-up of 40 subjects with MC, noting incidental CNS involvement at postmortem examination; and a fatal stroke in another subject. Petty and colleagues[91] 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 and 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) assay.

Ince and colleagues[92] described a subject with paranoid psychosis and MC who was later found to have right basal ganglia hemorrhage and multifocal SV occlusions by amorphous bland protein plugs, and abundant Russel bodies present in arterioles and venules, with relative sparing of capillaries.

Cacoub and colleagues[93] compared the features of subjects with HCV examined for systemic vasculitis manifestations of PAN or MC, noting 2 subjects with cerebral vasculitis in the former versus none in the latter. Cacoub and colleagues[94]

described 3 subjects with CNS involvement with HCV infection and MC, 1 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 subject had a hemorrhagic occipital lobe lesion in association with cerebellar infarction and abnormal periventricular hyperintensities. A third subject had abnormal white matter hyperintensities.

Ferri and colleagues[95] studied the demographic, clinical, and serologic features and survival of 231 subjects with MC seen between 1972 and 2001. There was widespread vasculitis involving small-sized to medium-sized arteries, capillaries, and venules with greater than 2 or more visceral organs, including the CNS, kidney, gut, and lung, in a small percentage of subjects, with the exception of focal dystonia in 1 subject during interferon treatment. The investigators[95] found no other manifestations of CNS involvement related to MC.

Filipini and colleagues[96] reported a 63-year-old woman with acute severe encephalopathy HCV-related MC, dysarthria, and hemiplegia. Fragoso and colleagues[97] 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 colleagues[98] reported the CNS findings in 40 subjects 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 with HCV and healthy controls. Terrier and colleagues[99] analyzed the data of 242 subjects registered in the CryoVas survey, ascertaining CNS involvement in 5 (2%) subjects without specifying whether stroke was encountered. Terrier and Cacoub[100] reviewed CNS findings in HCV-seronegative and seropositive MC in CryoVas, noting 2 (.7%) subjects among the former with CNS involvement, compared with 9 (5%) subjects among the latter group evidencing CNS involvement but without further mention as to presence of stroke in any of the subjects.

Cryoglobulinemia is rarely reported in the pediatric literature. One comparison cohort[101] showed a significantly higher prevalence of prolonged fever, arthralgia, arthritis, and cutaneous involvement in children compared with adults. There are no prospective controlled trials of treatment in children to assess relative efficacy of the various available agents; however, Giménez-Roca and colleagues[102] described successful treatment of pediatric CV with rituximab.

Hypocomplementemic urticarial vasculitis–C1q

HUV-C1q is an uncommon immune complex–mediated entity characterized by urticaria with persistent acquired hypocomplementemia.[103] It is associated with several systemic findings, including leukocytoclastic vasculitis, severe angioedema, laryngeal edema, pulmonary involvement, arthritis, arthralgia, glomerulonephritis, and uveitis. These manifestations should be present for at least 6 months. Laboratory findings include low complement levels of classical pathway, namely C1q, C2, C3, and C4. The disease marker is the serum presence of anti-C1q antibodies.

The disorder 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; joint swelling; and variable abdominal distress. Circulating hypocomplementemia and C1q antibodies are associated with necrotizing SVV in skin biopsy tissue, affecting arterioles, capillaries, and venules. Apart from orbital pseudotumor with ptosis, diplopia, and headache in 1 subject with HUV syndrome, there was no mention of CNS involvement or stroke in a review of 18 subjects with HUV-C1q.[104] Nor was stroke

mentioned in a review of 4 subjects studied at postmortem examination with HUV-C1q.[105]

Buck and colleagues[106] cited rare CNS manifestations in HUV-C1q, including aseptic meningitis, pseudotumor cerebri, transverse myelitis but not stroke or cerebral vasculitis. Grotz and colleagues[107] did not mention stroke or CNS vasculitis in HUV-C1q in a case report and review of the literature of HUV-C1q. In a review of urticarial vasculitis and HUV syndrome, Davies and Brewer[108] attributed development of pseudotumor cerebri to vasculitis of the venous sinus system. Ludivico and colleagues[109] suggested that chronic pseudotumor cerebri, as in their subjects, was a diagnosis of exclusion, possibly related to chronic corticosteroid use, and did not cite subjects with cerebral vasculitis or stroke.

The diagnosis and management of HUV-C1q was reviewed in 3 children by Pasini and colleagues[110] emphasizing the need for prompt diagnosis and treatment for concomitant renal involvement.

Variable Vessel Vasculitides

Behçet disease

Behçet disease (BD) is a rare disease encountered along the Silk Road in 20 to 420 per 100,000 in Turkey, 80 per 100,000 in Iran, and 0.64 per 100,000 in the United Kingom.[111] The disorder is characterized by relapsing aphthous ulcers of the mouth, eye, and genitalia.[112] The most widely used diagnostic criteria of BD were formulated by the International Study Group (ISG)[113] that included recurrent oral ulcerations plus any 2 of genital ulceration, typically defined eye lesions, typical skin lesions, or a positive pathergy. Recurrent oral ulcerations were categorized as minor aphthous, major aphthous, and herpetiform ulcerations that recurred at least 3 times in a 12-month period. Recurrent genital ulcerations were 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 acneiform nodules in postadolescent subjects not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitivity was defined as positive when a sterile pustule developed after 24 to 48 hours at the site of a needle prick to the skin.[114] Although the usual onset of BD is in the third or fourth decade of life, pediatric onset patients have been described.[115]

Two population-based studies, both fulfilling ISG criteria, studied prevalence data for BD, including 1 from France[116] and another from the United States.[117] The overall prevalence in France was 7.1 per 100,000, with immigrants of North African and Asian ancestry manifesting significantly higher prevalence rates of BD than those of European ancestry (17.5 per 100,000 compared with 2.4 per 100,000), comparable with those of North Africa and Asia. This suggested that BD risk was not related to age at immigration but has a primarily hereditary basis. The point prevalence of BD in the United States was 5.2 per 100,000. Genetic studies that focused on molecules related to innate immune responses identified an association with the endothelial nitric oxide (eNOS) gene located on chromosome 7q35-36, a variant of which causes deficient NOS, contributes to the pathogenesis of endothelial abnormalities, and increases thrombotic tendency in BD.

Uluduz and colleagues[118] studied 2 large Istanbul BD cohorts totaling 728 subjects, ascertaining and comparing pediatric-onset (26 subjects) and adult-onset (702 subjects) neuro-BD (NBD). The mean age of pediatric-onset of BD and NBD onset were 13 and 13.5 years, respectively, compared with adult-onset BD and NBD of 26 and 32 years, respectively. The commonest initial neurologic symptom in the

pediatric-onset subjects was headache in 92%, followed by seizures in 11.5%, compared with adult-onset BD that manifested corticospinal tract signs in 59% followed by headache in 58% and dysarthria in 23%. Significant differences in neurologic involvement consisted of a higher frequency of cerebral venous sinus thrombosis (CVST) so noted in 88.5% of children and 17% of adults, whereas parenchymal involvement was noted in 74.8% of adults compared with 11.6% of children. None of the children had associated cortical venous infarcts. Oral ulcers were noted in 100% of both groups, and there were no significant statistical differences in the occurrence of skin lesion, uveitis, or arthralgia; however, genital ulcers were less common in children compared with adults (54% compared with 84%).

Headache may be due to migraine, tension-type headache, uveitis, or the direct consequence of NBD. A case-control study of headache in BD reported by Haghighi and colleagues[119] found that 65% of subjects suffered from chronic headache due to migraine with aura in 1.7%, migraine without aura in 25%, tension headache in 24%, NBD in 8%, uveitis in 3%, and the remainder were due to other factors. Frontal and occipital headache and deep-seated pain around the eyes were presenting symptoms in several subjects with imminent florid involvement later studied at postmortem examination,[120–123] or as a clue to silent neurologic involvement in other cohorts so studied.[124] Cognitive impairment involving mainly memory functions occurs in BD without overt NBD, so noted in 46% of BD subjects compared with none in control subjects, with high disease activity and prednisone dosage independently associated with cognitive impairment.[125]

Siva and Saip[126] classified neurologic involvement into 2 major primary types: a primarily vascular-inflammatory mechanism with focal or multifocal parenchymal involvement, presenting most often as a subacute brainstem syndrome; and an unrelated vasculitis type with few symptoms and more favorable prognosis, due to isolated CVST and intracranial hypertension. A secondary form results instead from CNS involvement, such as cerebral emboli from cardiac disease, intracranial hypertension from superior vena cava syndrome, and neurotoxicity of specific mediations used in treatment. Mortality among neurologically complicated, clinicopathologically confirmed approaches 41%, with 59% occurring within 1 year of onset of neurologic involvement. Among nonfatal cases, residual neurologic signs are common. The neuropathological findings in BD in brain biopsies and postmortem examination have been remarkably consistent among patients over the past several decades, evidencing perivascular cuffing of small meningovascular and parenchymal arteries and veins[120,121,123,127,128]; rarely, medium-sized arteries displaying fibrinoid degeneration and recanalization; and examples of venous thrombosis, generally with frank necrotizing vasculitis. The inflammatory cell infiltrates were generally composed of lymphocytes, both T-cells and B-cells; macrophages; rarely, plasma cells; and eosinophils, with reactive astrocytosis and microscopic gliosis in neighboring cerebral, cerebellar, and brainstem white matter.

Matsumoto and colleagues[129] noted large-vessel lesions in 7 of 8 subjects aged 31 to 56 years with BD, including saccular aneurysms of the sinus of Valsalva or aortic arch; thoracic and abdominal aorta; pulmonary, femoral, and iliac arteries; and thrombotic occlusions in the pulmonary vein and superior and inferior vena. Aortitis, noted histologically in 6 of the 8 subjects, was active in 1, scarred in 6, and intermixed in another. Active aortitis was characterized by intense infiltration of inflammatory cells in the media and adventitia more frequently than in the interim with occasional giant cell formation. The scar stage was characterized by fibrous thickening of the intima and adventitia with condensation of the elastic lamina and proliferation of vasa vasorum with slight perivascular lymphocytic and plasma cell infiltrates. The subjects with

large venous occlusions had thrombophlebitis with luminal obstruction by organized thrombi.

CVST in BD presents with subacute or chronic onset of symptoms of isolated intracranial hypertension accompanied by headache, blurred vision, and diplopia[130] compared with those without BD in whom the onset is typically acute and associated with headache, hemiparesis, aphasia, and seizure. Venous infarcts occur in up to 63% of those with CVST of other causes, and in only 6% of subjects with BD. The rarity of venous infarcts, long delay to diagnosis, and clinical signs of isolated intracranial hypertension are more typical of BD-related CVST in which prothrombosis is presumed to commence as an endothelial dysfunction that takes longer to develop. Although anticoagulation would not be recommended for BD-related CVST, it might be considered in association with arterial occlusions, with both venous and arterial occlusive episodes warranting prompt consideration of corticosteroids alone or in association with another immunosuppressant agent.

Cogan syndrome

Cogan syndrome (CS) is a rare multisystem inflammatory vascular disease, characterized by nonsyphilitic interstitial keratitis (IK) and vestibuloauditory symptoms. A review of 79 cases of CS by Bicknell and Holland[131] found that more than half had nervous system involvement, including electroencephalographic or spinal fluid abnormality, headache, psychosis, coma, convulsion, neuropathy, and stroke. CS should be considered when neurologic deficits are accompanied by eye, ear, and systemic symptoms.

Gluth and colleagues[132] reviewed a cohort of CS patients seen at the Mayo Clinic between 1940 and 2002. The commonest symptoms at presentation were sudden hearing loss (50%), balance disturbance (40%), ocular irritation (32%), photophobia (23%), tinnitus (13%), and blurred vision (10%). Systemic symptoms noted alone at presentation included headache (40%), arthralgia (35%), fever (27%), myalgia (23%), abdominal pain (22%), rash (12%), peripheral neuropathy (10%), hematuria (7%), meningismus (5%), encephalitis (5%), and cerebral infarction. Otolaryngologic symptoms noted in the course of the disease included hearing loss (100%), vertigo or dizziness (90%), tinnitus (80%), ataxia (53%), oscillopsia (25%); similarly, those related to inflammatory eye involvement included interstitial keratitis (77%), iritis or uveitis (37%), scleritis or episcleritis (23%), and conjunctivitis (10%). Laboratory evidence of elevated ANCA antibodies was detected in 2 of 21 patients (10%), both in a perinuclear pattern.

There is ample literature to attest to the variable caliber of vessels affected by the underlying vasculitic process. Pathologically proven necrotizing vasculitis in association with CS was confirmed at postmortem examination alone in 3 patients,[133–135] by examination of subcutaneous nodular tissue and amputated limbs in life, and confirmed at postmortem examination in another patient[136]; and by examination of biopsy tissue alone in 10 living patients.[133,134,137–141]

Crawford[133] observed 3 patients with systemic necrotizing vasculitis, both whom had headache at onset of CS. Postmortem examination in the first patient (case 1) with frontal headaches and IK before onset of vestibuloauditory symptoms showed necrotizing arteritis involving small arteries and arterioles of the brain, gastrointestinal tract, and kidneys, in addition to cerebral edema and petechial hemorrhages.

Eisenstein and Taubenhaus[134] reported a second postmortem description of CS and systemic vasculitis without preceding headache, in association with terminal heart failure (case 1), in which fibrinoid necrosis of an affected aortic valve extended to the endocardium and intimal surface of the aorta. There was marked intimal thickening

and fibrosis of several small intramural branches of the coronary arteries combined with dense perivascular infiltration by lymphocytes and polymorphonuclear cells.

Fisher and Hellstrom[136] described a third subject with CS and systemic vasculitis, also without obvious headache, in whom initial biopsy of a subcutaneous nodule showed marked infiltration by polymorphonuclear cells throughout all coats and into the surrounding tissue of a large vein and artery, as well as in smaller arteries by a severe lymphocytic infiltrate. The amputated extremities of the same subject showed intense inflammatory cell infiltration and necrosis of the media of the distal tibial and smaller muscular arteries, with focal fibrous intimal thickening; and, rarely, organized thrombi reminiscent of thromboangiitis obliterans or Buerger disease. Postmortem examination of the eyes and ears demonstrated IK, degeneration of the vestibular and spiral ganglia, edema of the cochlea and semicircular canals, and inflammation of the ligamentum spirale, without vascular changes. Vasculitic lesions noted in the amputated extremities were seen in some viscera.

Cogan and Dickerson[135] described a subject with CS and fatal aortitis, also without preceding headache, noting severe thickening of small arteries of the aortic wall with reduplication of the elastica, destruction of smooth and elastic tissue of the media, and infiltration of the intima and media by polymorphonuclear and mononuclear inflammatory cells. Vollertsen and colleagues[142] noted generalized aortic dilatation of the aorta at postmortem examination in 1 subject without mention of necrotizing vasculitis. In an analysis of vessels other than the aorta in 5 subjects, 2 had vasculitis in biopsy tissue of small muscular femoral arteries at the time of femoral arterial thrombosis, 1 had chronic venous inflammation at the site of thrombosis of the right arm, 1 had intimal fibrosis suggestive of resolved vasculitis, and 1 had a normal temporal artery biopsy.

Darougar and colleagues[143] described a child with CS, antibodies to *Chlamydia psittaci*, and sudden cardiac arrest in whom postmortem examination showed destructive atrial and coronary artery, and aortic lesions in association with lymphocytic inflammation of the intima but without frank vasculitis.

Lunardi and colleagues[144] used pooled IgG from 8 subjects with CS to screen a random peptide library to identify possible autoantibodies in CS in a peptide library. One isolated immunodominant peptide, which showed similarly with the autoantigens Systemic Sjögren's SAntibody (SSA), also called anti-Ro, and reovirus III major core protein lambda 1, and the peptide sequence of tyrosine phosphatase-1 (CD148 [clusters of differentiation]), expressed on the sensory epithelia of the inner ear and on endothelial cells. IgG antibodies against the peptide purified from patient sera recognized CD148 protein, bound human cochlea, and inhibited proliferation of cells expressing CD148. The same antibodies bound connexin 26, gene mutations of which lead to congenital inner-ear deafness, and were able to induce the feature of CD in mice.

Early recognition of the diagnosis of childhood CS is important in instituting corticosteroid therapy to preserve hearing, especially when hearing loss is a later occurrence. A combination of oral and intravenous corticosteroids may be considered in children who partly but not fully improve. Chaudhuri and colleagues[145] described a 7-year-old boy who was promptly diagnosed after concomitant headache, IK, and sensorineural hearing loss occurred, leading to commencement of prednisone 1 mg per kilogram per day and prednisolone acetate ophthalmic 1% solution, leading to resolution of IK. The addition of pulse intravenous methylprednisolone at 30 mg per kilogram per day for 5 doses in conjunction with a 1-month course of prednisone, however, led to marked improvement in hearing loss.

Chronic auditory and ophthalmologic childhood disease may occur before recognition of CS, similarly warranting aggressive management. Orsoni and colleagues[146] described 2 children with chronic ocular inflammation and hearing loss prompting consideration of CS. A 6-year-old boy had recurrent bilateral keratoconjunctivitis, followed at age 13 years by sudden hearing loss, headache, asthenia, and recurrent arthralgia, leading to the diagnosis of CS. A 3-year-old boy had chronic bilateral uveitis from age 6 months, followed by sudden hearing loss at age 5 years, accompanied by headaches and arthralgia, prompting consideration of CS. Both children were treated with combination (noncorticosteroid) immunosuppressant for 6 months, leading to resolution first of headache and arthralgia in the first 2 months in both children, followed by improvement in ocular inflammation and auditory symptoms in the first child but not in the other.

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