Epidemiology of Neurovasculitis

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KEYWORDS

• Global • Burden • Vasculitis

KEY POINTS

- 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 calibers.
- The Chapel Hill Consensus Conferences have provided consensus on nosology and definitions for the commonest forms of adult-onset vasculitides.
- The Pediatric Rheumatology European Society and the European League against Rheumatism have proposed specific classification criteria for the commonest childhood vasculitides.
- Although not included in the 2013 Global Burden of Disease Study, adult and childhood vasculitides are a significant source of morbidity and mortality globally.
- Management relies on the use of immunosuppressant and immune modulatory therapy.

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 calibers. 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 on the vessels involved and provides a scheme for the neurologic aspects thereof (**Box 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 involvement of intraparenchymal arteries, arterioles, capillaries, veins, and venules, with a disease mechanism related to antineutrophil cytoplasmic antibody (ANCA) and immune

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Box 1
Classification of primary systemic vasculitides

Large vessel vasculitis

Giant cell arteritis

Takayasu arteritis

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
- Cryoglobulinemia
- IgA vasculitis (Henoch-Schönlein)
- Hypocomplementemic urticarial vasculitis (anti-C1q)

Variable vessel vasculitis

Behçet disease

Cogan syndrome

Single-organ vasculitis

Primary CNS vasculitis

Idiopathic aortitis (IgG4)

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, and microscopic polyangiitis (MPA) (microscopic polyarteritis), whereas vasculitic disorders associated with immune complexes include immunoglobulin A (IgA) vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryglobulinemic 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 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 cause, 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 central nervous system (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 with 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 on vessel size, similar to the CHCC nomenclature.[2] In 2008, the EULAR, PRES, and the Pediatric Rheumatology International Trials Organization reported their methodology and overall clinical, laboratory, and radiographic characteristics for several childhood systemic vasculitides[5] followed by a final validated classification.[6]

HISTORICAL ASPECTS

The early history of vasculitis is debatable, but one fact is clear, the earliest patients with vasculitis appeared to have had neurologic involvement. It is thought that 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. The first American patient was described in 1908.[7] This 35-year-old man presented 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, aneurysmal 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, 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 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. Although early publications used the term infantile PAN, 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.

Contemporaneously, SVV syndromes were recognized and differentiated from PAN. Early investigators[11–13] described MPA among 34 patients that 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 5 deaths were attributed to CNS involvement by vasculitis during periods of disease at 4 and 8 months, respectively; however, that could not be confirmed because postmortem examinations were not performed. The disorder was later reclassified by the CHCC[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 2 organs most affected, with variable systemic necrotizing vasculitis.

The first patient with EGPA was probably case 1 of Lamb[14] 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[15] 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 that was found within vessel walls and in extravascular connective tissue of major organ systems, leading to cardiac, pulmonary, gastrointestinal, skin, peripheral nervous system (PNS), and CNS manifestations. In 1977, Chumbley and coworkers[16] 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. 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[17] emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils, and extravascular granulomas suggested by Churg and Strauss[15] occurred contemporaneously in only a minority of patients. Moreover, such histologic findings could be encountered as well 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 investigators 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)[18] developed criteria for the classification of EGPA that included ascertainment of 4 or more of the following: asthma, eosinophilia of greater than 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[19] described the syndrome of GPA that included granuloma in the nasopharynx, sinuses, and lower respiratory tract with focal segmental glomerulonephritis and disseminated SVV. Nervous system involvement in GPA was found in up to one-half of patients. Fauci and colleagues[20] and Hoffman and colleagues[21] at the National Institutes of Health (NIH), 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 (MNM) with CNS abnormalities in 8% to 10% of patients. CNS involvement included stroke, cranial nerve abnormalities, and diabetes insipidus. Fauci and colleagues[20] 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.[21] The astute conclusion based mainly on pathologic features was later substantiated by their common association with ANCA, but not so for PAN.

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 and colleagues[22,23] separated the hypersensitivity vasculitides from allergic granulomatous angiitis, rheumatic arteritis, 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. Hypersensitivity vasculitis was likened to the anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits. Osler[24] first appreciated the relation of purpuric attacks to cerebral manifestations in the report of a patient with transient hemiparesis, and 3 others with potentially fatal cerebral hemorrhages. Gairdner[25] described HSP among 12 patients with anaphylactoid purpura, including one child who developed rash, colic, melanotic 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[26] described the clinicopathological findings in 2 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[27,28] was circumstantially convincing enough to substitute the term IgAV for HSP.

Wintrobe and Buell[29] described cryoglobulinemia in a patient with progressive frontal headache, facial pain, Raynaud symptoms, recurrent nosebleeds, exertional

dyspnea, palpitation, and changes in the eyegrounds 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 and differed from Bence-Jones proteinuria of other myeloma patients. Lerner and Watson[30] noted the association with purpura, and later Lerner and Watson[31] described its occurrence in 10% of pathologic sera.

Recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions that lasted 24 hours 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[32]; however, 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 and human C1q, 2 patients consistently produced bands against the former, and 2 others reacted strongly with purified C1q. Skin biopsies showed leukocytoclasia characteristic of necrotizing vasculitis in one patient; anaphylactoid purpura in 2 others, and mild nonspecific perivascular infiltration another. Immunofluorescence of skin specimens performed in 3 patients showed fixation of Ig in the patient with necrotizing vasculitis, whereas in 2 others with a pathologic picture of anaphylactoid purpura or nonspecific dermal infiltrate, immunofluorescence was negative. Renal biopsy in 2 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, which 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[33] characterized C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among 4 additional patients. Wisnieski and Naff[34] 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. Named for the site of granulomatous giant cell inflammation and vessel involvement, those with biopsy-proven temporal arteritis and associated blindness due to vasculitic involvement of ophthalmic and posterior ciliary vessels were classified as cranial arteritis. The occasional finding of giant cell lesions along the aorta, along its branches, and in other medium- and large-sized arteries at autopsy in other patients warranted the additional diagnosis of generalized GCA. The pathologic heterogeneity of temporal arteritis was further demonstrated by the finding of intracranial lesions in several patients who also qualified for the diagnosis of granulomatous angiitis of the nervous system (GANS).[35] PNS involvement in GCA was exceedingly uncommon in which early 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 eventuating in vascular thrombosis, intimal proliferation, and fibrosis. 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.[36] This pulseless disease and occlusive thromboaortopathy or TAK disease 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 local signs of vasculitis were recognized in up to two-thirds of patients. It is the commonest LVV among Asian women.

One other form of inflammatory aortic disease or aortitis was coming to light in the surgical literature with equally broad and far-reaching implications for concepts of autoimmunity. In 1972, Walker and colleagues[37] 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 limbs and presence of peripheral pulses, less likelihood of unusual presenting features, elevated erythrocyte sedimentation rate (ESR), and lack of calcification on preoperative abdominal radiographs. In 1985, Pennell and coworkers[38] reported inflammatory aortic or iliac aneurysms in 4.5% of 2816 patients undergoing repair for abdominal aortic aneurysm from 1955 to 1985. Ultrasound and computed tomographic 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 2001, Hamano and colleagues[39] noted a high concentration 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[40] 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, 3 important observations were made. First, Sakata and colleagues[41] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues[42] concluded that IAAA was an IgG-related disease (IgG4-RD) together with RPF. Third, Ito and colleagues[43] 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 were aortic and periaortic lesions of an IgG4-RD. One year later in 2009, Khosroshahi and colleagues[44] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels with progression to autoimmune pancreatitis, and Stone and coworkers[45] 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[46] recognized the disorder of relapsing aphthous ulcers of the mouth, eye, and genitalia, the clinicopathological details of which were described in later detail by Behçet and Matteson[47,48] in 2 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. The first well-documented American patient with nervous system involvement of BD was described by Wolf and coworkers,[49] 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[50] 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 a severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis (IK) and explosive Menière disease was made. In retrospect, he was probably the first reported patient with CS of nonsyphilitic IK. Vestibuloauditory symptoms were later described by Cogan[51] after whom CS was named. In a review of 30 patients seen at the National Eye Institute of the NIH by Cogan,[51] 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 to 6 months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of 1 to 3 months, certainly no longer than 2 years.

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.[52,53] Such studies indicated that proximal stretches of each of the major nerves were supplied 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 microvessels, which by their repeated division and anastomosis outlined an unbroken vascular net that assured continuous vascular supply. Because 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[54] 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[55] ascribed progressive weakness and sensory loss in the arms and subsequently in the legs distally from the knees in their patient 8 with extensive MNM 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.

Diverse syndromes of adult and childhood primary CNS vasculitis with very different clinical presentation, histopathology, and prognosis have been recognized. Primary CNS vasculitis indicative of granulomatous angiitis of the nervous system (GANS) was first described by Harbitz in 1922[56] 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 comprising lymphocytes, multinucleate giant cells, and epithelioid cells with vessel necrosis and extension into the brain along involved veins and arteries of varying calibers. Over the ensuing quarter century, additional patients were reported under the rubric of allergic angiitis and granulomatosis, GCA, and sarcoidosis. The identification of angiographic beading and a sausagelike appearance of cerebral vessels at sites of presumed arteritis captured the attention of Cupps and Fauci[57] in other patients with 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 3 patients with IACNS defined angiographically, and another with biopsy-proven GANS of the filum terminale, led to prospective diagnostic and therapeutic recommendations. 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 term emphasizing the granulomatous histology. Giant cells and epithelioid cells, usually found at autopsy in GANS, were an inconsistent finding in a meningeal and brain biopsy, and therefore, were considered unnecessary for antemortem diagnosis. In the same year of 1988, Calabrese and Mallek[58] proposed criteria for the diagnosis of primary angiitis of the central nervous system vasculitis (PACNS), whereas Younger and colleagues[59] contemporaneously described the limits of granulomatous angiitis of the brain and GANS. The past quarter century has witnessed an expansion in the present understanding of primary CNS vasculitis in children and adults.

EPIDEMIOLOGY

The publication of recent genome-wide association studies (GWAS) has brought awareness to the understanding and susceptibility factors and designated genetic risk loci for many of the vasculitides supporting the interplay of immunologic, environmental, and shared genetic susceptibility in the etiopathogenesis of these disorders. They show a very complex cause in which both environmental and genetic factors contribute to the predisposition and clinical phenotype. With an incidence and prevalence of primary systemic vasculitis that is steadily increasing, and an impact that is being reported worldwide in developed countries, governments, nongovernmental organizations, and other key stakeholders have not developed sufficient programs for the prevention and surveillance of these disorders. This section focuses on the epidemiology of the major large-, medium-, and small-sized vessel vasculitides shown in **Box 1**. There is a recent review of the epidemiology and classification of primary systemic vasculitides.[60]

Large Vessel Vasculitis

Giant cell arteritis

Background GCA is a chronic granulomatous vasculitis of large- and medium-sized vessels that frequently affect the thoracic aorta and its branches. Both GCA and

PMR, a related disorder, are probably polygenic disease in which multiple environmental and genetic factors influence susceptibility and severity. For the purpose of epidemiologic studies and in clinical practice, GCA has been classified by 5 discriminatory features that include age greater than 50 years at onset, new onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, ESR greater than 50 mm/h, and biopsy, including an artery showing necrotizing arteritis, characterized by a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells. Unrecognized and therefore untreated or inadequately treated, there is a high likelihood of large artery complications, including increased morbidity and mortality, especially due to aortic aneurysm and dissection, and large artery stenosis.

Epidemiology The epidemiology of GCA was reviewed by Gonzalez-Gay and colleagues.[61] Since 2000, relatively large cohort studies exemplifying the epidemiologic aspects of GCA in different regions of the world were reported from Australia, Germany, Israel, Japan, New Zealand, Norway, Spain, Sweden, the United Kingdom, and the United States (US).[62–74] Smaller nonepidemiological case series of patients with GCA reported in Brazil, Saudi Arabia, and Mexico exemplifying the incalculably low incidence,[75–77] and similarly, in Japan[66] where a nationwide survey of GCA was untaken despite the relatively low incidence, demonstrated a prevalence of 1.47 cases per 100,000 population. The highest known incidence of GCA was reported without major differences between northern and western Norway compared with those of Southern Norway. By comparison, very low incidence rates of GCA were found in Saudi Arabian, Mexican, and Japanese populations. The global incidence and prevalence of GCA are summarized in **Table 1**.

According to Herlyn and colleagues,[64] who studied inhabitants of the city of Lubeck and the rural region of Segeberg in northern Germany, GCA was the most prevalent systemic vasculitis in 2006 with 171 per million inhabitants followed by GPA with a prevalence rate of 98 per million inhabitants. The prevalence rate of GCA doubled in northern Germany from in those aged 50 years or more from 240 to 440 per million inhabitants between 1994 and 2006, and from 87 to 171 per million population overall. There was a difference in period prevalence and incidence rates between the urban and rural areas, with an incidence of GCA of 27.1/million/y in Lubeck compared

Table 1
Global incidence and prevalence of giant cell arteritis

Authors[a]	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Kobayashi et al	Japan	1997	1.47	—
Herlyn et al	Germany	2006	2.71	171 per 10^6
Dunstan et al	Australia	1992–2011	3.20	—
Bas-Lando et al	Israel	1980–2004	9.50	—
Gonzalez-Gay et al	Spain	1981–2005	10.13	—
Gonzalez-Gay et al	New Zealand	1996–2005	12.7	—
Mohammad et al	Sweden	1997–2010	13.3	—
Salvarani et al	US	1950–1999	18.8	—
Smeeth et al	UK	1990–2001	22.0	—
Haugeberg et al	Norway	1992–1996	27.50	—
	Norway	1992–1996	36.70	—
	Norway	1992–1996	32.8	—

[a] See text.

with 14.7/million/y in Segeberg ($P = .2$), whereas respective prevalence rates were 237 and 116 per million population overall, and 586 and 311 per million inhabitants aged 50 years or more. Differences in incidence between regional populations of the world may be explained in part by immunogenetic and environmental factors that account for differences in susceptibility and may contribute to severity and outcome. In 1980, Kemp and coworkers[78] performed HLA tissue-type antigen determinations for A-B, C-antigens in the sera of 88 mixed cases of clinical GCA and polymyalgia rheumatica (PMR) with an overwhelming representation of women and only sporadic familial occurrence, demonstrating no significant deviation from a sample compared with 3164 blood donor controls. In 1983, Armstrong and colleagues[79] studied 55 patients with GCA and PMR, typed for HLA A, B, C, and DR loci, noting a significantly increased frequency of DR4, Cw3, and Cw6, with the increase in Cw3 possibly attributed to linkage disequilibrium to DR4. Among 128 DNA samples for 128 patients and 145 ethnically matched controls in a case-control association study to determine whether those with patients with GCA and PMR sample from Lugo in northwestern Spain exhibited identical HLA class II associations, Dababneh and colleagues[80] found that the association of HLA-DRB 1*0401 and GCA reached statistical significance in the total GCA group of patients, less so for DRG1*0101 and *0102. An association was also observed between the RA DRB1 shared epitope (SE) and GCA that was primarily accounted by the presence of a single copy of the SE; moreover, an SE-bearing allele of DRB1 was observed in those with jaw claudication and visual manifestations. The genetic susceptibility to GCA has been supported by the contribution of shared HLA class II gene polymorphisms in mannose-binding lectin variant alleles, in DR4, DR3, Cw3, and MHC class I and HLA-B gene polymorphisms.[81–91]

Takayasu Disease

Background

In contrast to GCA, TAK occurs in those less than 40 years of age and presents with large vessel-sized vasculitis of the aorta and its branches. For the purpose of epidemiologic studies, the case definition has generally followed the ACR 1990 criteria for the classification of TAK.[92] An understanding of the inflammatory lesions in TAK, like that of GCA, has been advanced by immunologic studies, revealing a clearer understanding of the pathophysiology, which may be impacted by the genetic background of different global regions. The inflammatory cell infiltrate in aortic tissue specimens of affected patients is composed of neutrophils, macrophages, $CD4^+$, and $CD8^+$ T cells, natural killer (NK) cells, and macrophages. Infiltrating $\alpha\delta$T cells and NK cells appear to facilitate endothelial cell apoptosis through production of perforin and killer cell lectinlike receptor subfamily K. The latter activating C-type lectin family receptor triggers NK cells and costimulates $CD8^+$ α/β T-cell receptor + T cells, whereas $CD4^+$ Th1 cells that secrete interferon-γ promote giant cell and granulomatous lesion formation. Peripheral T cells, notably Th1 and Th17, contribute to the pathophysiology of GCA and TAK as do major histocompatibility complex class (MHC) I and II molecules and endothelial intracellular adhesion molecules, expressed in tissue lesions of the aorta with TAK.

Epidemiology

Two GWAS conducted in TAK identifying 379 UK cases and 1985 controls and 451 US/Turkish cases and 1115 controls, respectively,[93,94] noted strong associations with *IL12B* located at the 5q33.3 chromosome locus (rs6871626), and susceptibility to the Max-like protein X (*MAX*) gene transcription factor-like 4 positioned at the 17q21.2 chromosome locus (rs665268), whereas those in the United Kingdom alone

exhibited independent associations at the 6p21.32 chromosome locus in *HLA-DQB1/HLA-DRB1* (rs113452171; rs189754752). *HLA-DQB1* specifies the autoimmune response against insulin-producing islet cells that leads to insulin-dependent diabetes mellitus, whereas the function of *HLA-DRB1* is to present processed foreign antigens to T cells. The US/Turkish group reported another susceptibility locus at the Fc fragment of IgG, low affinity IIa and IIIa receptor (*FCGR2A/3A*) at the 1q23.3 chromosome locus (rs10919543), leading to increased mRNA expression of *FCGR2A*, and proteasome-assembling chaperone 1 (*PSMG1*). With receptors present on monocytes, macrophages, neutrophils, NK cells, and T and B lymphocytes, *FCGR2A/3A* play an essential role in the protection of the organism against foreign antigens by removing antigen-antibody complexes from the circulation and participate in diverse functions such as phagocytosis of immune complexes and modulation of antibody production by B cells. Located at the 21q22.2 chromosome locus, *PSMG1* is involved in the maturation of the mammalian 20S proteasomes with a yet clear implication for TAK.

The global incidence and prevalence of TAK is summarized in **Table 2**. Watts and colleagues[95] reviewed the primary care UK General Practice Research Database and the secondary care–based Norfolk Vasculitis Register from 2000 to 2005. With a population of 445,000, 16 cases with a first diagnosis of TAK were identified with an annual incidence of 0.8 per million. The annual prevalence of TAK was 4.7 per million, with an increase during the course of the study period from 3.6 to 6.3 per million. Mohammad and Mandl[96] studied 3 health care districts of southern Sweden with a total population of 983,419 as of 2011 to identify incident cases of TAK among 5 hospitals in the study area and in all private Rheumatology clinics between 1997 and 2011, noting 13 cases fulfilling the ACR 1990 criteria for TAK. Among them, 8 were of Swedish ancestry, 1 Asian, 2 Arabs, 1 African, and 1 northern European descent. The annual incidence rate was estimated at 0.8 per million for the whole population. The point prevalence as of June 2012 was estimated at 13.2 per million for the whole population. The incidence findings were comparable with the reported incidence of 0.8, 0.5, and 0.4 per million, respectively, in previous studies from Sweden, Germany, and eastern Denmark,[97–99] although the prevalence of TAK was somewhat higher than the prevalence of 6.4 per million previously reported in Sweden.

MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis Nodosa

Background

The ACR 1990[100] and the CHCC[2] criteria for PAN have been used in the case definitions of adult cases in most epidemiologic studies as well as the criteria of the Turkish Pediatric Vasculitis Study Group[4,101] for pediatric cases, stratified into cutaneous and classic PAN. This author was unable to find GWAS for PAN.

Table 2
Global incidence and prevalence of Takayasu arteritis

Authors[a]	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Watts et al	UK	2000–2005	0.8	4.7
Mohammad et al	Sweden	1997–2011	0.8	—
Waern et al	Sweden	1969–1976	0.8	6.4
Reinhold-Keller et al	Germany	1998–2000	0.5	—
Dreyer et al	Demark	1990–2009	0.4	—

[a] See text.

Epidemiology

The global incidence and prevalence of PAN are shown in **Table 3**. Mahr and colleagues[102] defined PAN as a predominantly medium-sized vessel that occurs alone or in association with hepatitis B virus (HBV) infection, with angiographically documented aneurysms or histologic proof of vessel inflammation, without glomerulonephritis, lung hemorrhage, or ANCA positivity. An analysis of the prevalence of PAN, MPA, GPA, and EGPA in Seine-St. Denis, a northeastern suburb of Paris, included a population of 1,093,515 adults, 28% of were of non-European ancestry. Their capture-recapture study of the entire calendar year of 2000 identified cases by general practitioners, departments of all of the public hospitals, 2 large private clinics, and the National Health Insurance System. The prevalence of PAN was estimated at 30.7 per million adults; however, previous studies based on the most restrictive and biopsy-dependent CHCC[2] criteria estimated PAN to be 9 per million adults, in comparison to 33 per million based on the less specific ACR criteria[100] that fail to discriminate between MPA and PAN. The total prevalence estimate for all disorders was 90.3 per million, which substratified for geographic origin showed a 2-fold higher incidence rate for subjects of European than non-European ancestry, respectively, 104.7 compared with 52.5 per million. Not more than 30% of the PAN cases appeared to be HBV-related with most diagnosed during the 1980s, suggesting that the reported incidence of HBV-associated PAN of 77 per million so noted in a small population of Alaskan Eskimos with high rates of HBV infection[103] was currently decreasing as a consequence of vaccination campaigns and the improved safety of blood products. Mohammad and colleagues[104] studied incident cases of PAN, GPA, MPA, and EGPA in 2 health care districts of South Sweden of central and southwest Skåne containing 14 municipalities with a population of 641,763 for the period 1997 to 2006 from hospital databases identifying 144 cases of primary systemic vasculitis, of which 6 were PAN. The annual incidence rates were 21.8 per million for all patients and 0.9 per million for PAN. Watts and colleagues[105] studied incident cases of PAN, GPA, MPA, and EGPA in 2 regions of Europe, among general medical practices of the Norwich Health Authority (NHA) in Norfolk, UK covering 413,500 patients, and in the referral center of Lugo, Spain at the Hospital Xeral-Calde, with a population of 250,000 people between 1988 and 1998, noting an overall incidence of primary systemic vasculitis that was 18.9 Norwich compared with 18.3 per million in Spain, with a higher incidence of PAN in Norwich than in Spain, 9.7 versus 6.2 per million, respectively. Omerod and Cook[106] studied the prevalence and incidence for primary systemic vasculitides for the two 5-year periods of 1995 to 1999, and 2000 to 2004, in

Table 3
Global incidence and prevalence of polyarteritis nodosa

Authors[a]	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Jennette et al	US	2012	—	30.7
Lightfoot et al	US	1990	—	9.0
Mohammad et al	Sweden	1997–2006	0.9	—
Watts et al	UK[b]	1988–1998	9.7	—
	Spain[c]	1988–1998	6.2	—
Omerod & Cook	UK[a] + Spain[b]	1995–1999	2.3	—
	UK[a] + Spain[b]	2000–2004	1.1	—

[a] See text.
[b] Norwich.
[c] Lugo.

the Australian Capital Territory and the surrounding rural regions. Altogether, 41 cases of primary systemic vasculitides including PAN, GPA, MPA, and EGPA were identified between 1995 and 1999, and 67 between 2000 and 2004. Their study[106] yielded a prevalence of 95 and 148 per million, with a similar annual incidence of 17 per million for Norwich, UK and Lugo, Spain, and disease-specific incidences for PAN of 2.2 and 1.1 for the 2 successive periods.

Kawasaki Disease

Background

KD, or mucocutaneous lymph node syndrome, is an acute, self-limited systemic vasculitis of medium- and small-sized vessels occurring predominantly in children aged 6 months to 5 years. It is the second commonest childhood vasculitis and the leading cause of acquired childhood heart disease in developed countries. The distribution is worldwide with an incidence in Japanese populations 10- to 15-fold greater than in Caucasians. Before revision of the criteria for KD, the classification was based either on Japanese[107] or on the American Heart Association (AHA) classification.[108] The former criteria, used in Japanese epidemiologic studies of KD, required the presence of 5 of the following 6 criteria, including characteristic fever, bilateral conjunctivitis, changes in lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and cervical lymphadenopathy, whereas those of the latter criteria used in American and Caucasian studies generally required fever plus 4 of the remaining 5 criteria. Two recent modifications to the criteria for KD made by the EULAR/PRES consensus criteria conference,[4] which may alter the carriage of epidemiologic studies in the future, included the addition of perineal desquamation describing changes in the extremities; moreover, fewer than 4 of the remaining 5 criteria were deemed necessary in the presence of fever and coronary arterial involvement demonstrated by echocardiography. To emphasize pediatric vasculitis disease even before retrospective and prospective epidemiologic studies, a half century of 1,335,045 postmortem examinations from the Annual of Pathological Autopsy Cases in Japan from 1958 to 2008 identified 380 cases of vasculitis in children, more than one-half of which were KD and other disease entities, including unclassified vasculitis, PAN, purpuric vasculitis, TAK, and others. Moreover, the postmortem findings for 24 of 125 childhood vasculitides performed before 1976 and diagnosed as non-KD were later consistent with KD.

Epidemiology

The global incidence and prevalence of KD are shown in **Table 4**. Saundankar and colleagues[109] identified hospitalized patients in Western Australia with the diagnosis of KD, noting a steady increase in the mean annual incidence from 7.96 between 1990 and 1999 to 9.34 per 100,000 children aged less than 5 years between 2000 and 2009, with the peak incidence of 15.7 per 100,000 in 2005. Lin and colleagues[110] identified hospitalized discharges with the diagnosis of KD in Ontario, noting a mean annual incidence of 26.2 per 100,000 for less than 5 year olds, and 6.7 per 100,000 for 5- to 9-year-old children, and 0.9 per 100,000 for those 10 to 14 years old, that steadily increased from 14.39 to 26.24 per 100,000 from 1995 to 2006. Ma and colleagues[111] studied all children sent to one of 50 hospitals in Shanghai, noting a mean annual incidence of 46.32 per 100,000 children less than 5 years of age that steadily increased from 36.78 to 53.28 between 2003 and 2007. Li and coworkers[112] identified cases of KD less than 5 years of age among 212 hospitals in the Sichuan Province, noting a steady increase in the incidence in the children from 8.57 to 9.81 per 100,000, with an average incidence throughout the latest 5 years of 7.06 per 100,000. Du and coworkers[113] conducted a hospital-based survey of KD in 45 Beijing

Table 4
Global incidence and prevalence of Kawasaki disease

Authors[i]	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Saundankar et al	Australia	1990–1999	7.96 per 10^6	—
	Australia	2000–2009	9.34	—
	Australia	2005	15.7	—
Lin et al	Canada[a]	1995–2006	26.2[b]	—
	Canada[a]	1995–2006	6.8[c]	—
	Canada[a]	1995	14.39[d]	—
	Canada[a]	2006	26.24[d]	—
Ma et al	China[e]	2003–2007	46.32[b]	—
	China[e]	2003	36.78[b]	—
	China[e]	2007	53.28[b]	—
Li et al	China[f]	1997–2001	7.06[b]	—
	China[f]	1997	8.57[b]	—
	China[f]	2001	9.81[b]	—
Du et al	China[g]	2000–2004	49.4[b]	—
	China[g]	2000	40.9[b]	—
	China[g]	2004	55.1[b]	—
Fischer et al	Denmark	1981–2004	4.5–5.0	—
Holman et al	Hawaii	1996–2006	50.4	—
Ng et al	Hong Kong	1994–1997	26.0	—
	Hong Kong	1994–1997	39.0	—
Singh et al	North India	1994	0.51	—
	North India	2007	4.5	—
Nakamura et al	Japan	2009	206.2	—
	Japan	2010	239.6	—
Park et al	Korea	2006–2008	113.1	—
	Korea	2006	108.7	—
	Korea	2008	113.1	—
Schiller et al	Sweden	1990–1992	2.9	—
	Sweden	1990–1992	6.2[b]	—
Lue et al	Taiwan	2006	66.24[b]	—
Huang et al	Taiwan	2003–2006	153.0	—
	Taiwan	2003–2006	69.0[b]	—
Harnden et al	UK	1991	4.8	—
	UK	2000	9.2	—
Holman et al	US	2006	20.8	—

[a] Ontario.
[b] Age less than 5 years.
[c] Age 5 to 9 years.
[d] Age 10 to 14 years.
[e] Shanghai.
[f] Sichuan Province.
[g] Beijing.
[i] See text.

hospitals identifying 1107 KD patients with a mean annual incidence of 49.4 per 100,000 less than 5-year-old children and a steady increase from 2000 to 2004 that varied from 40.9 to 55.1 per 100,000. Fischer and colleagues[114] performed a population-based hospital study of KD children in Denmark from 1981 to 2004 identifying 360 children younger than 15 years and noting a mean annual incidence of 4.5

to 5 per 100,000 person-years with a gradual increase over the study period. Holman and colleagues[115] conducted a retrospective analysis of children aged less than 18 years, notably those less than 5 years, hospitalized in Hawaiian hospitals from 1996 to 2006, noting a mean annual incidence of 50.4 per 100,000 children less than 5 years of age ranging from 45.5 to 56.5. Japanese children who had the highest mean annual incidence of 210.5 per 100,000 exceeded the mean Asian and Pacific children annual incidence of 62.9 per 100,000 children, followed by native Hawaiian children with an incidence of 86.9, other Asian children with an incidence of 84.9, and Chinese children with an incidence of 83.2 per 100,000, exceeding that of whites with an incidence of KD of 13.7 per 100,000 children. Ng and colleagues[116] conducted retrospective and prospective studies of KD in Hong Kong between 1994 and 1997 and from 1997 to 2000, respectively, identifying 696 children less than 15 years of age and noting a higher incidence of KD in the prospective period (39 vs 26 per 100,000 children). Singh and colleagues[117] analyzed the records of children with KD less than 15 years of age in Chandigarh, North India identifying 196 children. There was an increasing incidence of disease from 0.51 cases to 4.5 cases during the period from 1994 to 2007. Nakamura and coworkers[118] conducted the 21st nationwide survey of 23,730 KD children treated between 2009 and 2010 and noted an annual incidence rate of 206.2 and 239.6 per 100,000, establishing the highest rate ever for Japan in 2010. Park and coworkers[119] surveyed Korean hospitals for the period of 20062008 and identified 9039 KD children, noting an outbreak rate of 108.7 in 2006 that increased to 113.1 per 100,000 in 2008, with a mean annual incidence of 113.1 per 100,000 children. Schiller and contributors[120] examined a national prospective study over a 2-year period from 1990 to 1992 of KD children recording an annual incidence rate of 2.9 per 100,000 children younger than 16 years, and a rate of 6.2 per 100,000 children less than 5 years of age. Lue and colleagues[121] conducted nationwide hospital surveys of KD in Taiwan in 2006, noting an incidence of 66.24 per 100,000 children less than 5 years of age representing the highest of any preceding survey. Huang and colleagues[122] investigated the epidemiology of KD using national insurance claims between 2003 and 2006, noting an annual incidence of KD of 153 per 100,000 in less than 1-year-old children with an overall incidence of 69 per 100,000 children aged less than 5 years. Harnden and colleagues[123] analyzed hospital admission data in England for the period 1991–2000 of childhood KD, identifying 2215 emergency admissions representing an incidence that increased from 4.8 to 9.2 per 100,000 in this time period. Holman and coworkers[124] performed a retrospective analysis of emergency childhood admission in the United States using the Kids' Inpatient Database and a Nationwide Inpatient Sample for 2006 noting an incidence of 20.8 per 100,000 children.

Eight GWAS and linkage analysis studies of KD[125–129] have led to susceptibility genetic loci for KD. Onouchi and colleagues[125] performed a nonparametric GWAS of sibling pairs on 75 full sibling pairs, 3 sibling trios, and 1 half-sibling identifying candidate gene locus at 12q24 (maximum logarithm of odds [LOD] score = 2.69), with possible linkage to 4q35, 5q35, 5q34, 6q27, 7p15, 8q24, 18q23, 19q13, Xp22, and Xq27. Moreover, 90 genes were thought to be expressed in organs related to immune function among the 128 genes that mapped within 1 LOD confidence interval of the linkage position on chromosome 12. Burgner and coworkers[126] on behalf of the International Kawasaki Disease Genetics Consortium investigated genetic determinants of KD susceptibility in a GWAS of 119 Caucasian KD patients and 135 matched controls using the AHA criteria. The investigators[126] noted associations with 40 single-nucleotide polymorphisms (SNP) and 6 haplotypes, however, most significantly at *NAALADL2* (rs17531088) and *ZRHX3* (rs7199343). The latter,

also known as ATBF1, which encodes a large enhancer-binding transcription factor known to be polymorphic and interactive with several proteins including protein inhibitor of activated signal transducer and activator of transcription-3, is activated by interleukin (IL)-6 involved in innate immune reactivity. The function of the N-acetylated α-linked acidic dipeptidase-like 2 gene, which showed the greatest change in transcript levels between acute and convalescent KD, contributes to Cornelia de Lange syndrome, a multisystem malformation syndrome. Tsai and coworkers[127] conducted a GWAS in a Han Chinese population in 250 KD patients and 446 controls residing in Taiwan. The most strongly associated SNP were detected in 3 novel loci close to the coatomer protein complex β-2 subunits (*COPB2*) gene (rs1873668, rs4243399, rs16849083) as well as in the intronic region of the endoplasmic reticulum amino peptidase 1 (*ERAP1*) gene (rs14981). COPB2 coats non-clathrin-coated vesicles and is essential for Golgi budding and vesicular trafficking, whereas ERAP1 plays a role in trimming peptides to the optimal length for HLA class I presentation cleaving cell surface receptors for proinflammatory cytokines. Kim and coworkers[128] on behalf of the Korean Kawasaki Disease Genetics Consortium conducted a GWAS among 186 Korean KD patients and 600 controls noting susceptibility loci for KD at the 1p31 region and 2p13.3 chromosomal loci. A putative KD susceptibility locus (rs5277409) mapped to chromosome 1p31 and the coronary artery lesion (CAL) locus (rs7604693) mapped to the Pellino 1 protein (*PELI1*) (rs7604693) gene in the 2p13.3 region encoding PEL1, an intermediate component in the signaling cascade initiated by Toll-like receptors and the IL1 receptor (*IL1R*) gene, that are associated with innate and adaptive immune responses. Khor and colleagues[129] performed a GWAS in 2173 KD patients of European and Asian descent, noting 2 significant loci in the Fc fragment of IgG, low-affinity 2A receptor (*FCGR2A*) (rs1801274), and for the rs2233152 SNP near the melanoma inhibitory activity (*MIA*), inositol 1,4,5-trisphosphate 3-kinase C (*ITPKC*) gene. Whereas the FCGR2A, present on monocytes, macrophages, neutrophils, NK cells, T and B cells, participates in the phagocytosis of immune complexes and modulation of antibody production by B cells, ITPKC acts as a negative regulator of T-cell activation through the Ca^{2+}/NFAT signaling pathway, contributing to immune hyperactivity. Lee and coworkers[130] performed a GWAS in 622 KD patients and 1107 controls in a Han Chinese population residing in Taiwan, noting 2 loci significantly associated with KD, including one at the B-lymphoid tyrosine kinase (*BLK*) gene and the other at *CD40*. Whereas the *BLK* gene appears to play an important role in the expression of B-cell signaling, activation, and antibody secretion, *CD40* is instead a member of the tumor necrosis factor receptor superfamily, and its interaction with the CD40 ligand (CD40L) leads to cross-talk integrating strong antigenic signals and microbial stimuli to induce IL-17-producing $CD4^+$ T cells that contribute to inflammation and the development of autoimmune disease. Onouchi and coworkers[131] performed a GWAS in 428 Japanese KD patients and 3379 controls noting significant associations in the *FAM167A-BLK* region at 8p22-23 (rs2254546) in the *HLA* region at 6p21.3 (rs2857151), and in the *CD40* region at 20q13 (rs48130030), also replicating the association of a function SNP of *FCGR2A* (rs1801274). Although ubiquitously expressed, the function of *FAM167A* has not been well characterized. Yan and coworkers[132] analyzed variants of 6 SNP in 358 Japanese KD patients and 815 controls identifying 3, rs1801274, rs2857151, and rs22554546, respectively, corresponding to *FCGR2A, HLA*, and *BLK* genes, noting significant effect and stronger association on KD than single-, 2-, and 3-locus combinations; moreover, a significant association to CAL was noted in KD with high-risk genotypes at both rs1801274 and rs2857151.

SMALL-SIZED VESSEL VASCULITIS

Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Background

Early observations of ANCA differentiated clinicopathological subtypes.[133] 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 involve its catalytic site.[134] An AAV classification appears to better recognize ANCA disease and predict prognosis than other any existing clinical classification system.[135] However, as with other autoimmune disorders, the cause 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. 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 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.[136] An immunofluorescence technique (IFT) has been standard method for routine determination of ANCA in vasculitis using ethanol-fixed human neutrophils as substrate. Two main immunofluorescence patterns are distinguished, a cytoplasmic ANCA and perinuclear ANCA. The 1999 International Consensus Statement on testing and reporting ANCA[137] 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 lacks sensitivity. Capture ELISA is superior in overall diagnostic performance to direct ELISA,[138] but the sensitivity of capture ELISA may be reduced by the capturing antibodies hiding relevant epitopes. 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.[139]

Although the clinical classification of the AAV has been controversial, the European Medicines Agency algorithm has provided 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. As there were no validated diagnostic criteria for AAV, the Diagnostic and Classification Criteria for Vasculitis Study, developed by Watts and colleagues,[140] led to the consensus development and validation of diagnostic criteria by an algorithm to avoid inclusion of patients with other conditions. So defined, Watts

and colleagues noted an annual incidence of 11.3 for GPA and 5.9 per million for MPA, with respective prevalence at the end of calendar year 2008 of 145.9 for GPA and 63.1 per million for MPA. Lyons and colleagues[136] conducted a GWAS in a cohort of 1233 UK subjects with AAV and 5884 controls noting both MHC and non-MHC associations with AAV, with the strongest genetic association with the antigenic specificity of ANCA, not with the clinical syndrome. Those with PR3 ANCA were associated with *HLA-DP* (rs3117242) at the 6p21.32 chromosome locus as well as those encoding α1-antitrypsin (*SERPINA1–SERPINA11*) (rs7151526) at the 14q32 chromosome locus and PR3 (*PRTN3*) (rs62132295) at the 19p13.3 chromosome locus, while anti-MPO ANCA was associated with *HLA-DQ* (rs5000634) at the 6p21.32 chromosome locus. These studies confirmed that the pathogenesis of AAV had a genetic component and that the genetic distinction between GPA and MPA was associated with ANCA specificity. Moreover, the response against the PR3 autoantigen was a central pathogenic feature of PR3-AAV, distinct from MPO-AAV.

Epidemiology

The global incidence and prevalence are summarized in **Table 5**. Watts and colleagues,[141] Omerod and Cook,[106] and Mohammad and colleagues[104] evaluated the epidemiologic aspects of AAV globally in adults. In 2 regions of Europe, Norwich, UK and Lugo, Spain, the incidence rate of GPA in Norwich was 10.6 per million compared with that in Lugo of 4.9 per million for 2008 with virtually equal age distribution of 34.1 per million between aged 45 and 74 years, suggesting that environmental factors might be important in the their etiopathogenesis. In a 10-year study of primary

Table 5
Global incidence and prevalence of ANCA-associated vasculitis

Authors[i]	Country	Study Period	Incidence per 10^6	Prevalence per 10^6
Watts et al	UK	1988–1992	8.7[a]	—
	UK	1988–1992	6.8[b]	—
	UK	1988–1992	1.5[c]	—
	UK	1993–1997	10.3[a]	—
	UK	1993–1997	8.9[b]	—
	UK	1993–1997	3.7[c]	—
Ormerod et al	Australia + UK	1995–1999	8.8[a]	64.3[a]
		2000–2004	8.4[a]	95.0[a]
		1995–1999	2.3[b]	17.5[b]
		2000–2004	5.0[b]	39.1[b]
		1995–1999	2.3[c,d,e]	11.7[c]
		2000–2004	2.2[c]	22.3[c]
Mahr et al	Seine-St. Denis County, Paris	2000	—	23.7[a]
	Seine-St. Denis County, Paris	2000	—	25.1[b]
	Seine-St. Denis County, Paris	2000	—	10.7[c]
Mohammad et al	Sweden	1997–2006	9.8[a]	—
	Sweden	1997–2006	10.1[b]	—
	Sweden	1997–2006	0.9[c]	—

[a] GPA.
[b] MPA.
[c] EGPA.
[d] Capital Territory.
[e] New South Wales.
[i] See text.

systemic vasculitis in the United Kingdom[141] in the NHA from 1988 to 1997, the annual incidence of GPA was 9.7, EGPA was 2.7, and MPA was 8.0 per million during the entire study period; however, a comparison of the period from 1988 to 1992 with 1993 to 1997 showed respective annual incidences toward an increase in all conditions (8.7 for GPA, 1.5 for EGPA, and 6.8 for MPA, compared with 10.3 for GPA, 3.7 for EGPA, and 8.9 for MPA). In a comparison of primary systemic vasculitis in the Australian Capital Territory and southeastern New South Wales between 1995 and 1999, and between 2000 and 2004, Omerod and colleagues[106] noted similar disease-specific incidences for each of the 2 periods, with 8.8 and 8.4 per million for GPA, 2.3 and 5.0 per million for MPA, and 2.3 and 2.2 per million for EGPA in the Australian Capital Territory compared with southeastern New South Wales with a trend for higher values in MPA and GPA in rural areas. A similar relation was found in disease-specific prevalence for each of the 2 periods, with 64.3 and 95.0 per million for GPA, 17.5 and 39.1 per million for MPA, and 11.7 and 22.3 per million for EGPA in the Australian Capital Territory compared with southeastern New South Wales. In incident cases of primary systemic vasculitis identified in Seine-St. Denis County, Paris, Mahr and colleagues[102] estimated the prevalence of GPA 23.7, MPA 25.1, and EGPA 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 (104.7 5 per million) compared with others of non-European ancestry (52.5 per million). Mohammad and colleagues[104] estimated incident cases of GPA, MPA, and EGPA in southern Sweden, respectively, of 9.8, 10.1, and 0.9 per million in a total population of 641,000 between 1997 and 2006, with a progressive increase in age-specific incidence rates over the study period.

IMMUNE COMPLEX VASCULITIS

Cryoglobulinemic Vasculitis

Background

CV is a prototypic immune complex vasculitis. Cryoglobulins reversibly precipitate at temperatures less than 37°C. They are composed of IgG and IgM, complement, lipoprotein, and antigenic protein moieties. They are classified into 3 types with implications for clinical and etiologic specificity. Type 1 is composed of a single monoclonal IgM or IgG antibody; type II, mixed, has monoclonal IgM, possessing activity against polyclonal IgG; and type III has mixed polyclonal and nonimmunoglobulin molecules in the form of immunoglobulin–anti-immunoglobulin immune complexes. Types I and II cryoglobulins are associated with lymphoproliferative diseases, particularly multiple myeloma and Waldenström macroglobulinemia. Type III cryoglobulins are associated with infection and collagen vascular diseases. One subgroup, termed essential mixed cryoglobulinemia (EMC), harbors circulating hepatitis C virus (HCV) RNA and corresponding antibodies in the cryoprecipitate. Type I cryoglobulins cause the hyperviscosity syndrome.

Four vascular lesions are noted in cryoglobulinemia: (1) occlusion of small and large vessels in those with high levels of cryoglobulins of type I or II; (2) bland thrombosis of small arteries and arterioles; (3) endothelial swelling, proliferation, and basement membrane thickening; and (4) leukocytoclastic vasculitis. True vasculitis is occasionally seen, mainly in those with associated PAN. Dermatitis is the most conspicuous feature accompanied by palpable purpura that persists for a week to 10 days, heralded by a sharp or burning sensation. Purpura is noted in all types but is more common with type III and in EMC. PNS and CNS manifestations are more common with types II and III. Renal disease is a major feature of EMC. Hepatic disease is far

more common with this syndrome by virtue of its association with HCV. The appearance of high levels of cryoglobulins in the blood in patients reporting cold sensitivity and vasomotor symptoms led to the presumption that cryoprecipitation is the cause of ischemia of arterioles and capillaries due to hyperviscosity and the direct plugging of small vessels. However, it is now known that the cryoprecipitate, when present, may be tangential to the pathogenesis of the clinical syndrome and even an artifact for several reasons. First, cryoprecipitation occurs in systemic organs of normal temperature. Second, the temperature at which precipitates occur in vitro is far less than that achieved in the body. Third, symptoms do not correlate with serum cryoglobulin levels, viscosity, or cryoprecipitate concentration. Fourth, in EMC in which levels of cryoglobulins are typically quite low, the abnormality can still be explained on the basis of immune-complex deposition. Several factors that may contribute to the clinical manifestations of cryoglobulinemia include intravascular activation of complement and the clotting cascade by aggregated immunoglobulin and immune complexes; secondary vessel wall damage; cold agglutination of erythrocytes; local tissue reaction to precipitated proteins; and vascular endothelial cell proliferation. Nervous system manifestations in types I and II disease are related to vascular occlusion with or without vasculitis. Cryoglobulinemia should be considered in patients with features of characteristic skin lesions, MNM, hyperviscosity, easily coagulable blood, IgM monoclonal paraproteinemia, and risk factors for HCV infection. If found, the presence of cryoglobulinemia will direct the performance of bone marrow studies, nerve biopsy, and studies for HCV and HIV-1 infection, AIDS, occult cancer, infection, plasma cell dyscrasia, and collagen vascular disease.

Epidemiology

This author did not find reports of the global prevalence and incidence of CV. Recognizing the etiopathogenesis of HCV infection in mixed cryoglobulinemia (MC), it is noteworthy that the Global Burden of Disease, Injuries, and Risk Factors (GBD) 2010 that produced age-standardized prevalence estimates for each of 21 GBD regions using a model-based meta-analysis[142] found that the prevalence and number of people with anti-HCV increased from 2.3% (95% uncertainty interval [UI]: 2.1%–2.5%) to 2.8% (95% UI: 2.6%–3.1%) and greater than 122 million to greater than 185 million between 1990 and 2005. The highest prevalences (>3.5%) were found in Central and East Asia and North Africa/Middle East. Cacoub and coauthors[143] noted that the presence of the DR11 phenotype was associated with a significantly increased risk for the development of type II MC in patients with chronic HCV infection. In contrast, HLA-DR7 protected against the production of type II MC, suggesting that host immune response genes may play a role in the pathogenesis of HCVF-associated MC. One GWAS of HCV and CV was reported by Zignego and colleagues,[144] who compared 899,641 SNP compared between cases and controls, noting the most significant association on chromosome locus 6p21.32 at which an SNP rs2071286, located within an intronic region of *NOTCH4*, conferred 2.15 times the odds of having cryoglobulin-related vasculitis within chronically infected patients for each risk allele. The second most significant association was found nearly 400 kilobases within the MHC between *HLA-DRB1* and *HLA-DQA1* at SNP 9461776 (odds ratio = 2.16, $P = 1.16E{-}07$).

Behçet Disease

Background

This disorder is a prototypic VVV characterized by relapsing aphthous ulcers of the mouth, eye, and genitalia. The most widely used diagnostic criteria of BD were

formulated by the International Study Group (ISG)[145] that included recurrent oral ulcerations plus any 2 of genital ulceration, typical 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 patients 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. Although the usual onset of BD is in the third or fourth decade of life, pediatric onset patients have been described. Uluduz and colleagues[146] studied 2 large Istanbul BD cohorts totaling 728 patients, ascertaining and comparing pediatric-onset (26 patients) and adult adult-onset (702 patients) neurologic Behçet disease (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. The commonest initial neurologic symptom in the pediatric-onset patients 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 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%).

Epidemiology

Although this author was unable to find comparative incidence rates for BD, 2 population-based studies, both fulfilling ISG criteria,[145] studied prevalence data for BD, including one from France[147] and another from the United States.[148] 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 suggesting that BD risk was not related to age at immigration but was a primarily hereditary basis. The point prevalence of BD in the US was 5.2 per 100,000.

Genetic studies that focused on molecules related to innate immune responses[149] identified an association with endothelial nitric oxide (eNOS) gene located on chromosome 7q35-36, a variant of which causes deficient NOS and contributes to the pathogenesis of endothelial abnormalities and increases thrombotic tendency in BD. Dhifallah and colleagues[150] identified a polymorphism of eNOS that was associated with BD susceptibility as well as skin lesions. Park and coworkers[151] identified SNP of the promoter and exons regions in the cytotoxic T lymphocyte antigen 4 genes that predisposed to BD related to the immunologic abnormalities and disease expression associated with BD. Kim and colleagues[152] noted that genital ulceration, eye involvement, and NBD were associated with mannose-binding lectin 2 (MBL2) polymorphisms and production of high levels of MBL or functional MBL.

GWAS data have produced a major step forward by in the genetic of BD,[153] providing insights into the underlying mechanisms in BD with the discovery of a

new susceptibility gene that implicates defects in sensing and processing of microbial and endogenous danger signals as well as the regulation of innate and adaptive immune responses. Fei and colleagues[154] conducted a GWAS identifying a genetic association between BD and SNP in KIAA1529, the BD-risk allele (rs2061634) that led to a substitution of serine to cysteine at amino acid position 995 in the KIAA1529 protein. Hou and coworkers[155] conducted a GWAS suggesting that *STAT4* SNP (rs7574070, rs7572482, rs897200) was a novel locus underlying BD in a model in which upregulation of *STAT4* expression and subsequent *STAT4*-driven production of inflammatory cytokines, such as IL-17, constituted a potential etiopathogenic pathway. Lee and colleagues[156] conducted a GWAS suggesting that GIMAP cluster mapped to chromosome 7q36.1 (rs1608157) in a minor dominant model (rs11769828), representing a novel susceptibility locus for BD that is involved in T-cell survival, and that T-cell aberration could contribute to the development of this disease.

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