Systemic Diseases and Drug-Induced Vasculitis

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AIDS	acquired immune deficiency syndrome
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
Anti-Sm	antibody to the so-called Smith antigen
APLA	anti-phospholipid antibodies
BS	Behçet syndrome
CMV	cytomegalovirus
CSS	Churg-Strauss syndrome
CT	computer tomography
CVST	cerebral venous sinus thrombosis
dsDNA	double-stranded DNA
HAART	high activity antiretroviral treatment
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV-1	human T-cell lymphotrophic virus-1
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
MHC	major histocompatibility antigen
MRI	magnetic resonance imaging
NBS	neuro-Behçet syndrome
NPSLE	neuropsychological complications of SLE
PACNS	primary angiitis of the central nervous system
PAN	polyarteritis nodosa
PET	positron emission tomography
PML	progressive multifocal leukoencephalopathy
SLE	systemic lupus erythematosus
SS	Sjögren syndrome
VZV	varicella zoster virus
WG	Wegener granulomatosis

Inflammatory diseases of the CNS blood vessels are a large heterogeneous group with multiple causes sharing certain pathological features, particularly intramural inflammation and necrotic changes within the vascular wall. Unlike infectious vasculitides secondary to direct infection of blood vessels by organisms, non-infectious CNS vasculitides appear to result from immunological injury. Non- infectious cerebral vasculitides are challenging to clinicians because of the variable clinical symptoms, the difficulties establishing a correct diagnosis, the need for specific therapy, and the poor outcome. They are also difficult for the pathologist; their etiology and pathogenesis are controversial and the histopathological features are variable and non-specific.

Classification of CNS vasculitides is essential since they require different treatments and have varying prognoses. To date, there is no generally accepted classification of vasculitides. The American College of Rheumatology consensus conference for the nomenclature of systemic vasculitides proposed a classification based on clinical criteria (26). The 1993 Chapel Hill Classification is based on the caliber of involved vessels (31) (Table 1) and other classifications rely on pathogenetic mechanisms (32) (Table 2).

Recently, many of the effector mechanisms that mediate inflammatory vascular damage have been defined (11, 67). Cytokine-mediated changes in the expression and function of adhesion molecules, in combination with activation of leukocytes and endothelial cells, are the primary factors involved in vessel damage. There are several potential mechanisms of vessel damage in vasculitis (Table 2). *Pathogenic circulating antigen-antibody immune complexes* containing activated complement are deposited in vessels at sites of increased permeability leading to endothelial damage, production of chemotactic factors, infiltration of neutrophils and monocytes, stimulation of clotting and kinin pathways, and release of cytokines, oxygen radicals, and proteolytic enzymes. This mechanism plays an important role in Henoch-Schönlein purpura, drug-related cutaneous vasculitis, hepatitis B-associated polyarteritis nodosa (PAN) and essential mixed cryoglobulinemia (related to hepatitis C). Other potential pathogenetic mechanisms include *anti-endothelial cell antibody-mediated vessel damage* (in Takayashu arteritis, PAN and Kawasaki disease) and *direct damage* to the vessel by infectious agents or tumor cells. *Abnormal production of ANCA* can lead to neutrophil-mediated vascular injury in ANCA-associated vasculitis. In some type of vasculitis (giant cell, Takayasu, Wegener, Churg-Strauss), there is a *granulomatous reaction* initiated by a T-cell mediated immune response directed against an antigen (probably an infection-related supra antigen).

PRIMARY VASCULITIS
Vasculitis of vessels with large caliber
Takayasu arteritis
Giant cell or temporal arteritis
Vasculitis of vessels with middle size caliber
Polyarteritis nodosa
Kawasaki syndrome
Vasculitis of vessels with small caliber
Wegener granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis
Other vasculitides
Behçet disease
SECONDARY VASCULITIS
Systemic lupus erythematous
Sjögren syndrome
Infections: viral, spirochetal, bacterial, parasital
Malignancy-related vasculitis
Illicit drug-induced vasculitis

Table 1. Classification of cerebral vasculitides according to the caliber of the vessels involved. From the Consensus conference for the nomenclature of systemic vasculitis, Chapel Hill, North Carolina, USA (31) and Ferro (11).

On a practical level, CNS vasculitis may be divided into *primary* or *secondary*. Primary cranial or cerebral vasculitides include Takayasu arteritis (chapter 18), giant cell arteritis (chapter 17), and primary or granulomatous angiitis of the CNS (chapter 19), it usually requires a biopsy for diagnosis, and the outcome is often poor. Secondary inflammation of CNS blood vessels includes manifestations of systemic diseases, malignancy-related vas-

IMMUNOLOGICAL INJURY

Cell mediated inflammation

- Takayasu arteritis
- Giant cell or temporal arteritis
- Primary angiitis of the CNS
- Kawasaki syndrome

Immune complex-mediated inflammation

- Systemic lupus erythematosus
- Polyarteritis nodosa
- Behçet syndrome
- Infection-induced vasculitides (group A streptococcus, hepatitis B or C virus)
- Some malignancy-related vasculitides
- Some drug-induced vasculitides

Antineutrophil cytoplasmic antibody (ANCA) mediated inflammation

- Wegener granulomatosis
- Churg-Strauss syndrome
- Some drug-induced vasculitides

Mixed immunologic disorder

- Sjögren syndrome

DIRECT INFECTION OF BLOOD VESSELS

Bacterial

Viral (varicella-zoster virus, Epstein-Barr virus)

Others (fungal, protozoal, mycoplasmal, rickettsial)

Table 2. Classification of cerebral vasculitides based on proposed pathogenetic mechanisms (32).

culitis, and illicit drug-induced vasculitis. In secondary CNS vasculitis, the prognosis depends on that of the systemic disease, although involvement of the CNS is an adverse feature. The diagnosis relies mostly on general examination, imaging, immunological serological tests or pathological examination of systemic organs, rather than on neuropathology. The characteristic features of CNS vasculitis in those disorders are not clearly established and are rather non-specific. Neuropathological studies, mostly post-mortem are very few and comparable changes have been described in different disorders. Some other disorders that may mimic cerebral vasculitis are listed in Table 3.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune disorders without organ specificity. It is characterized by the production of numerous auto-antibodies directed against multiple nuclear components, particularly antinuclear antibodies (ANA). The classification criteria established by the American College of Rheumatology include a wide variety of clinical and serological features associated with this condition but no single truly "pathognomonic" feature (25). Even the characteristic malar butterfly rash on the face for which the disease is named, is not always present.

Epidemiology of SLE. *Incidence and prevalence.* SLE prevalence is estimated at about 1 per 2000 and its incidence is about 4 per 100 000 cases/year. The prevalence varies between ethnic groups. SLE is most frequent and severe in Afro-Caribbeans followed by Asians, Hispanics, and whites in decreasing order (33). Although SLE-related morbidity remains high, the prognosis for survival has improved from a 5-year survival of 51% in the 1950s to >90% at present (3a, 4). *Sex and age distribution.* Although SLE usually has an onset in the 20s and 30s, it may present at any age, even in early childhood. It is predominantly a disease of women, with a female-to-male ratio of 9:1, in the age group with women at childbearing age.

Risk factors. Genetic, hormonal and environmental factors have all been implicated in SLE. Sex hormones seem to exert an important influence on both the occurrence and manifestations. There is a relatively high incidence of SLE in Klinefelter syndrome (males with XXY karyotype) which is associated with abnormalities in oestrogen metabolism (53).

Viruses may trigger the autoimmune reaction leading to the production of

OTHER VASCULOPATHIES

- Susac syndrome
- Homocysteinuria
- Ehlers-Danlos syndrome
- Radiation vasculopathy
- Köhlmeyer–Degos disease
- Fibromuscular dysplasia
- Fabry disease
- Moya moya disease
- Amyloid angiopathy
- CADASIL
- Marfan syndrome
- Pseudoxanthoma elasticum

OTHER IMMUNE/INFLAMMATORY DISEASES

- Sarcoidosis
- SLE with APLA
- Behçet syndrome
- Multiple sclerosis/acute disseminated encephalomyelitis
- Thyroid encephalopathy

INFECTIONS

- Lyme disease
- AIDS
- Endocarditis
- Whipple disease
- Viral encephalitis
- Legionella/mycoplasma pneumonia

TUMOURS AND MALIGNANCIES

- Atrial myxoma
- Multifocal glioma
- Cerebral lymphoma
- Paraneoplastic disease

OTHERS

- Multiple cholesterol emboli
- Thrombotic thrombocytopenic purpura
- Cerebral sinus thrombosis
- Mitochondrial disease

Table 3. Some disorders that may mimic cerebral vasculitis (60).

pathogenic autoantibodies. Reactivation of BK polyomavirus has been associated with the production of antibodies to double-stranded DNA (dsDNA) in Norwegian studies (53). Certain drugs such as isoniazid, procainamide, hydralazine, D-penicillamine and certain anticonvulsants can induce an SLE-like syndrome, usually characterized by anti-histone rather than anti-dsDNA antibodies. There is a milder course of disease and total remission when the causative drug is withdrawn (53). Exposure to ultraviolet light is another environmental factor that exacerbates the disease.

Clinical features of SLE. SLE is a chronic, remitting and relapsing illness with acute or insidious onset, mainly affecting the skin, joints, kidney and serous membranes. It may involve any organ but renal and CNS involvement are regarded as the most serious. Intracranial pathology is the main cause of death in up to 19% of cases.

Signs and symptoms. Neuropsychological complications of SLE (NPSLE) are very common affecting between 50% and 90% of SLE patients, depending on diagnostic criteria. Complications are widely diverse including cerebrovascular disease, headaches, movement disorders, cranial neuropathy, seizures, psychiatric disorders and cognitive dysfunction (5). The diversity reflects the different underlying mechanisms of CNS dysfunction. Clinically it is important to separate complications due to: *i)* direct effects of SLE (inflammatory syndrome or circulating antiphospholipid antibodies (APLA)), *ii)* indirect effects of involvement of other organs (hypertension, thrombocytopenia, renal insufficiency), *iii)* effects secondary to treatment (complications of prolonged steroid therapy or drug-induced immunodeficiency), and *iv)* reactive symptoms related to the diagnosis of a serious illness and altered quality of life (anxiety/depression).

Imaging. MRI changes while common, are neither invariable nor specific. They may be found in the absence of clinical NPSLE and include increased signal in the white matter, cortico-subcortical atrophy, cerebral infarcts and venous thrombosis. Cerebral perfusion deficits have also been detected by single photon emission computed tomography (SPECT) (34). Fluid attenuated inversion recovery (FLAIR) increases diagnostic sensitivity in NPSLE by about 5% over conventional T2 weighted imaging (65).

Laboratory findings. Antinuclear antibodies (ANA) are found by indirect immunofluorescence in over 95% of patients with SLE. This test is sensitive but not specific and is found in other autoimmune disorders. Furthermore, 5% to 15% of normal individuals have low titers of these antibodies. Among ANA, antibodies to dsDNA and the so-called Smith (Sm) antigen are virtually specific for SLE but do not correlate well with NPSLE. When specific antibodies are absent, antinucleosome antibodies are useful for the diagnosis of SLE. Other antibodies may be looked for in particular clinical presentations: anti-P ribosomal protein in diffuse involvement of the CNS, APLA in focal, ischemic manifestations. APLA are present in 40% to 50% of SLE. Patients with primary antiphospholipid syndrome (chapter 8) may develop these antibodies and clinical symptoms without associated SLE.

CSF examination may reveal raised protein and a neutrophil or lymphocyte pleiocytosis. Its main importance is to exclude infectious complications of immunosuppressive treatment.

Neuropathology of SLE. Neuropathological studies of SLE are very few due to the improved prognosis and rarity of cerebral biopsy (8, 10). The most common change in brain parenchyma is multiple foci of infarction (Figure 1). However, vascular changes are often non-specific due to the delay between the onset of symptoms and neuropathological examination. Fibrinoid necrosis, mononuclear inflammatory infiltrates and fibrous thickening of the vessel walls (Figure 1) are regarded as compatible with chronic vasculitis (10, 24). Vascular thromboses are rarer; some may be secondary to Libmann-Sacks endocarditis (8), but circulating APLA probably play a major causative role.

Differential diagnosis of SLE. As the vascular changes in neurolupus are non-specific, the main diagnostic difficulty is to relate the cerebrovascular lesions to SLE and this can only be done based on clinical and immunological data. The real diagnostic dilemma is to determine the underlying pathogenic mechanism of the vascular changes. Immunocomplex-mediated vasculitis is supported by demonstrating deposition of immunoglobulins and complement in the blood vessel walls on biopsies from extracranial tissues, which are easily accessible. Studies on intracranial blood vessels are very scarce (24). The absence of marked vascular pathology in some studies (8) favours a thrombotic cause of symptoms related to circulating APLA (34). It is possible, indeed likely, that both mechanisms may be responsible.

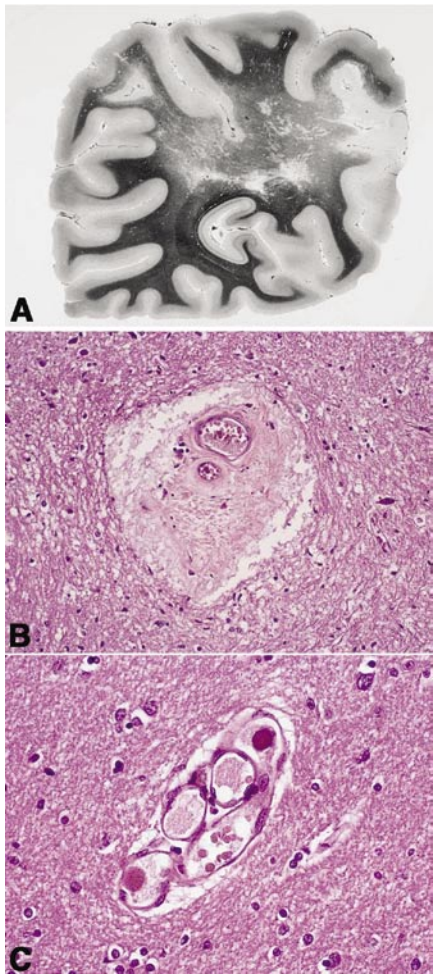

Figure 1. *Chronic vascular changes in a woman with chronic treated SLE.* **A.** Multiple disseminated old ischemic lesions in the left occipital lobe (Loyez stain for myelin). **B.** Fibrous thickening of the vessel walls with a few inflammatory cells in the perivascular space and (**C**) glomeruloid change in a vessel with multiple small lumena. H&E.

Genetics of SLE. SLE is genetically complex; both the major histocompatibility complex (MHC) and multiple non-MHC genes (72) contribute to the disease. HLA association studies support the concept that MHC genes regulate production of specific antibodies rather than conferring a generalized predisposition to SLE. Specific polymorphisms of HLA-DQ locus have been linked to the production of anti-dsDNA, anti-Sm and APLA (59). HLA A1, B8 and DR3 have been associated with familial SLE. Some SLE patients with inherited deficiencies of early components of the complement cascade (C1q, C2 and C4) develop a SLE-like disease. Lack of complement presumably impairs removal of circulating immune complexes by phagocytes, thus favouring tissue deposition (3).

Pathogenesis of SLE. Besides the focal ischemic lesions to which both an immunocomplex-related vasculitis and circulating APLA may contribute, other mechanisms may produce diffuse encephalitic damage. These include antineuronal antibodies interacting with the cerebral parenchyma (anti-lymphocyte and anti-P ribosomal protein antibodies [20]), immune complex deposition in the choroid plexus (9) and cytokines (75).

Future directions and therapy of SLE. Symptomatic treatment is important in patients with encephalopathy, epilepsy, chorea, and/or psychiatric symptoms. Disease-modifying therapies depend on the presumed underlying mechanisms. Ischemic focal manifestations associated with APLA require long lasting anticoagulant treatment. Those related to vasculitis with a diffuse CNS manifestation require immunotherapy, most often intravenous methyl prednisolone followed by oral steroids as the main treatment. Cyclophosphamide may be given for severe or steroid-resistant disease, with azathioprine to maintain remission and limit steroids. Plasmapheresis synchronized with cyclophosphamide and intravenous immunoglobulin may prove useful.

POLYARTERITIS NODOSA

According to the Chapel Hill nomenclature, PAN is a generalized primary necrotizing vasculitis involving small and medium-sized arteries in the absence of glomerulopathy and involvement of arterioles, venules and capillaries.

Synonyms and historical annotations. The disease was described first by Küssmaul and Meyer and is sometimes referred to as "Küssmaul-Meyer disease." The term "polyarteritis nodosa" emphasises the involvement of multiple vessels but other terms are sometimes used. "Periarteritis nodosa" stresses the perivascular inflammation and "panarteritis nodosa" notes that all the three layers of the arterial wall are affected by the disease.

Epidemiology. *Incidence and prevalence.* PAN is an uncommon condition with an annual incidence of 0.7 per 100 000 and prevalence of 6.3 per 100 000 (61). It is a severe disease. The 5-year survival rate has improved from less than 15% in untreated patients to 75% to 80% following immunosuppressive therapy (13).

Sex and age distribution. It is typically a disease of middle age with onset at around 40 to 50 years, males are affected twice as commonly as females.

Risk factors. In general, there is no known precipitating cause. Hepatitis B virus (HBV) infection has been observed in a varying percentage of patients ranging from 36% in 1985 to less than 7% currently. Hepatitis C virus (HCV) infection is found in smaller proportions in patients without cryoglobulinemia. Rare associations have also been reported with other viruses such as Parvovirus B19, cytomegalovirus (CMV), human T-cell leukemia/lymphotrophic virus-1 (HTLV1) and human immunodeficiency virus (HIV) (15).

Clinical features of PAN. *Signs and symptoms.* PAN usually presents as a severe generalized disorder with fever, weight loss, malaise and weakness. Purpura, subcutaneous nodules, joint manifestations and diffuse myalgia are often seen. Other symptoms depend on which organs are involved and include malignant hypertension caused by renal ischemia, ischemic gastrointestinal tract disorders and more rarely cardiac involvement.

Involvement of the peripheral nervous system causing classically mononeuritis multiplex is an early symptom affecting 50% to 75% of patients. The skeletal muscles are also frequently affected in 40% to 80% of patients. Involvement of the CNS is less common and the reported frequencies are highly variable from 4% to 53% of cases, reflecting the difficulty in diagnosis. It usually occurs at a late stage and is a sinister feature, representing the second most common cause of death in patients with PAN (34). Lesions may be focal, multifocal or diffuse, affecting any part of the brain. This explains the protean manifestations and the absence of pathognomonic or even typical clinical features. Headache, focal and generalized seizures, stroke-like episodes causing hemispheric or brainstem deficit, acute and subacute encephalopathies, progressive cognitive changes, behavioural disturbance, chorea, myoclonus and other movement disorders, optic and other cranial neuropathies may all be found. The course is commonly acute or subacute, but monophasic, chronic progressive, and spontaneously relapsing-remitting presentations all occur.

Imaging. MRI is more sensitive than computed tomography and may detect multiple CNS lesions even when only one is clinically apparent. Normal MRI almost excludes intracranial vasculitis, but there are no pathognomonic MRI findings in vasculitis. Single or multiple territorial infarcts and hemorrhages, and nonspecific T2 hyperintense lesions involving the cortex, white matter, and basal ganglia may be seen. The angiographic findings characteristic of vasculitis include segmental (often multifocal) narrowing and areas of localized dilatation or beading, often with areas of occlusion, or more rarely with aneurysms. These findings are non-specific and can be seen in other conditions. A normal arteriogram does not exclude vasculitis since vessels under 100 to 200 μm in diameter cannot be visualized.

Laboratory findings. There is no single simple investigation to confirm cerebral vasculitis. CSF examination is often abnormal with changes in cell count and/or protein, but lacks specificity like the erythrocyte sedimentation rate. A negative serum antineutrophil cytoplasmic

antibodies (ANCA) result is important to distinguish PAN from small vessels vasculitides (Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis).

Neuropathology of PAN. PAN involves medium-sized arterioles but the caliber varies according to some authors (21), and must be measured in a healthy portion of the vessel. Classically affected vessels have a diameter >150 µm. In peripheral nerve and skeletal muscle biopsies, affected vessels may be smaller with a diameter of 45 to 210 µm. The necrotizing lesions are always very patchy with a predilection for the branching points of blood vessels. Most lesions are no more than one mm in length and do not necessarily involve the whole circumference of the artery. Active lesions show fibrinoid necrosis of the media and transmural infiltration by inflammatory cells (Figure 2). The cells are mostly CD8+ lymphocytes and macrophages, polymorphonuclear neutrophils (PMN) undergoing leucocytoclasis in the areas of fibrinoid necrosis, a few eosinophils and plasma cells may be found in the adventitia. The necrotic wall can undergo microaneurysmal dilatation. Thrombosis is also frequent and in healed vessels, all layers of the artery show fibrous scarring and residual inflammation is represented by lymphocytes (Figure 2). Different blood vessels at varying stages of the disease, ie showing active and healed lesions are very characteristic of PAN, but are not present in HIV-associated PAN which has a monophasic course.

Differential diagnosis of PAN. In general, the diagnosis of cerebral vasculitis requires the exclusion of other possibilities (Table 3), and confirmation of intracranial vasculitis. This is achieved by imaging even though the signs are far from specific and may be seen in vasospasm related to subarachnoid hemorrhage, drugs or severe hypertension, diabetes with intracranial atheroma, embolus recanalization, radiation, infectious or carcinomatous leptomeningitis, sickle-cell disease, reversible angiopathies, dissection etc (11). The diagnosis of PAN relies on histopathological demonstration of characteristic vascular changes in accessible tissue mainly skeletal muscle and/or peripheral nerve, the vasa nervorum of which are frequently affected.

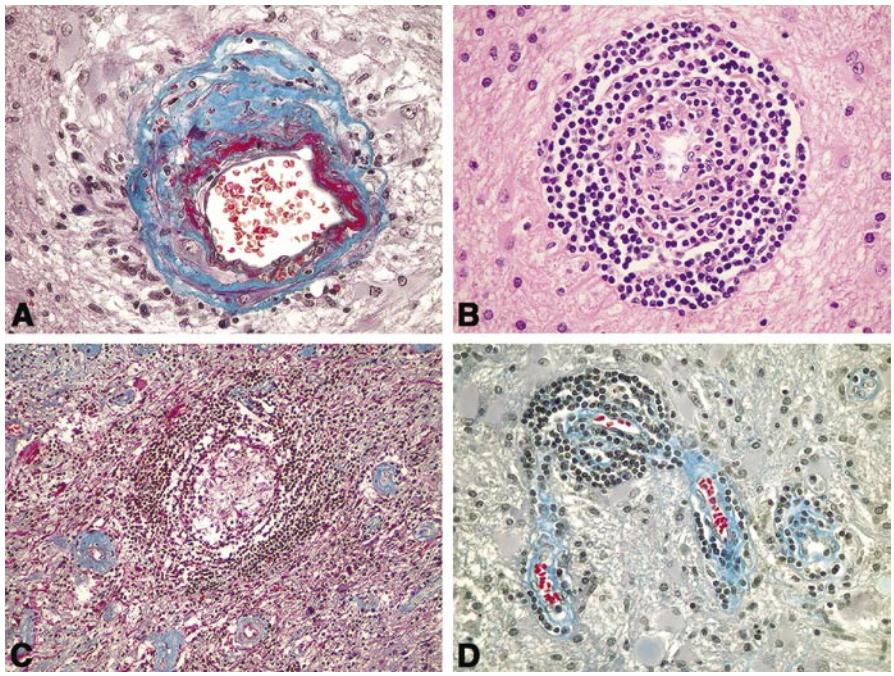

Figure 2. *Involvement of the cerebral vessels in a case of PAN.* **A.** Fibrinoid necrosis of the media, (**B**) transmural infiltration by inflammatory cells, (**C**) thrombosis and perivascular inflammation, note fibrous thickening of neighboring vessels, (**D**) chronic changes with fibrosis of vessels and lymphocytic perivascular inflammation. **A, C, D**: Masson Trichrome; **B**: H&E. Courtesy of Dr Michèle Kujas, Lab de Neuropathologie Raymond Escourolle (Pr. J.J. Hauw) La Salpêtrière, Paris.

Genetics of PAN. Rare cases of familial PAN have been described (54). A high prevalence of PAN has been reported in patients with familial Mediterranean fever caused by mutations in the gene encoding pyrin (70a).

Pathogenesis of PAN. The etiology and pathogenesis of PAN have not definitely been established but the most commonly implicated mechanism is an immune complex mediated vasculitis. Immunoglobulins and complement deposits may be identified in the vascular lesions. A number of inciting antigens including autoantigens, drugs and microorganisms, particularly HBV, HCV and HIV are implicated. However, the exact pathogenetic relationship between PAN and viruses is still not certain; in situ replication of HIV has been demonstrated in the vessel wall but neither HBV nor HCV have been found. In some patients, active replication of HBV is indicated by HBV antigen and viral DNA in serum, suggesting it may play a causative role in PAN.

The CNS lesions are most often due to vasculitis of the cerebral arteries causing ischemia or hemorrhages (rupture of microaneurysm). They may also be secondary to malignant arterial hypertension due to renal vasculitis.

Future directions and therapy. PAN is a severe disease requiring aggressive immunosuppressive therapy. Steroid therapy is the main treatment; however, in forms with a bad prognosis, particularly those with CNS involvement, immunosuppressive treatment has proved beneficial. In PAN associated with HBV infection, treatment by steroids and cyclophosphamide may worsen the liver disease that can lead to cirrhosis and cancer. In those patients, a short (1 week) course of steroids followed by plasmapheresis and antiviral treatment (lamivudine and interferon-alpha) is recommended.

KAWASAKI DISEASE

Kawasaki disease (KD) is an acute febrile, multisystem vasculitis of unknown etiology mostly affecting children under 5 years. Large, medium and small arteries are involved, most often the coronary arteries and there is an associated muco-

cutaneous syndrome with lymph node enlargement.

Synonyms and historical annotations. KD was first described by Kawasaki in 1967 and is sometimes referred to as mucocutaneous lymph node syndrome.

Epidemiology. First recognized in Japan, KD has a worldwide distribution. In Japan the annual incidence is 100 cases per 100 000 children under 5 years; in China, the United States, and United Kingdom, the incidence is lower but appears to be increasing (74). Over half the patients are younger than 2 years. Incidence is higher in boys. Approximately 20% develop cardiovascular complications ranging in severity from asymptomatic coronary arteritis to giant coronary artery aneurysms. In 1% of patients, coronary arteritis causes sudden death.

Clinical features. *Signs and symptoms.* The main clinical features of KD are fever lasting 5 days or more, conjunctival and oral erythema, cervical adenopathy, skin rash and edema of the palms and soles with desquamation (35). Cardiovascular complications, diarrhea and arthralgia are later manifestations. Involvement of the CNS is a rare but sometimes serious complication. It occurs in 0.4% of children and causes seizures, ataxia, cerebral infarction, hemiplegia and subdural effusion (70). Pronounced irritability, lethargy and aseptic meningitis are quite common, the other more severe neurological manifestations are rarer (68). The prognosis of neurological complications is generally good. Sequelae (myoclonic seizures, mild hemiparesis) are rare.

Imaging. MRI scans are usually normal in the acute stage. CNS manifestations in KD may be due to focal impairment of blood flow caused by cerebral vasculitis. Localized cerebral hypoperfusion has been shown with PET in some patients in the absence of neurological symptoms (28).

Neuropathology of KD. KD is a necrotizing arteritis with a distribution similar to PAN. In KD, inflammation usually affects the entire vessel wall and fibrinoid necrosis is less prominent. Cerebral vasculitis has been identified in post mortem cases and diffuse inflammatory lesions including leptomeningitis, choriomeningitis, ganglionitis were observed by Amano et al (2) in a series of 37 autopsy cases.

Differential diagnosis. The diagnosis of KD is based on clinical criteria (42) and does not require biopsy.

Experimental models. Intraperitoneal injection of Lactobacillus casei or Candida albicans extract induces coronary arteritis similar to KD in animal models; involvement of the CNS is not mentioned (69).

Pathogenesis and genetics. Although an infectious cause for KD has been suspected, there is no obvious association with any specific organism, including Rickettsia or Coxiella burnettii. The vasculitis has an immune basis, characterized by T-cell and macrophage activation, secretion of cytokines and autoantibodies to endothelial and smooth muscle cells. Genetic polymorphisms influence the cytokine profile following an inflammatory stimulus. Some cytokine polymorphisms, like tumor necrosis factor-alpha elevation, may influence KD susceptibility (52).

Future directions and therapy. Combined intravenous immunoglobulin (IVIG) and aspirin during the acute phase of KD produces a more marked anti-inflammatory effect and reduction in coronary artery abnormalities than aspirin alone. Ten percent of patients are resistant to IVIG therapy. Some patients with severe disease resistant to IVIG therapy may be safely treated with steroids (27).

ANCA-ASSOCIATED VASCULITIDES

Wegener granulomatosis (WG), microscopic polyangiitis and Churg-Strauss syndrome (CSS) are small-to medium vessel vasculitides linked by overlapping pathology and the presence of antineutrophil cytoplasmic antibodies (ANCA).

Synonyms. CSS is sometimes called allergic granulomatosis and angiitis syndrome.

Epidemiology. A study from Norfolk, United Kingdom, reported annual incidences of 8.5 cases per million for WG, 3.6 cases per million for microscopic polyangiitis, and 2.4 cases per million for CSS (74). Whites comprised over 90% of cases. The mean age at diagnosis is about 55 years. WG affected men somewhat more often than women; the average age was 40 years. Genetic factors, drugs especially hydralazine and propylthiouracil, chemicals and/or infectious agents are risk factors for ANCA-associated disease.

Clinical features. *Signs and symptoms.* There is substantial overlap in the clinical features of ANCA-associated vasculitides and diagnosis can be difficult. WG is characterized by the triad of *i)* acute necrotizing granulomas of the upper respiratory tract and/or the lungs, *ii)* focal necrotizing or granulomatous vasculitis of small- to medium-sized vessels in the lungs and upper airways but affecting other sites, and *iii)* focal or necrotizing often crescentic glomerulonephritis. Limited WG is restricted to the respiratory tract.

Microscopic polyangiitis is characterized by necrotizing glomerulonephritis and pulmonary capillaritis. It may involve the skin, mucous membranes, lung, brain, heart, gastrointestinal tract and muscles. In many cases the lesions are limited to a cutaneous vasculitis.

In CSS, there is a strong association with allergic rhinitis, bronchial asthma and eosinophilia over 10%. Vessels of the lung, heart, spleen, peripheral nerves and skin are frequently involved.

Neurological manifestations due to either vasculitis or granulomatous inflammation in WG are seen in about 30% of patients. Peripheral neuropathy and cranial neuropathy are the most frequent. Stroke is a rare complication and usually represents extension of primary disease in the air sinuses, orbit or auditory canal, or is related to hypertension or rarely to small vessel vasculitis (50). In a series of CSS, two-thirds of patients had neurological involvement, predominantly peripheral neuropathies, followed by stroke and ischemic optic neuropathy. In all cases, asthma preceded PNS or CNS involvement (62). Intracerebral hemorrhage may also occur (43). Involvement of CNS is exceptional in microscopic polyangiitis (56). CNS involvement usually occurs at a late stage of ANCA-associated vasculi-

tis and with modern immunosuppressive therapy the disease seldom spreads into the brain.

Imaging. Because of the size of the predominantly affected vessels, angiograms are usually normal. The spectrum of CT and MRI findings in WG includes dural thickening or mass lesions due to granulomas, enhancing cerebral infarcts and MRI signal abnormalities in the brain stem and white matter (51).

Laboratory findings. In WG, cytoplasmic ANCA (c-ANCA) are present in the serum of 90% of patients with active generalized disease and are a good marker of disease activity. Over 80% of patients have perinuclear ANCA (p-ANCA) in microscopic poyangiitis and 70% in CSS. c-ANCA pattern corresponds to proteinase 3-ANCA and p-ANCA to myeloperoxidase-ANCA. The great majority of patients with drug-induced vasculitides have high titres of p-ANCA, which are also more common in CSS and in polyangiitis than in WG (64).

Neuropathology of ANCA-associated vasculitides. Fibrinoid necrosis is regarded as the hallmark of ANCA-associated disease but it may be found in other vasculitides such as PAN, SLE or malignant hypertension. Segmental fibrinoid necrosis of the media may be present, but pathology is often limited to infiltration of the vessel wall by neutrophils which become fragmented near the vessel wall (leukocytoclasis). All lesions tend to be of the same age. The range of granulomatous inflammation found in WG includes palisading granulomas, scattered giant cells, poorly formed granulomas, and focal or confluent non-caseous central necrotizing granulomas. There is a dense non-specific inflammatory background and coalescence of neutrophilic microabscesses leads to extensive foci of geographic necrosis.

In CSS intravascular and extravascular granulomas are found with infiltration of vessels and perivascular tissues by eosinophils. The presence of eosinophils is characteristic of CSS, but is also seen in WG and microscopic polyangiitis.

Differential diagnosis. The main differential diagnoses are lymphomatoid granulomatosis, lethal midline granuloma and small vessel vasculitis. Lymphomatoid granulomatosis has nodular pulmonary infiltrates of lymphoid and plasmacytoid cells, often atypical. There is no fibrinoid necrosis. Although the infiltrates invade vessels, simulating vasculitis, it is not a true vasculitis and is regarded as a lymphoproliferative disorder. About a third of patients develop similar lesions in the kidney, liver and brain. Lethal midline granuloma is a destructive often fatal vasculitis of major midline structures of the head. Neurological manifestations result from direct invasion of the orbit and face, jugular vein, sigmoid and cavernous sinus leading to thrombosis, sepsis, meningitis and haemorrhage (78). Small vessels vasculitis may occur in Henoch-Schönlein purpura, essential mixed cryoglobulinemia, hypersensitivity vasculitis and certain connective tissue disorders. However involvement of the CNS is exceptional in these disorders.

Experimental models. Recombinase-activating gene 2 (RAG-2)-deficient mice given antimyeloperoxidase antibodies develop clinical features of ANCA-associated vasculitis, including crescentic glomerulonephritis and systemic necrotizing vasculitis (76).

Genetics. Rare cases of familial WG and CSS have been described (44).

Pathogenesis. The ANCA-associated vasculitides are complex immune-mediated disorders in which tissue injury results from the interaction of an initiating inflammatory event and the production of ANCA to previously shielded epitopes of neutrophil granule proteins. ANCA produce tissue damage via interactions between primed neutrophils and endothelial cells.

Therapy and future directions. Treatment of severe ANCA-associated vasculitis is a combination of a short course of cyclophosphamide to induce remission, followed by longer treatment with either azathioprine or methotrexate to maintain remission. Patients with milder manifestations can be treated with steroids alone. Mortality and morbidity remain substantial even with aggressive therapy. Infections are a major cause of death.

SJÖGREN SYNDROME

Sjögren syndrome (SS) is an autoimmune disorder characterized by keratoconjunctivitis sicca and xerostomia resulting from immunologically mediated destruction of the lacrimal and salivary glands. The syndrome is classified as primary SS, also known as the sicca syndrome. Secondary SS is associated with another autoimune disease, eg, rheumatoid arthritis, SLE, scleroderma, polymyositis, Hashimoto thyroiditis, primary biliary cirrhosis.

Epidemiology. SS is the most frequent autoimmune disease after rheumatoid arthritis with a prevalence of 4.8% of adult population. SS is more common in women with a sex-ratio of 9:1 and can develop at any age from 15 to 65 years. An SS-like syndrome can occur in HTLV-1, HIV-1 and HCV infection (39).

Clinical features. *Signs and symptoms.* In addition to keratoconjunctivitis, dry mouth and salivary gland enlargement, extraglandular manifestations include synovitis, diffuse pulmonary disease, myositis and peripheral neuropathy. CNS involvement is estimated at 20% to 30% in primary SS and can precede the sicca syndrome. Symptoms and signs may be focal (hemiparesis, focal epilepsy, optic neuritis, transverse myelitis or a multiple sclerosis-like syndrome) or diffuse (aseptic meningo-encephalitis, progressive encephalopathy or dementia). Psychiatric disorders, particularly anxiety and depression have been reported but whether they are directly caused by SS is controversial. CNS involvement can be due to antineuronal antibodies or to an autoimmune inflammatory cerebral vasculopathy mainly affecting small vessels, especially venules in the white matter.

Imaging. There are no specific CT or MRI abnormalities. MRI is useful for detecting asymptomatic CNS involvement. Multiple areas of increased signal on T2 in periventricular white matter are associated with focal CNS involvement (11). Angiograms are either normal or suggestive of small vessel arteritis.

Laboratory findings. Rheumatoid factor, ANA or anti-Ro/anti-La (anti-SSA/-SSB) are often positive. Cases with high titers

of anti-Ro antibodies tend to have more serious CNS focal disease (11). A new antibody, anti-alpha-fodrin, detected in SS and in SLE, seems to be more reliable than anti-Ro for the diagnosis of SS. It may be associated with some extraglandular manifestations characteristically seen in patients with SS (73). CSF is either normal or can show increased proteins or intrathecal synthesis of gammaglobulins.

Morphology. The earliest histologic change in the major and the minor salivary glands is periductal and perivascular lymphocytic infiltration. There are few post-mortem reports. CNS pathology is variable. Vasculitis or vasculopathy mainly affects small venules in the white matter and may be associated with microinfarcts and neuronal loss with astrocytic gliosis (39). The perivascular infiltrate is mainly lymphocytes, plasma cells and macrophages and may extend to the leptomeninges (1). Necrotizing arteritis of medium sized arteries resembling PAN has also been described.

Differential diagnosis. Multiple sclerosis is the major differential diagnosis and can be excluded by salivary gland biopsy. SLE and Hashimoto encephalitis have to be considered because of the association of these diseases with SS.

Experimental models.
A number of transgenic mice have been studied. There is no mention of CNS involvement (45).

Genetics. Primary SS is a complex polygenic disorder with many genes interacting with environmental factors. There is an association with human leukocyte antigen types HLA-B8, -DR3, and DRW52 (57).

Pathogenesis. In SS there is increased apoptosis in epithelial cells leading to an accumulation of degradation products of cytoskeleton proteins such as alpha- and beta-fodrin. Numerous nuclear autoantigens are also presented to the immune system. Significant polyclonal activation of B-lymphocytes is probably mediated, at least partly, by a major increase in molecules of the tumor necrosis factor family. Permanent stimulation of autoreactive B cells favours oncogenesis and could lead to the development of B-cell lymphoma with autoantibody activity (45). Patients with SS have approximately 40 times the risk of developing marginal zone B-cell lymphomas.

Therapy. Steroid therapy is usually prescribed first. With increasing risk of lymphoid malignancies, plasma exchange and immunosuppressive drugs can be added.

BEHÇET SYNDROME

Behçet syndrome (BS) is a multi-system vascular-inflammatory disease of unknown origin, causing mucocutaneous lesions, uveitis, and frequent nervous system involvement.

Epidemiology. There is a geographic variation; the prevalence of BS in the United States and northern Europe is 1 per 100 000, in Mediterranean countries, the Middle East, Japan and the Far-East prevalence is 10 to 100 per 100 000. BS also shows a geographical variation in disease expression. Neuro-Behçet syndrome (NBS) is seen in 5% to 10% of patients. The male to female ratio in BS is almost equal, but in NBS the ratio is 4:1. The mean age of onset of BS is in the third decade, with neurological involvement 5 years later (66).

Clinical features of BS. The International Study Group for BS in 1990 defined criteria for diagnosis of BS: recurrent oral ulcerations, plus 2 of the following: recurrent genital ulcerations, skin lesions, eye lesions and a positive pathergy test (29).

Signs and symptoms. Neurological involvement in BS may be subclassified into 2 major forms: *i)* intra-axial or CNS-NBS is attributable to small vein inflammatory disease with focal or multifocal CNS parenchymal involvement, and is seen in the majority of patients, and *ii)* extra-axial NBS caused by cerebral venous sinus thrombosis (CVST) with limited symptoms and a better neurological prognosis. Arterial involvement resulting in CNS vascular disease is rare. It is very uncommon for the 2 subtypes to occur in the same individual. Rarely neuropsychological and peripheral nervous system involvement may occur. Neurological complications of treatment or systemic effects are included in the secondary neurological consequences of the syndrome.

The onset of NBS seldom precedes the oral ulcers or other systemic manifestations. The clinical course may be a single illness, improving with or without sequelae, or may be relapsing/ remitting with secondary progression in some patients; less commonly there is a primary progressive illness. Neurological morbidity and mortality is high; 50% of NBS patients have moderate to severe disability after 10 years of the disease. Patients with CVST may present with a single episode; recurrences are rare.

Headache is the most common neurological, often the presenting symptom. The most common manifestation of CNS-NBS is a subacute brainstem syndrome with different combinations of cranial nerve palsies, cerebellar signs (ataxia, dysarthria), unilateral or bilateral pyramidal features, and mild confusion with or without impaired consciousness. Cognitive-behavioural changes, self-limiting or progressive myelopathy, and extrapyramidal signs and seizures may be seen, but are uncommon (66).

CVST develops in 10% to 20% of BS patients with neurological involvement. Thrombosis of the venous sinuses may cause raised intracranial pressure with severe headache, mental changes and ophthalmoplegia. In some patients the only manifestation is headache. Any dural sinus may be affected, but the superior sagittal sinus is the most commonly thrombosed. CVST in BS is strongly associated with systemic major vessel disease.

Psychiatric symptoms occur in 5% to 25.5% of the NBS cases (66). Variable involvement of PNS (mononeuritis multiplex, peripheral neuropathy prominent in the lower extremities and poly-radiculoneuritis) may occur. Muscle involvement is uncommon.

Imaging. CT scanning is usually normal. MRI is more sensitive and reliable and shows oedema in acute phase lesions. MRI with MRI venography is the best imaging modality for CVST. In CNS-NBS lesions are generally located within the brainstem, occasionally extending to the diencephalon, or less commonly in

periventricular and subcortical white matter. The most commonly affected region is the midbrain, followed by the pontobulbar region. Imaging studies do not support an arterial vasculitis as lesions are not compatible with arterial territories. Furthermore, perilesional edema during acute disease tends to disappear or be minimal in follow-up studies, consistent with venous infarction. Diffusion MRI and proton magnetic resonance spectroscopy findings suggestive of vasogenic edema rather than infarction have been seen in acute disease (63).

Laboratory findings. The CSF sometimes shows pleocytosis and raised protein and IgG, but more often is normal.

Neuropathology of BS. There may be gross brain changes; thickening of the leptomeninges and cerebral swelling are described but more often there is mild atrophy and ventricular dilatation. Areas of necrosis are usually not conspicuous, but gliosis may be palpable and visible. Degeneration of pyramidal, optic and other tracts is sometimes seen. In occasional cases, there is thrombosis of the superior sagittal, cavernous or other sinuses and rarely aneurysms, presumed to result from vasculitis (22).

The pathology in NBS with CNS involvement depends on the treatment and stage of disease (40). In the acute stage, parenchymal infiltration by neutrophils has been observed (22). There are small hemorrhages and microthrombi in vessels. In chronic cases there is meningoencephalitis with scattered, focal destructive lesions in the parenchyma distributed randomly throughout the grey and white matter, often maximal in the diencephalon and brainstem (rhombencephalitis). The leptomeninges and the Virchow-Robin spaces are densely packed with a lymphocyte-predominant infiltrate. The parenchymal changes consist of tissue rarefaction or frank necrosis and cavitation with macrophage response, microglial nodules and reactive astrocytosis. Secondary tract degeneration may also be seen.

Vasculitis is regarded as the underlying lesion but cerebral vessel changes are non-specific and definite vasculitis is not present in all cases (22). The most frequent finding is perivascular infiltration by T- and B-lymphocytes and neutrophils around small venules. It may be associated with leukocytoclastic vasculitis and/or fibrinoid necrosis (78).

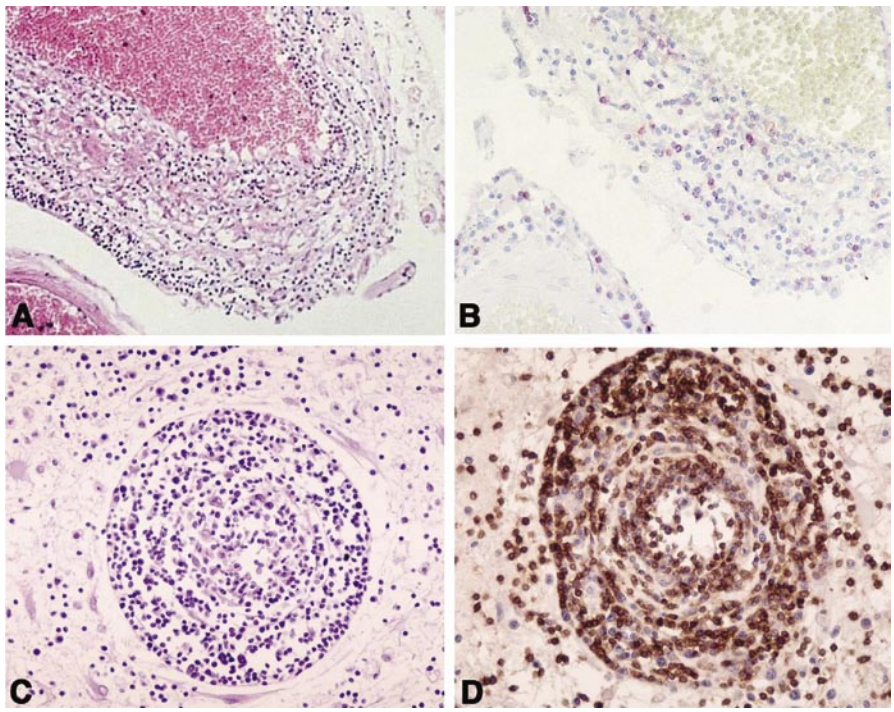

Figure 3. *Cerebral vasculitis in HIV infection.* **A, B.** Asymptomatic preAIDS patient: Transmural infiltration of a leptomeningeal blood vessel by mononuclear cells (**A**), mainly CD8+ T-lymphocytes (**B**: red). **C, D.** Immune reconstitution inflammatory syndrome in a patient with AIDS-related PML who received HAART: Massive infiltration of the walls of an intraparenchymal vessel by mononuclear cells (**C**), mostly CD8+ T-lymphocytes (**D**: brown). **A, C:** H&E, **B, D:** CD8 immunostaining.

Differential diagnosis. The specific diagnosis is based on the associated systemic findings. In pure or predominant NBS, multiple sclerosis, sarcoidosis and infections (herpes, listeria, tuberculosis) must be excluded.

Genetics and pathogenesis. The etiology of BS is still not understood. Genetic, immunological and bacterial factors, viral agents (41) and coagulation abnormalities have all been considered. BS is not a genetic disease although clustering of BS patients in families is well known.

The association between BS and HLA-B51 has been confirmed in many ethnic groups. However, it is still unknown whether the HLA-B51 gene is responsible for BS, or if some other nearby genes in linkage disequilibrium with B51 are important. Kaya et al (36) suggested that HLA-B51 may be a marker for the increased risk of thrombophlebitis in BS patients. The authors also reported that HLA-B35 conferred a decreased risk of thrombophlebitis. As in many vasculitides, antiendothelial antibodies have been reported in BS, but there is little insight as to their target antigen.

Therapy. Treatment options are limited in NBS; steroids are used for acute exacerbations, but currently there is no effective treatment for recurrent and progressive NBS.

HIV-RELATED VASCULITIS

A wide range of inflammatory vascular diseases affecting the PNS (14) and the CNS (6) may occur in HIV-infected patients at different stages of the disease. Vascular inflammation appears multifactorial and may result from HIV-induced immunologic abnormalities and exposure to foreign antigens such as HIV itself, other infectious agents and drugs.

In early HIV infection, transmural infiltration of cerebral and leptomeningeal blood vessels, mainly veins by mononuclear cells is frequent. There is no necrosis, granulomas or leukocytoclasis. It is generally considered part of the reversible immune systemic CD8+ T-cell reaction fol-

lowing primary infection by HIV (Figure 3). The vasculitis is usually asymptomatic; however, white matter changes visible on MRI and postmortem examination are likely to be due to breakdown of the blood brain barrier due to vasculitis (19).

In later stages, granulomatous (58, 77) or necrotizing (71) cerebral vascular lesions have been described in patients with AIDS or AIDS-related complex and were responsible for infarcts. The exact relationship between the vascular lesions and HIV infection is uncertain. In some cases, the presence of multinucleated giant cells supports a direct role for HIV itself (58, 77). Other cases have been attributed to varicella-zoster infection (17). In pediatric AIDS, chronic lesions of the basal meningeal arteries with destruction of the elastic lamina, thinning of the media, intimal fibrous thickening and aneurysmal dilatation were described and could be associated with granulomatous angiitis. The cause of the arteriopathy has not been proven, but several of the children had varicella zoster skin infection (37).

Recently, an "immune reconstitution inflammatory syndrome" has been described in AIDS patients receiving highly active antiretroviral combination treatment (HAART). They presented with paradoxical clinical deterioration despite biologically efficient treatment. This syndrome is believed to result from an overactive response of a newly reconstituted immune system to infectious antigens (HIV, mycobacteria, CMV, Cryptococcus or JC virus) present in the patient when therapy was started. In some patients with HIV encephalitis (47) or AIDS-related progressive multifocal leukoencephalopathy (PML) (48), neuropathological studies revealed an unusually intense parenchymal and perivascular inflammatory reaction. Vessel walls were infiltrated by mononuclear cells mostly CD8+ lymphocytes (Figure 3) and macrophages. The vasculitis could explain PML changes on MRI that became contrast-enhancing following HAART institution.

MALIGNANCY-RELATED VASCULITIS

Vasculitides of the nervous system may occur in patients with neoplasia. They predominantly involve the peripheral nervous system and resemble a systemic necrotizing vasculitis, granulomatous vasculitis or small vessels hypersensitivity vasculitis (49).

CNS vasculitis is particularly associated with Hodgkin disease (55). In most cases it presents as primary (granulomatous) angiitis of the CNS (PACNS, see chapter 19). The neurological symptoms may precede the diagnosis of the underlying neoplasm and brain biopsy is necessary for definite diagnosis. The inflammatory changes involve the small and medium vessels of the brain and spinal cord, arterioles and venules, and consist of an infiltration of the vessel walls by histiocytes, giant cells and mononuclear cells, and focal non-caseating necrosis.

The etiology of PACNS is unclear, but in addition to Hodgkin and non-Hodgkin lymphomas, it has been associated with varicella-zoster virus (VZV), immunodeficiency virus (HIV) or sarcoidosis. In some cases, reactivation of VZV in the context of lymphoma-induced immunedeficiency (16) has been speculated. In other cases, a paraneoplastic mechanisms due to cross-reacting antineuronal antibodies induced by the tumor seems more likely (23). A combination of steroids and chemotherapy appears to be the best treatment for both conditions. Patients who presented with PACNS prior to the diagnosis of Hodgkin disease have a better prognosis (55).

ILLICIT DRUG-INDUCED VASCULITIS

Drug abuse is an important, probably underestimated, cause of stroke in young adults. The cerebrovascular lesions consist of ischemic and hemorrhagic strokes, subarachnoid and intracerebral hemorrhages, and cerebral ischemia.

Apart from HIV-related vasculitis, a number of pathogenic mechanisms may be responsible, including pharmacologically-induced vasospasm and/or acute hypertension, impaired hemostasis and platelet function, decreased cerebral blood flow (due to hypotension and/or positional vascular compression secondary to respiratory depression), septic emboli or migration of injected contaminant adjuvant (30).

Drug-induced vasculitis has been suggested by imaging, but there are very few confirmatory neuropathological studies. Moreover, non-inflammatory "benign angiopathies" were found on cerebral biopsy in cocaine abusers with suggestive angiography (46). Occasional cases of biopsy-proven cerebral vasculitis in cocaine abusers have been reported (12, 38). The vasculitis seems to be non-infectious and possibly allergic. The inflammatory infiltrate is mainly lymphocytic and some patients respond to immunosuppressive therapy.

Necrotizing angiitis affecting cerebral arteries and arterioles was found at postmortem examination in drug addicts who used multiple amphetamine drugs (7). There is a high frequency of intracerebral hemorrhages in cocaine, phenylpropanolamine and amphetamine misusers suggesting that necrotizing vasculitis might be more common that previously thought. The association between possibly immune complex-mediated polyarteritis nodosa and hepatitis B and C may be one explanation for necrotizing vasculitis in drug abusers infected with these viruses. Interestingly, necrotizing arteritis is not a feature of amphetamine cerebrovascular injury in primate models (78).

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