

NEUROLOGY AND MEDICINE

Neurology of the vasculitides and connective tissue diseases

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Neurological and psychiatric abnormalities are frequent complications of systemic autoimmune and inflammatory diseases. The range and acuity of these abnormalities vary widely, as do the immunopathogenic mechanisms. Progress in the understanding of likely mechanisms and potential therapies in these groups of disorders has come from diverse areas of investigation. Studies during the past decade detail the intrinsic role of the vasculature in the physiology of inflammation. Numerous small soluble molecules mediate autocrine and paracrine effects within and between cells of the vasculature, tissue parenchyma, and haematopoietic system. Further, various pathological processes use the same mediators to actively target or passively injure blood vessels. These processes, which may result in acute or chronic vascular injury, are clearly evident in many of the systemic autoimmune diseases. In addition, systemwide responses to inflammatory stress or local injury evoke cascades and feedback loops of hormones and neurotransmitters. Although these responses are adaptive to the acute situation, they may contribute to the chronic injury when persistently activated. In another area, autoantibodies, prominent in many autoimmune diseases, are potential causes of cellular dysfunction. Distinguishing among the protective, pathogenic, and neutral role of autoantibodies, however, requires careful study.

The vasculitides and connective tissue diseases provide an avenue for investigating the pathophysiology of immune injury among the vasculature of the central and peripheral nervous systems, the viscera, and the skin. In the vasculitides, the blood vessels are the central target of acute immune injury; in the connective tissue diseases they are one of the targets in processes with tempos ranging from indolent and chronic to acute and fulminant. Neurological abnormalities occur prominently in some of these diseases and infrequently in others. Here, we update information on some of the vasculitides and connective tissue diseases most often encountered by the neurologist or neuroscientist with an emphasis on the neurovascular abnormalities (table 1).

Keywords: vasculitides; connective tissue diseases

Table 1 The vasculitides

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| Polyarteritis nodosa* |
| Churg-Strauss angiitis* |
| Hypersensitivity vasculitis |
| Wegener's granulomatosis* |
| Lymphomatoid granulomatosis |
| Temporal arteritis* |
| Takayasu's arteritis |
| Behçet's disease |
| Isolated angiitis of the CNS* |
| Kawasaki's disease |
| CNS vasculitis secondary to infections* |
| CNS/PNS vasculitis secondary to neoplasia* |
| CNS/PNS vasculitis secondary to toxins* |
| Connective tissue diseases |
| Rheumatoid arthritis* |
| Systemic lupus erythematosus* |
| Sjögren's disease* |
| Progressive systemic sclerosis |
| Dermatomyositis/polymyositis |

*Discussed in text.

Background

The vasculitides are a group of diseases and disorders sharing the central feature of inflammation of the blood vessel wall with attendant tissue ischaemia. Because involvement of the blood vessel is intrinsic to inflammation of any type, vasculitis may be a manifestation of diverse diseases. When inflammation targets the vasculature and tissue injury results from ischaemia, the disease itself is called a vasculitis. Many varieties of vasculitis exist. Some are named on the basis of distinctive clinical features, others are recognised on the basis of a known aetiology. Classification of the primary and secondary vasculitides still depends on clinical and histological characteristics although recent advances in understanding immunopathogenic mechanisms offer additional diagnostic tools.

Clinically, preferential involvement of certain organs renders many of the diseases distinctive. Histologically, the type and size of vessel, the character of the inflammatory infiltrate, and the presence of necrosis, aneurysm formation, and cicatrization in the vessel wall contribute defining information. Recent studies of adhesion molecules, cytokines and their receptors, and neuropeptides add to the histopathological repertoire. The predominant mechanism of tissue damage is ischaemia resulting from impairment of blood flow from physical disruption of the vessel wall from the cellular infiltrate, haemorrhage from the altered wall competence, increased coagulation

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from changes in the normally anticoagulant endothelial cell surface, and increased vasomotor reactivity due to injury related release of certain neuropeptides.

The connective tissue diseases are systemic inflammatory diseases sharing the common features of involvement of muscle, joints, and skin. A component of these diseases is often a vasculitis or other immune mediated changes in the vasculature. However, with the possible exception of Sjogren's disease, vasculitis of the CNS rarely occurs. In addition to the ischaemia related injuries to the nervous system other mechanisms are widely investigated but not yet clearly established.

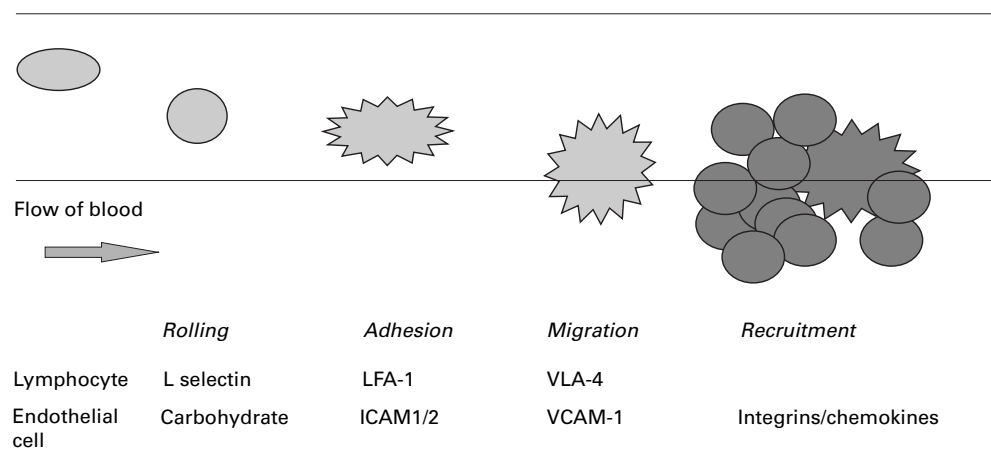
Immunopathogenic mechanisms in the development of inflammation

The vascular-immune response depends in part on vessel size as well as location. Blood vessels of different sizes subserve disparate functions. The interaction of the microvasculature with the immune system is critical to physiological inflammation. Numerous features render the cells of these vessels uniquely situated to connect the immune, vascular, and coagulation systems. Medium sized and larger vessels also possess properties suitable to their function specifically through their smooth muscle cells and their innervation by the vasanervorum. Currently, the role of these factors is better defined in their physiology than their pathology. The charge of the vessel lining and the presence of hormone receptors are other features being investigated for a role in the immune response

LEUCOCYTE-ENDOTHELIAL INTERACTIONS

The vascular endothelium, a highly specialised, metabolically active monolayer of cells, contributes to functional specialisation of different organs, maintains thromboresistance and vascular tone, directs lymphocyte circulation, and regulates inflammation and immune interactions. The dynamic interactions between endothelial cells, leucocytes, and platelets contribute to numerous physiologically important mechanisms. In the development of inflammation, a pivotal step involves leucocyte recruitment and attachment in the presence of blood flow. Leucocyte attachment to the endothelium is mediated by a multiple receptor-ligand system belonging to three families of related proteins: the selectins, the integrins, and the immunoglobulin superfamily. Families of chemoattractants further recruit specific cells along a concentration gradient, amplifying and increasing the diversity of cells in the infiltrate. The spatial and temporal development of selectins, chemoattractants, adhesion molecules, and integrins results in recruitment of leucocytes to a specific tissue site.¹⁻⁵ The figure outlines a series of events in rolling, adhesion, and migration.

Tissue injury depends on the ultimate location of fully activated leucocytes. In neutrophil mediated tissue injury, neutrophils, following a chemoattractant gradient, completely traverse the wall, and enter the tissue parenchyma. In this scenario, the final stages of activation, degranulation, and generation of toxic oxygen metabolites occur in the tissue with minimal changes in the vessel wall. However, if neutrophils are fully activated within the



A sequence of reciprocal interactions between a lymphocyte and endothelial cell resulting in inflammatory infiltrate. The location of the vasculitis, type of inflammatory infiltrate and persistence of vascular inflammation are determined by adhesion molecules, cytokines, leukotrienes, activated complement components, and microbial products. Subsequent steps of inflammation, penetration in the vessel wall, and release of injurious products, vary with individual immunopathogenic mechanisms. A loose binding enabled by the expression of a carbohydrate moiety or endothelial P selectin and leucocyte L selectin initiate the capture (rolling) of leucocytes from the flowing blood. Then the expression of integrins mediate the adhesion (arrest) stage. Leucocyte β_1 and β_2 integrins binding to their ligands such as VCAM and ICAM (members of the immunoglobulin superfamily of adhesion molecules) mediate firmer adhesion of the leucocyte to the endothelium. ICAM-1 is at least one ligand for the CD18 family of leucocyte integrins. Proinflammatory cytokines such as IL-1, IL-8, TNF, MCP-1, PAF, LTB₄, and C5a up regulate expression of these receptor ligand molecules on endothelial cells and leucocytes. After firm adhesion, leucocytes then traverse the vessel wall. This last step, diapedesis of the leucocytes between or through endothelial cells, involves homotypic adhesion of PECAM-1 (CD31) expressed on both leucocytes and endothelium. Chemoattractants are diffusely appearing molecules that recruit individual cell types and are thereby crucial in determining the cellular composition of the infiltrate. Because they function along a concentration gradient, they also influence the location of the infiltrate. MIP-1a seems to be a chemoattractant for B cells, cytotoxic T cells, and CD4 positive T cells. MIP-1b is a chemoattractant for eosinophils, monocytes, and T cells. Numerous other cloned chemokines, including IL-8, also contribute to endothelial-leucocyte adhesion.

vessel wall (as they are in many cases of vasculitis) then the release of lytic granules (including collagenases, proteases, and elastases) and toxic radicals (including hydroxyl radicals and hydrogen peroxide) injures the vessel wall itself.⁶⁻¹⁰ The most severe injuries cause mural necrosis leading to haemorrhage and thrombosis.

T lymphocyte mediated interactions in the vessel wall occur often but the mechanisms of vascular injury are less well defined.¹¹ Although T cell mediated vascular inflammation may result from antigen specific adhesion of T lymphocytes to endothelial cells (such as is seen in transplantation rejection and graft versus host disease), the presence of lymphocytes in an inflammatory lesion does not identify an antigen specific process. Cytokine initiated and amplified activation of either lymphocytes or endothelial cells provide a mechanism for cellular attachment in the absence of antigen. A characteristic of lymphocytes, distinguishing them from neutrophils, is their egress from the tissue with re-entry into the circulation. These memory lymphocytes respond more quickly to stimuli and are often more refractory to deletion.

Other cells participate in the cell mediated vasculitides. Important cells, particularly in the progression of inflammation from acute to chronic, are monocytes which when mature become macrophages. These cells also release cytokines that recruit more monocytes, macrophages, and lymphocytes to the site of injury. Notably, they also possess regulatory functions and may crucially down regulate the inflammatory responses. Platelets contribute to vascular damage by mechanisms distinct from their role in coagulation. Their cell surface receptors include class I MHC, P selectin, IgG receptors, low affinity IgE receptors, and receptors for von Willebrand factor and fibrinogen. A wide variety of substances activate platelets including adrenaline, adenosine diphosphate, collagen, serotonin, membrane attack complex of complement, vasopressin, platelet activating factor, and immune complexes. Activated platelets release various proinflammatory mediators that generate complement activation and augment neutrophil mediated injury. The eosinophil, characteristically present in lesions of patients with Churg-Strauss angiitis, also participates in the pathogenesis of vascular injury.¹²

IMMUNE COMPLEX MEDIATED

Immune complexes (antigen-antibody complexes) are a normal part of an immune response and are regularly cleared from the body. Immune complexes localised in vessel walls, either by deposition from the circulation or in situ formation, may be pathogenic¹³⁻¹⁴ depending on the characteristics of the host response, the nature of the stimulus, physical interactions between the complex and the vessel wall, and the presence of concurrent inflammation. Immune complexes can initiate a series of events recruiting an inflammatory response. The Fc portion of the IgG and IgM antibody molecules in the complexes engages

Fc receptors on neutrophils and monocytes both attaching these cells to the site of immune complex localisation and inducing degranulation and release of proinflammatory molecules. Immune complexes also activate complement components which induce various inflammatory events. C2a and C3a increase vascular permeability and neutrophil degranulation. C5a attracts neutrophils and monocytes to the region. The membrane attack complex, C5b-9, injures matrix materials and cells in the vessel wall. The results of these events are necrosis of the vessel wall, an exudative inflammatory response, and usually healing with prominent scarring. Immune complex mediated tissue damage is prominent in some of the vasculitides (hypersensitivity vasculitis) and connective tissue diseases.

AUTOANTIBODY MEDIATED

Several antibodies have a demonstrable *in vitro* and likely *in vivo* role in certain types of vasculitis.¹⁵ *In vitro* studies of Kawasaki's disease, an acute viral vasculitis of children, disclosed that antibodies to endothelial cells bind to neoantigens induced by interleukin-1 (IL-1) and tumour necrosis factor (TNF) on cultured endothelial cells and lyse their targets.¹⁶ This disorder, which only occasionally has neurological manifestations, illustrates the necessity for multiple coexistent signals for the development of pathological damage.

Antineutrophil cytoplasmic antibodies (ANCA) are a group of antibodies reactive with the neutrophils.¹⁷⁻²⁰ ANCA have two histological patterns: cANCA and pANCA which correlate with two different autoantigens, myeloperoxidase and proteinase 3 (PC-3), respectively. cANCA are strongly associated with Wegener's granulomatosis and microscopic polyarteritis. *In vitro*, ANCA have several effects. Binding of ANCA to neutrophils or monocytes *in vitro* stimulates the cells to undergo a respiratory burst that generates toxic oxygen metabolites, and to secrete proinflammatory mediators such as LTB₄, IL-8, and MCP-1 which recruit more neutrophils and monocytes. The neutrophils also degranulate, releasing lytic enzymes which may injure the vascular endothelium. Whether this series of events occurs *in vivo* is less clearly defined.²¹ ANCA associated vasculitides are characterised histologically by a neutrophil rich inflammatory infiltrate.

Local and systemic consequences of vascular inflammation

Obstruction of blood flow by induration of the vessel wall is only one component of tissue damage from inflammation. Secondary consequences, both local and systemic, contribute to the tissue injury. Acutely, several phenomena closely linked to inflammation also influence blood flow. Of these, vascular tone and coagulation are identifiable and amenable to therapeutic modulation. Blood flow is largely determined by tissue demands—viable tissue signals for changes in flow contingent to metabolic needs. This yoking of tissue metabolic demands with blood flow can be disrupted by

injury to the tissue, the vasculature, and, probably, the neuroendocrine system. Of note to clinicians is the limitation in using diagnostic studies which measure flow, such as single photon emission computed tomography (SPECT), to determine vascular integrity.

VASCULAR TONE

Maintenance of vascular tone is carefully regulated under normal circumstances. Intrinsic modulation of vascular tone depends, in part, on elaboration of both vasorelaxants (including prostacyclin, nitric oxide, endothelium derived relaxation factor), and vasoconstrictors (including endothelin). In inflammation, the release of endothelin by activated endothelial cells adds to ischaemic tissue injury by vasoconstriction.²²⁻²⁴ This feature is also of clinical diagnostic concern in interpretation of studies measuring vascular calibre, such as cerebral angiography or digital imaging.

COAGULATION

Several events intimately connected with, but temporally dispersed from the initial events, prominently contribute to the clinical features of vasculitis. Of these, coagulation is best studied. The convergence of procoagulant and anticoagulant properties associated with the endothelium normally exerts a net anticoagulant effect. Additional endothelial antiplatelet and fibrinolytic properties contribute to the maintenance of thromboresistance. During inflammation, the balance changes and the endothelial surface exerts a net procoagulant effect.²⁵⁻²⁸ The cytokines IL-1 and TNF have prominent procoagulant effects on the endothelium.

Systemic effects

Acute stress or local injury, including inflammation, activates pathways that function to reduce inflammation and also set a tone for future responses to inflammation. The activity of this neuroendocrine system depends on factors such as genetic responsiveness, early life stressors, and concurrent inflammation. Two limbs of the neuroendocrine system, the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-brainstem-autonomic nervous system mediate vital integrative responses. The HPA axis responds to various stressful and inflammatory stimuli with secretion of corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) which stimulate the release of adrenocorticotrophin (ACTH), among other molecules, from the pituitary, which, in turn, stimulate the release of cortisol from the adrenals. The cortisol feeds back on the adrenal, pituitary, hypothalamus, hippocampus, and frontal cortex, which then reduce the synthesis of cortisol and reduce the stress response. To the best of our current understanding, the brain requires cortisol within a limited range of concentrations; both too much and too little endanger neurons. Further, the regions of the brain which are vulnerable to cortisol influenced injury are those regions, including the hippocampus, which have a notable regulatory effect on the HPA

axis. Cortisol additionally has effects on leucocytes and endothelium, which have glucocorticoid receptors. In addition to cortisol, the intermediary molecules such as CRH and AVP have endocrine, behavioural, and immunological effects.

Another neuroendocrine limb also has broad and prominent effects. Information from the hypothalamus to brainstem nuclei activates diffuse adrenergical pathways that also effect behaviour, immune responses, and endocrine pathways. On the afferent side, information travels from the thorax and abdomen through the vagus nerve to the brain stem and from there projects to the hypothalamus and above.²⁹ All of these pathways are prominent in the responses to chronic inflammation and may contribute to the chronic changes in the cerebrovasculature.

FEATURES OF THE CNS VASCULATURE

Inflammation of the CNS vessels is less frequent than inflammation of the visceral or peripheral nervous system vasculature. Many of the central neurological complications in polyarteritis nodosa, for example, appear later in the course of disease and seem more likely to result from hypertensive or chronic vaso-occlusive changes than segmental inflammation of the vessel wall. This is also true of the connective tissue disease, systemic lupus erythematosus. Degenerative or vaso-occlusive cerebrovascular abnormalities appear but inflammatory vascular disease is rare even when the deposition of circulating immunoglobulin results in vasculitis in other organs.

Explanations for this relative paucity of inflammation in the CNS vasculature include diminished signalling, reduced trafficking, or tighter regulatory control over inflammation. Endothelial cells of the CNS are physically and biochemically distinctive, as are the microglia and astrocytes that contribute to tight endothelial junctions in the blood-brain barrier and prominently participate in the immune interactions within the immune system. Their tight intercellular junctions, paucity of micropinocytotic vessels, and high concentrations of γ -glutamyltranspeptidase are three examples. Lymphocyte traffic through the CNS is normally limited. Recent studies show that lymphocyte adhesion to brain endothelium is less than 5% compared with 15%-20% in other organs.³⁰⁻³² Activated lymphocytes do traverse the cerebral endothelium and enter the CNS, presumably performing a surveillance function. It seems likely that a low constitutive expression of pertinent adhesion molecules contributes to the low proclivity of cerebral vessels for vasculitis. For example, ICAM1 seems to be expressed constitutively only at low levels on brain endothelium *in vivo*, by contrast with other tissue endothelium. Also, although cerebral endothelial cells are capable of expressing MHC class I and II molecules (restriction elements for antigen presentation to the T cell receptor of CD8+ T cells and CD4+ helper T cells respectively) this occurs less often than in endothelium of the systemic vasculature.^{5 33 34} Further, molecules regulating

inflammation such as TGF- β , which down regulate adhesion of leucocytes, may play a more prominent part in the CNS than the systemic vasculature.

Clinical diseases

THE VASCULITIDES

The *idiopathic vasculitides* encompass various diseases. Classification and epidemiology of these unusual and pleomorphic vascular disorders remain topics of active discussion and study. Despite several recent attempts at classification, there is still debate about both the specificity and sensitivity of criteria used in individual diagnostic categories. Notably, the term *idiopathic* is not synonymous with *primary*; the *idiopathic vasculitides* do have underlying causes; however, they are not yet identified. The *secondary vasculitides* are prominent in their own right by both their frequency of occurrence and the necessity for accurate diagnosis to ensure proper therapy. The *connective tissue diseases* occur more often than the *vasculitides*, but as a rule, their clinical features are more pleomorphic and the mechanisms more enigmatic. Rheumatoid arthritis is a partial exception as a great deal of information about inflammation exists, immune regulation in the synovium has been studied, and biological therapies based on these studies are clinically available.

Polyarteritis nodosa

Polyarteritis nodosa, which affects medium and small sized vessels throughout the body, is the classic systemic necrotising vasculitis defined by both the widespread organ involvement and the necrosis prominent in the wall of affected vessels. It has various clinical manifestations, a range of severity, and, probably, numerous causes. Recently, hepatitis B associated *polyarteritis nodosa* was separated from other forms of *polyarteritis nodosa* to emphasise that the addition of antiviral agents in association with immunosuppressive and anti-inflammatory therapy improves the outcome. The distinction between *polyarteritis nodosa* and microscopic *polyarteritis nodosa*, which is based on clinically restricted disease and an association with ANCA in the latter, has regrouped current classifications of *polyarteritis nodosa*.³⁵⁻³⁷

Systemic symptoms of fever, malaise, and weight loss often herald the disease. Over half of the patients have either arthralgias or a rash. The skin lesions may be either erythematous, purpuric, nodular, or vasculitic. Renal involvement occurs in over 70% of patients, although an abnormal urinary sediment is more frequent than uraemia. Hypertension due to renal disease develops in about half the patients. Gastrointestinal changes, including abdominal pain, haemorrhage, pancreatitis, and gut infarction, occur in about 45% of patients and are a prominent cause of morbidity and mortality.

The five year survival of patients with *polyarteritis nodosa* rose from 18% untreated to 55% with corticosteroid therapy alone to about 79% with the current combination therapy of prednisone and cyclophosphamide.³⁸⁻⁴⁰ The mortality is greatest in the

first year of the disease and historically remains most closely associated with organ failure, particularly of the gastrointestinal tract.⁴¹ Substantial experience by several groups disclosed that the later complications of *polyarteritis nodosa* do affect survival. The longer term morbidity of the disease results from degenerative and hypertensive vascular disease affecting the heart, CNS, and kidneys. It is not clear whether the origin of the degeneration is a subclinical vasculitis in the coronary and cerebral vasculature healing with fibrosis and scarring or whether the vasculopathy is primarily degenerative and exacerbated by hypertension and medications such as prednisone. We anticipate, although it is not yet studied, that addition of therapeutic agents that minimise platelet aggregation and vasoconstriction to the lowest clinically effective dosages of corticosteroids will reduce the longer term complications of the disease.

Neurologically, both central and peripheral nervous system abnormalities occur but the frequency, tempo, and histology vary.⁴² Peripheral neuropathies, which are both frequent (50-75% of patients) and early (often presenting features of disease), are considered one of the defining features of the disease. Several patterns of neuropathy occur.⁴³⁻⁴⁵ Histological evidence of vascular inflammation in the *vasanervorum* and active axonal degeneration with asymmetric involvement between or within fascicles are typical. In histological studies of biopsies from muscle and nerves in patients with *polyarteritis nodosa* the cellular infiltrate consisted mainly of macrophages and T lymphocytes, particularly the CD4+ subset. Infiltrating cells exhibit immunological activation markers such as IL-2R, transferrin receptor, and MHC class II antigen expression.⁴⁶

Except for seizures and subarachnoid haemorrhage that may occur early, CNS abnormalities, such as stroke, usually occur later in the course of disease. Abnormalities of the CNS develop in 40% of patients. Frequent presentations include encephalopathy, focal and multifocal lesions of the brain and spinal cord, subarachnoid haemorrhage, seizures, strokes, and cranial neuropathies.^{47,48} Seizures are seldom recurrent and are easily controlled. Visual or oculomotor abnormalities develop from vasculitis in the orbits, the optic nerve and tracts, and the visual cortex as well as the cranial nerves and brain regions controlling ocular motility.

Laboratory studies usually find some evidence of systemic inflammation but there are no blood studies diagnostic for vasculitis. Although criteria are evolving,⁴⁹ the diagnosis of *polyarteritis nodosa* remains largely dependent on the classic methods of angiography and biopsy. Visceral angiography often discloses evidence of aneurysms and is an important diagnostic study. Thus the diagnosis of *polyarteritis nodosa*—evidence of systemic inflammation, angiographic evidence of enteric vascular diseases, and histological evidence of vasculitis, often in a peripheral nerve—is often substantiated by the neurological disease:

Churg-Strauss angiitis

Churg-Strauss angiitis was first described in 1951, on the basis of distinctive features at postmortem examination of 13 patients who died after an illness characterised by fever, asthma, eosinophilia, and a systemic illness.⁵⁰ This disease was initially included with polyarteritis nodosa but is increasingly regarded as a distinct entity although a recognised overlap exists.⁵¹ Histologically, medium and small vessels are affected. A debate over the necessity for strict histological criteria (necrotising vasculitis, tissue infiltration by eosinophils, and extravascular granuloma) to make the diagnosis continues. The two diagnostically essential lesions are angiitis and extravascular necrotising granulomas usually with eosinophilic infiltrates.⁵² In any single biopsy specimen, however, the changes may seem very similar to Churg-Strauss angiitis.

The disease is often heralded by rhinitis and then increasingly severe asthma. This prodrome may precede the development of eosinophilia and systemic vasculitis by 2 to 20 years. Clinical and haematological features distinguish it from polyarteritis nodosa. Early features may include anaemia, weight loss, heart failure, recurrent pneumonia, and bloody diarrhoea. Pulmonary involvement is typical in Churg-Strauss angiitis and rare in polyarteritis nodosa. Similarly, the eosinophilia, which is characteristic in Churg-Strauss angiitis is not a feature of polyarteritis nodosa.⁵³ Cutaneous manifestations include palpable purpura, erythema, and subcutaneous nodules.

Neurological abnormalities are similar to those in polyarteritis nodosa. Peripheral neuropathies, classically mononeuropathies multiplex, predominate (50–75% of patients) over CNS changes (25%). The histological features of vasculitis in the peripheral nerve blood vessel may contain the typical features of eosinophils and granulomas. Encephalopathies occurring early in the course of the disease are more frequent than in polyarteritis nodosa, probably reflecting the small size of vessels involved. Abnormalities of the CNS, including stroke, visual loss, subarachnoid haemorrhage, and chorea, are described in 15%–20% of patients.^{54–57} However, in the absence of histological evidence of vasculitis in the brain the frequency of cerebrovascular inflammatory disease remains conjectural. Visual abnormalities are more recently described as a prominent part of the disease. Encephalopathies, abnormalities in cognition with or without changes in level of arousal, seem to be more frequent than in the other systemic necrotising vasculitides but whether this reflects increased incidence or increased recognition is not known. Laboratory features also reflect general systemic inflammation. Although the sedimentation rate is increased, and antinuclear antibodies may be present in low titre, no autoantibodies are diagnostic of the disease. ANCA are rarely present. Thus the clinical features again provide important information for diagnosis. Features traditionally defining Churg-Strauss angiitis are asthma, hypereosinophilia, and a

systemic small vessel vasculitis that often affects the peripheral nerves.

Wegener's granulomatosis

Wegener's granulomatosis is characterised by a necrotising, granulomatous vasculitis of the upper and lower respiratory tract, glomerulonephritis, and small vessel vasculitis. Most patients present with complaints of otitis, epistaxis, rhinorrhoea, or sinusitis. Destruction of the cartilaginous nasal septal support of the bridge of the nose causes a characteristic abnormality, the "saddle nose." Systemic symptoms such as fever, malaise, weight loss, and anorexia are almost invariably present. Pulmonary involvement, if not among the presenting symptoms, is almost invariably seen on chest radiography. Renal abnormalities range from mild with an abnormal urinary sediment to uraemia requiring dialysis.^{55–59}

Neurological abnormalities, which are occasionally a presenting feature of the disease, result from contiguous extension of the sinus granulomas, a small vessel vasculitis, or remote granulomas. Cranial neuropathies, reflecting erosion from contiguous granulomas, are prominent and include visual loss, hearing loss, proptosis, ophthalmoplegias, and facial and trigeminal neuropathies.^{60–62} It may be difficult to distinguish between an optic neuropathy due to granuloma and an optic neuropathy secondary to a small vessel vasculitis clinically, but, CT and MRI have greatly aided diagnosis and therapy. The small vessel vasculitis in Wegener's granulomatosis largely affects the peripheral nervous system, resulting in both mononeuritic multiplex as well as polyneuropathies, but may also affect the CNS parenchyma.⁶³

Despite early descriptions, recent data show that the histological features of Wegener's granulomatosis are extremely pleomorphic. Neither the extravascular destructive granuloma nor the several types of vasculitis (microvasculitis with prominent infiltration of polymorphonuclear cells, granulomatous vasculitis, and medium vessel vasculitis with fibrinoid necrosis) are specific for the disease. Accurate diagnosis rests with clinical, histological, and laboratory information.

In active disease the sedimentation rate is invariably increased and a leukocytosis and thrombocytosis are usually present. The urinary sediment shows haematuria, sterile pyuria, and red blood cell casts with proteinuria. Autoantibodies to cANCA are present sufficiently often that they are considered markers of disease—although their role in pathogenesis is still debated.⁶⁴ None of the forms of ANCA are currently useful in determining overall relapse rate, type of relapse, morbidity, or longevity. Chest radiography is useful diagnostically, as is brain MRI.

The use of cyclophosphamide therapy, given orally at 2 mg/kg/day, dramatically reduced the mortality of Wegener's granulomatosis and a combination of cyclophosphamide and corticosteroid induces remission in most patients.⁶⁵ The antimicrobial trimethoprim-sulfamethoxazole may be an effective adjunct therapy.

Temporal arteritis (giant cell arteritis)

Temporal arteritis (giant cell arteritis) typically affects people over the age of 50 and seems more prevalent among women of northern European background. Several studies show both a seasonal and cyclic (over 5–7 years) variation in incidence although the reasons for this remain unknown. Although this is a systemic arteritis, clinical features, except for malaise and arthralgias, seldom occur below the neck. When systemic features are prominent the diagnosis is more likely to be polyarteritis nodosa or Churg-Strauss angiitis. The clinical overlap of temporal arteritis with polymyalgia rheumatica requires rigorous attention to diagnostic criteria to facilitate correct diagnosis and therapy.^{66–69}

Headaches, tender temporal arteries, and jaw claudication predominate, although ischaemic optic neuropathies remain the feared complication. Occasionally, intracranial disease referable to the posterior circulation occurs.^{70–71} The natural history, based on several older series, indicates that the disease is self limiting although several exacerbations often occur before the symptoms subside. In current studies, survival is not diminished in patients with temporal arteritis compared with age matched cohorts. Corticosteroid therapy alone seems effective in preventing the devastating ischaemia to the visual system but there is little evidence that it alters the course of the disease. Corticosteroids are more effective given on a daily schedule than on alternate day dosing.⁷² When blindness arises, recovery of vision is infrequent, occurring in less than 15% of patients. The less frequent ophthalmoplegias share a better prognosis with substantial improvement or resolution in most patients.⁷³ Given the real and potential complications of the corticosteroid therapy, it is important, albeit difficult, to determine the necessary duration of therapy. Given the documented relapses with visual loss after short term corticosteroid therapy, most specialists in vasculitis continue the medication for at least a year. As corticosteroids administered over this time often cause complications, it is also important to establish the diagnosis as firmly as possible, with a temporal artery biopsy. This is positive in about 86% of the cases when performed on the symptomatic side and a sufficiently large sample is studied. Bilateral biopsies improve sensitivity by about 14%.⁷⁴

The laboratory abnormality most commonly found in temporal arteritis is an increased erythrocyte sedimentation rate, which occurs in the vast majority of patients. However, a few patients may have normal or only modestly increased sedimentation rates at the time of presentation, and relapses may not always be accompanied by an increase, indicating that long term management of these patients should include repeated clinical assessment.^{75–76}

Isolated angiitis of the CNS

Isolated angiitis of the CNS is an idiopathic vasculitis affecting blood vessels of the CNS within the dural reflections. Although this disease is rare, recognition has increased over the

past two decades concurrent with improvements in both diagnosis and therapy. Historically, the disease was called granulomatous angiitis on the basis of granulomas present on postmortem examination. However, antemortem granulomata are a variable and, often, absent histological feature. Further, other processes, particularly vasculitis secondary to certain viral infections and malignancies display intracranial granulomata. Thus the term isolated angiitis of the CNS was devised to describe cases in which the disease is clinically restricted to the CNS, no underlying aetiology is identifiable, and inflammation of the vasculature is defined histologically.^{77–78} Some authors use the term “primary angiitis of the CNS” but this a poorly defined term usually lacking histological confirmation. Further the term primary implies the absence of an underlying cause rather than a difficult to elucidate aetiology. Given the wide variety of processes and diseases that may be mistaken for CNS vasculitis, rigorous evaluations are necessary to exclude the numerous secondary causes of CNS vascular inflammation and alternative causes of vasculopathy.

Isolated angiitis of the CNS occurs predominantly in the fourth to sixth decades, although patients of ages from 7 to 71 have been described. In earlier postmortem series, males predominated but recent studies show an equal sex ratio. Neurological features are protean although typically persistent headaches, encephalopathy, and multifocal signs suggest the diagnosis. Strokes may be prominent in some patients but more often the small vessel abnormalities coalesce and are not clinically definable. Seizures occur in about 5% of patients and are usually focal. Both cranial neuropathies and myelopathies appear and may predominate in individual patients. Subarachnoid haemorrhage, when present, is typically mild. Behavioural or psychiatric features (in the absence of pre-existing disease) are increasingly recognised.^{79–81} Systemic features are absent from this disease, which targets the CNS vasculature. The presence of features referable to the joints, skin, or other organs should direct the diagnosis to systemic inflammatory diseases with secondary neurological involvement.

Diagnosis depends on a combination of clinical, angiographic, and histological features. Laboratory evidence of systemic inflammation is absent. Thus the sedimentation rate, antinuclear antibody, C reactive proteins, and haematological features of inflammation (thrombocytosis, leukocytosis, and anaemia) are not present. Neurodiagnostic studies, including CT and MRI, are often non-specifically abnormal. Brain CT has identified subarachnoid haemorrhages in individual patients. Abnormalities on MRI range from diffuse periventricular lucencies, enhancing arteries, and mass lesions, to diminished intensities in an arterial distribution. Analysis of CSF is abnormal in only half the patients and even then the abnormalities may simply be a mild pleocytosis or increase in protein. Angiography and biopsy, both keys to accurate diagnosis,

investigate blood vessels of different sizes and are subject to sampling error and misinterpretation. Angiography is the most sensitive neurodiagnostic study, although about 10% of patients with histologically confirmed vascular disease have a normal angiogram. Of even greater concern to accurate diagnosis is the fact that the angiographic features are not specific for isolated angiitis of the CNS; similar abnormalities may occur in non-inflammatory vasculopathies as well as vasculitis secondary to infections, drugs, and neoplasia. Angiography often shows single or multiple areas of beading along the course of a vessel, abrupt vessel terminations, hazy vessel margins, and neovascularisation.⁸²

For our studies in diagnosis and therapy, we use a modification of criteria published previously: (1) clinical features consistent with recurrent, multifocal, or diffuse disease; (2) exclusion of an underlying systemic inflammatory process or infection; (3) neuroradiographic studies, usually a cerebral angiogram, supporting diagnosis of vasculopathy; and (4) brain biopsy to establish the presence of vascular inflammation and exclude infection, neoplasia, or alternate causes of vasculopathy. Untreated, the disease recurs and disability progresses although the time frame is not clearly established. Early studies described the mortality in untreated patients as 9 months to a year. More recently, we have found that untreated disease may smolder over several years, although recurrent disease is the rule. Patients treated with prednisone alone have a high relapse rate, in one study greater than 90%. Therapy with cyclophosphamide, usually in combination with a low dosage of prednisone, results in a long term remission or cure in many patients. We cannot yet determine accurately the relapse rate given the rarity of the disease. The response to cyclophosphamide depends, in part, on the duration of therapy. An early series of patients treated for 6 months after clinical remission of symptoms developed a relapse in 30%. The current protocol of 12 months of therapy corresponds to a relapse rate lower than 10%. The outcome of individual neurological episodes is fairly good with many patients returning to normal function. As with other types of vascular injury, the occipital cortex heals poorly and hemianosias are usually persistent. The radiculopathies and myelopathy features encountered in some patients do heal, albeit, slowly. Episodes of mania or psychoses may be recurrent and difficult to treat but subside with treatment of the underlying vascular inflammation.

Secondary vasculitides

Vasculitis of the nervous system secondary to a known cause or underlying process is both frequent and clinically important. Patients with CNS vasculitis from secondary causes far exceed patients with an isolated, idiopathic vasculitis. A high index of suspicion for underlying aetiologies enables a clinician to promptly institute therapy for a vasculitis secondary to an infection, neoplasia, or toxin.

The range of infections that induce vascular inflammation is broad including bacteria, fungi, viruses, and protozoa.⁸³ The prolific vascular inflammation induced by bacteria is associated with prominent thromboses and haemorrhage.⁸⁴ Thus strokes are part of acute bacterial meningitis and responsible for much of the neurological sequelae. Other infectious agents often causing a CNS vasculitis, but more difficult to detect, are fungi, aspergillosis, cryptococcus, coccidioides immitis, mucormycoses, and histoplasma capsulatum.^{48 85-87} Neuroborreliosis also results in vasculitis.⁸⁸ The clinical features of these indolent infections range from subtle changes in cognition to fatal haemorrhagic infarctions. Infectious agents of diseases such as tuberculosis and syphilis also cause vasculitis, although systemic evidence of disease is typical. Numerous viruses (herpes simplex, varicella zoster, cytomegalovirus, and HIV) induce inflammation and necrosis of the cerebral blood vessel walls.⁸⁹⁻⁹¹ However, the range of vasculopathies associated with viruses is broad and some, such as herpes zoster, may show vaso-occlusive disease without inflammatory changes.

Toxins also cause vasculitis.⁹²⁻⁹⁵ The cutaneous disorder hypersensitivity vasculitis is associated with a wide variety of inciting agents, but complications of the CNS are few. Vasculitis of the CSF, however, is well reported after taking various illicit drugs, notably those with a prominent sympathomimetic effect, such as amphetamines. It remains difficult to determine a causative agent in a package that contains numerous diluents and additives. Cocaine and crack cocaine cause stroke and haemorrhage and have, occasionally, been associated with a vasculitis.

The unusual association of CNS vasculitis and neoplasia is intriguing. Clinically, it is most notable as a reminder of the importance of distinguishing between a vascular occlusion associated with encasement of the vessel by tumour and one due to a paraneoplastic inflammation of the vessel. Hodgkin's disease, however, is associated with a vasculitis that resolves with the treatment of the underlying disease. The association of a peripheral nervous system vasculitis and malignancy is also rare.⁹⁶⁻⁹⁸

CONNECTIVE TISSUE DISEASES

By contrast with the infrequently occurring vasculitides that feature a central involvement of blood vessels, albeit by several different mechanisms, the connective tissue diseases occur much more often, exhibit genetic susceptibilities, and possess a range of immunopathogenic mechanisms. The frequency of neurological and psychiatric abnormalities varies among the individual disorders. In addition, a more extensive array of mechanisms mediate tissue injury. Vascular disease remains important although histological evidence of vasculitis is variable. Other cellular mechanisms which result in parenchymal injury in visceral organs and the skin are being investigated for their role in neurological and psychiatric abnormalities.

Gromocyte-macrophage colony stimulating factor

Rheumatoid arthritis is a systemic autoimmune disease characterised by a symmetric inflammatory polyarthritis. Histological examination of the involved joints discloses synovial hypertrophy and chronic inflammation with invasion by activated T cells, macrophages, and plasma cells, as well as pannus formation. The release of inflammatory mediators and degradative enzymes such as metalloproteinases by the inflammatory cells results in progressive destruction of the cartilage and adjacent bone. Systemic manifestations occur in more severe cases and include nodules, consisting of palisading macrophages and, often occurring in areas of trauma, a vasculitis of small and medium sized arteries, and pleural, pulmonary, and pericardial involvement. As with other autoimmune diseases, women are more afflicted than men, suggesting a hormonal influence. The finding that rheumatoid arthritis usually remits during pregnancy, only to flare again postpartum, further underscores the importance of hormones in this disease.⁹⁹⁻¹⁰⁰

The rheumatoid factor, generally an IgM antibody specific for the Fc portion of IgG, was one of the first immunological abnormalities. Its presence was associated with more severe forms of disease. However, rheumatoid factors are not found in all patients with rheumatoid arthritis, and are found in other diseases without prominent articular manifestations, arguing against a major role for the antibody in pathogenesis.

The prevailing view maintains that rheumatoid arthritis is initiated by a T lymphocyte response to an exogenous or endogenous antigen, followed by a perpetuation of the inflammatory response, resulting in synovial proliferation and the release of inflammatory mediators. However, evidence for T lymphocyte involvement remains indirect. That more than 80% of white patients with rheumatoid arthritis have an HLA DR1 or DR4 allele containing a unique sequence of about five amino acids in the antigen binding cleft suggests that antigen presenting cells from these patients have the unique ability to bind a specific peptide antigen. As the only known function of these molecules is to present the bound peptide to CD4+ T cells, it has been proposed that presentations of an as yet unknown antigenic fragment to T cells, by this unique class II MHC molecule, initiates the disease. Evidence that T cell specific therapeutic agents such as cyclosporin are effective in rheumatoid arthritis also argues that T cells play a part.¹⁰¹

By contrast with the uncertainties about the initial steps in the development of rheumatoid arthritis, the role of cytokines in the inflammatory process is relatively well characterised. Key cytokines include TNF α and IL-1. These cytokines are secreted by cultured synovium and seem to be important in regulating the inflammatory response. Adding anti-TNF antibodies to cultured synovium decreases production of other proinflammatory cytokines such as IL-1, IL-6, GM-CSF, and IL-8,

whereas adding IL-1 decreases IL-6 and IL-8 but not TNF α . Transgenic mice overexpressing TNF α or IL-1 develop an erosive arthritis, further supporting a role for these cytokines in inflammatory arthritis. These findings have stimulated protocols using inhibitors to these cytokines, with encouraging early results.¹⁰⁰⁻¹⁰²⁻¹⁰³

The predominant neurological abnormalities are peripheral neuropathies. These develop from compression in regions of hypertrophic tendons and ligaments as well as from ischaemia to the vasa nervorum.¹⁰⁴⁻¹⁰⁶ The most dramatic and potentially devastating neurological complications are the cervical myelopathies and vertebral basilar occlusions from atlantoaxial displacement.¹⁰⁷⁻¹⁰⁹

Systemic lupus erythematosus

Systemic lupus erythematosus is a multisystem autoimmune disease characterised by circulating autoantibodies.¹¹⁰⁻¹¹¹ Features that define the disease are particular patterns of autoantibodies (such as those to dDNA or ribosomal proteins) and evidence of organ system damage, usually through immune complex deposition (for example, skin, kidneys) or direct autoantibody effects (for example, anaemia, thrombocytopenia). Other non-defining aspects of disease such as fever, arthralgias, and malaise seem to be mediated by cytokines and indicate the presence of systemic inflammation. The epidemiology of systemic lupus erythematosus is complex, reflecting the multiple genetic, hormonal, and environmental factors that contribute to the manifestation of disease. Relatives of patients with systemic lupus erythematosus have a higher incidence of other autoimmune disorders than the general population. The particular distribution of disease among women of child bearing age supports the hypothesis that hormonal factors influence disease activity—as do the effects of menarche and pregnancy. In most patients the disease is episodic; exacerbations may be precipitated by exposure to ultraviolet light, medications, or infections.

Neuropsychiatric systemic lupus erythematosus refers to the range of neurological, psychiatric, and behavioural abnormalities that occur in patients with systemic lupus erythematosus. Identifiable secondary causes of neurological or psychiatric abnormalities (which may account for up to half of episodes) such as infections, metabolic disorders, and toxins including side effects of medications must be excluded in each patient. The range and acuity of neuropsychiatric systemic lupus erythematosus abnormalities are broad; some features are severe and dramatically increase the morbidity and mortality of disease.¹¹²⁻¹¹⁹ Other features are transient or, if persistent, create only a minor disruption of lifestyle. Abnormalities of almost every region of the neuraxis are reported—but certain aspects are more prominent than others (table 2). Although numerous clinical features occur, the most often encountered (40%-50% of all patients with systemic lupus erythematosus) are (1) encephalopathies manifest by memory

Table 2 Features of neuropsychiatric systemic lupus erythematosus

| |
|---|
| Seizures: |
| Abnormalities in consciousness, cognition, and behaviour: |
| Encephalopathies: |
| Acute confusional states |
| Acute, or subacute changes in behaviour, cognition, or level of arousal |
| Dementias: |
| Isolated cognitive abnormalities: |
| Mild cognitive disorder |
| Mild/moderate cognitive impairment |
| Other: aphasias, neglect syndromes, dressing disorders |
| Mood disorders with or without psychoses: |
| Sleep disorders |
| Psychological disorders: |
| Somatiform disorders |
| Anxiety disorders |
| Personality disorders |
| Cerebrovascular disease: |
| Stroke |
| Multi-infarct disorders |
| Microvascular disease |
| Subarachnoid haemorrhage |
| Cerebral venous thromboses |
| Cranial neuropathies: |
| Optic neuropathies |
| Cranial neuropathies affecting extraocular muscles |
| Trigeminal neuropathy |
| Facial neuropathy |
| Ataxia |
| Movement disorders, particularly chorea |
| Myelopathies |
| Peripheral neuropathies |
| Radiculopathy |
| Plexopathy |
| Mononeuropathy |
| Polyneuropathy |
| Autonomic neuropathy |
| Myasthenia gravis |
| Myopathy |

loss, confusion, changes in cognition and sometimes, level of arousal, (2) seizures either focal or generalised, and (3) behavioural changes including depression, altered social interaction, changes in judgment, and anxiety. The encephalopathies may appear as acute confusional states, cognitive impairment sometimes demonstrated by abnormalities in information processing or specific patterns of memory loss. At times, subtle cognitive abnormalities may interfere with activities of daily living. Strokes occur in systemic lupus erythematosus although the actual frequency remains undefined. Microvascular disease is a frequent histological finding occurring in excess of documented clinical episodes of ischaemia. Medium and large vessel abnormalities are more closely associated with clinical events. Of the mechanisms causing blood vessel abnormalities, emboli, degenerative changes in the vessel wall, and coagulopathies are mentioned although their quantitative roles are not clear. It is likely that cerebral infarction is overdiagnosed in some patients when the focal motor abnormalities may have another cause (metabolic) and underdiagnosed in others, in whom the presence of diffuse microvascular changes may be mistaken for a metabolic encephalopathy. Seizures may be a presenting feature of systemic lupus erythematosus in up to 5% of patients. Their onset before evidence of systemic disease has suggested that particular regions of the brain, particularly the hippocampus, may be an early target of disease. The seizures themselves are typically easily treated with anticonvulsant medications, none of which are contraindicated in systemic lupus

erythematosus. Mood disorders seem to be overrepresented in systemic lupus erythematosus compared with other chronic illnesses. Psychoses are infrequent but dramatic; some studies suggest an association with a particular pattern of autoantibodies, antiribosomal P antibodies. Cranial neuropathies, particularly those affecting vision and extraocular movements, must be carefully evaluated to distinguish them from other disorders.

The pathogenesis of the neurological abnormalities are undefined but multiple contributions from autoantibodies reactive with neuronal tissue, ischaemia from coagulopathies, and cytokine associated changes in behaviour illustrate the interactions and potential synergisms of multiple forms of injury. Some diverse manifestations of neuropsychiatric systemic lupus erythematosus could share common mechanisms of injury. Glutamate, the principal excitatory neurotransmitter in the brain, mediates many normal neurological functions. However, overstimulation of the glutamate receptors initiates an excessive influx of calcium into neurons and mediates specific cell damage. Whether the cell recovers or dies depends on many processes including location of injury and other molecules present in the local milieu. Notably, glucocorticoids, either endogenously increased through stress or pharmacologically administered, increase the damage in this process. Further contributing to the dysregulation of the stress axis is the vulnerability of the hippocampus to seizures, hypoxic or ischaemic injury, and damage caused by glucocorticoids. Among the important roles of these cells are their prominent regulatory influences on inflammation, as well as reproductive and autonomic nervous system function. Studies investigating the integrity of this region of the brain in patients with systemic lupus erythematosus are proceeding.

Although acute inflammation of the cerebral vasculature is rare, the presence of systemic inflammation may affect the cerebrovasculature in other ways. IL-1 and IL-6 (both raised in serum of patients with systemic lupus erythematosus and the CSF of patients with neuropsychiatric systemic lupus erythematosus) affect the vascular endothelium in at least three clinically relevant ways: (1) increased expression of proinflammatory molecules and adhesion molecules, (2) changes in the net anticoagulant surface of the endothelium to a procoagulant surface, and (3) altering the balance of vasomotor tone to increased vasoconstriction through increased expression of endothelins. In a disease with persistent or recurrent inflammation, the consequences may be diminished blood flow or blood flow overly responsive to other influences.

Sjögren's disease

Sjögren's disease is a chronic autoimmune inflammatory disease characterised by diminished lacrimal and salivary secretion resulting in keratoconjunctivitis sicca and xerostomia. It is usually a relatively benign disease manifest primarily by exocrine gland impairment as a result of destructive mononuclear infiltrates of

the lacrimal and salivary glands. In some patients, however, visceral involvement occurs and a wide range of extraglandular manifestations may occur as a result of lymphoid infiltration of lung, kidney, skin, thyroid gland, stomach, liver, and muscle. There exists a strong association between Sjögren's disease and anti-Ro (SSA) antibodies, although anti-La antibodies also occur. The importance of these autoantibodies in the pathogenesis of the disease is not established. Diagnosis of Sjögren's disease rests on clinical features, lip biopsy demonstrating lymphocyte infiltration, and, usually, circulatory autoantibodies.¹²⁰

Neurological manifestations are more frequent in the peripheral nervous system than the CNS although the incidence is not clearly defined. Several patterns of neuropathy occur. In one series of nerve biopsies, however, eight out of 11 patients had findings consistent or highly suggestive of vasculitis; other patients had a perivascular inflammatory response. An alternative, distinctive neuropathy in Sjögren's disease is not vasculitis but a dorsal root ganglionitis. These patients present with a sensory neuropathy and ataxia usually associated with autonomic insufficiency.¹²¹⁻¹²³ Cranial neuropathies, particularly trigeminal neuropathy, are common and may occur in up to 40% of patients. Although other CNS abnormalities do occur their incidence and mechanisms remain undefined.¹²⁴⁻¹²⁶ The role of a CNS vasculitis as a part of Sjögren's disease remains an intriguing possibility that requires further study.

Summary

The vasculitides, a group of disorders characterised by inflammation of blood vessels, may constitute the primary manifestation of a clinical syndrome or develop secondary to other conditions such as infections and connective tissue diseases. The histological features, the clinical characteristics, and the presence of any underlying aetiology define the individual diseases. Classification, however, remains imprecise until we have a more complete understanding of the immunopathogenic mechanisms. Despite limited clinical and histological expressions of injury, vasculitis results from many different aetiologies and pathogenic mechanisms. Clinically, neurological abnormalities are a variable feature of the vasculitides. Their frequency ranges from rarely or not at all in diseases such as Kawasaki's syndrome to invariably in isolated angitis of the CNS.

The connective tissue diseases are clinically distinctive, both more frequent and enigmatic than the vasculitides. In rheumatoid arthritis, the neurological features are most often secondary to distortions of joint architecture. Systemic lupus erythematosus, on the other hand, displays numerous neurological abnormalities although the contributions from autoantibodies, immune complexes, cytokines, and hormones on tissue parenchyma or vasculature are not defined. The diagnostic criteria for Sjögren's syndrome are evolving. Whereas

the pathogenic mechanisms of the neuropathies are well defined; the CNS changes are poorly understood.

- Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 1994;76:301-14.
- Luscinskas FW, Brock AF, Arnaout MA, et al. Endothelial-leukocyte adhesion molecule-1 dependent and leukocyte (CD11/CD18)-dependent mechanisms contribute to polymorphonuclear leukocyte adhesion to cytokine-activated human vascular endothelium. *J Immunol* 1989;142:2257-63.
- Argenbright LW, Barton RW. Interactions of leukocyte integrins with intercellular adhesion molecule 1 in the production of inflammatory vascular injury in vivo. *J Clin Invest* 1992;89:259-72.
- Braquet P, Hosford D, Braquet M, et al. Role of cytokines and platelet-activating factor in microvascular immune injury. *Int Arch Allergy Appl Immunol* 1989;88:88-100.
- Pober JS, Collins T, Gimbrone MA Jr, et al. Inducible expression of class II major histocompatibility complex antigens and the immunogenicity of vascular endothelium. *Transplantation* 1986;41:141-6.
- Sacks T, Moldow C, Craddock P, et al. Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes. An in vitro model of immune vascular damage. *J Clin Invest* 1978;61:1161-7.
- Blann AD, Scott DGI. Activated, cytotoxic lymphocytes in systemic vasculitis. *Rheumatol Int* 1991;11:69-72.
- das Neves FC, Suassuna J, Leonelli M. Cell activation and the role of cell-mediated immunity in vasculitis. *Contrib Nephrol* 1991;94:13-21.
- Rothlein R, Kishimoto TK, Mainolfi E. Cross-linking of ICAM-1 induces co-signaling of an oxidative burst from mononuclear leukocytes. *J Immunol* 1994;152:2488-95.
- Osborn L. Leukocyte adhesion to endothelium in inflammation. *Cell* 1990;62:3-6.
- Burger DR, Vetto RM. Vascular endothelium as a major participant in T-lymphocyte immunity. *Cell Immunol* 1982;70:357-61.
- Tai PC, Holt ME, Denny P, et al. Deposition of eosinophil cationic protein in granulomas in allergic granulomatosis and vasculitis: the Churg-Strauss syndrome. *BMJ* 1984;289:400-2.
- Cochrane CG. Studies on the localization of circulating antigen-antibody complexes and other macromolecules in bessels. II. Pathogenetic and pharmacodynamic studies. *J Exp Med* 1963;118:503-13.
- Cochrane CG, Weigle WO. The cutaneous reaction to soluble antigen-antibody complexes. A comparison with the Arthus phenomenon. *J Exp Med* 1958;108:591-604.
- Kallenberg CGM. Autoantibodies in vasculitis: current perspectives. *Clin Exp Rheumatol* 1993;11:355-60.
- Leung DYM, Geha RS, Newburger JW, et al. Two monokines, interleukin 1 and tumor necrosis factor, render cultured vascular endothelial cells susceptible to lysis by antibodies circulating during Kawasaki syndrome. *J Exp Med* 1986;164:1958-72.
- van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985;425-9.
- Gross WL, Schmitt WH, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenetic aspects. *Clin Exp Immunol* 1993;91:1-12.
- Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 1988;318:1651-7.
- O'Donoghue DJ, Short CD, Brechley PEC, et al. Sequential development of systemic vasculitis with anti-neutrophil cytoplasmic antibodies complicating anti-glomerular basement membrane disease. *Clin Nephrol* 1989;32:251-5.
- Jennette JC, Falk RJ. Clinical and pathological classification of ANCA-associated vasculitis: what are the controversies? *Clin Exp Immunol* 1995;101:18-22.
- Hamann GF, del Zoppo GJ. Leukocyte involvement in vasomotor reactivity of the cerebral vasculature. *Stroke* 1994;25:2117-9.
- Brenner BM, Troy JL, Ballermann BJ. Endothelium-dependent vascular responses. *J Clin Invest* 1989;84:1373-8.
- Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. *N Engl J Med* 1994;330:1431-8.
- Bevilacqua MP, Pober JS, Majean GR, et al. Interleukin 1 (IL-1) induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. *J Exp Med* 1984;160:618-23.
- Rossi V, Breviario F, Ghezzi P, et al. Prostacyclin synthesis induced in vascular cells by interleukin-1. *Science* 1985;229:174-6.
- Stern DM, Bank I, Nawroth PP, et al. Self-regulation of procoagulant events on the endothelial cell surface. *J Exp Med* 1985;162:1223-35.
- Bevilacqua MP, Pober JS, Majean GR, et al. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci USA* 1986;83:4533-7.

- 29 Kent S, Bret-Dibat JL, Kelley KW, et al. Mechanisms of sickness-induced decreases in food-motivated behavior. *Neurosci Biobehav Rev* 1996;20:171-5.
- 30 Hickey WF. Migration of hematogenous cells through the blood-brain barrier and the initiation of CNS inflammation. *Brain Pathol* 1991;1:97-105.
- 31 Hart MN, Zsuzsanna F, Waldschmidt M, et al. Lymphocyte interacting adhesion molecules on brain microvascular cells. *Mol Immunol* 1990;27:1355-9.
- 32 Male D, Pryce G, Hughes C, et al. Lymphocyte migration into brain modelled in vitro: control by lymphocyte activation, cytokines, and antigen. *Cell Immunol* 1990;127:1-11.
- 33 Wong GHW, Bartlett PF, Clark-Lewis I, et al. Inducible expression of H-2 and Ia antigens on brain cells. *Nature* 1984;310:688-91.
- 34 Fabry Z, Waldschmidt MM, Hendrickson D, et al. Adhesion molecules on murine brain microvascular endothelial cells: expression and regulation of ICAM-1 and Lgp 55. *J Neuroimmunol* 1992;36:1-11.
- 35 Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187-92.
- 36 Savage COS, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med* 1985;220:467-83.
- 37 Scott DGI, Bacon PA, Elliot PJ, et al. Systemic vasculitis is a district general hospital 1972-80; clinical and laboratory features, classification, and prognosis in 80 cases. *Q J Med* 1982;51:292-311.
- 38 Frohnert PP, Sheps SG. Long-term follow-up study of periarteritis nodosa. *Am J Med* 1967;43:8-14.
- 39 Lieb ES, Restivo C, Paulus HE. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med* 1979;67:941-7.
- 40 Fauci AS, Katz P, Haynes BF, et al. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979;310:235-8.
- 41 Guillevin L, Le TH, Godeau P, et al. Clinical findings and prognosis of polyarteritis nodosa and Churg Strauss angitis: a study in 165 patients. *Br J Rheumatol* 1988;27:258-64.
- 42 Moore PM, Fauci AS. Neurologic manifestations of systemic vasculitis. A retrospective and prospective study of the clinicopathologic features and responses to therapy in 25 patients. *Am J Med Sci* 1981;71:517-24.
- 43 Bouche P, Leger JM, Travers MA, et al. Peripheral neuropathy in systemic vasculitis: clinical and electrophysiologic study of 22 patients. *Neurology* 1986;36:1598-602.
- 44 Hawke SH, Davies L, Pamphlett R, et al. Vasculitic neuropathy. A clinical and pathologic study. *Brain* 1991;114:2175-90.
- 45 Said G, Lacrois-Ciaudo C, Fujimura H. The peripheral neuropathy of necrotizing arteritis: a clinicopathologic study. *Ann Neurol* 1988;23:461-5.
- 46 Cid M, Grau JM, Casademont J, et al. Immunochemical characterization of inflammatory cells and immunologic markers in muscle and nerve biopsy specimens from patients with systemic polyarteritis nodosa. *Arthritis Rheum* 1994;37:1055-61.
- 47 Ford RG, Siekert RG. Central nervous system manifestation of periarteritis nodosa. *Neurology* 1965;15:114-22.
- 48 Moore PM, Fauci AS. Neurologic manifestations of systemic vasculitis. A retrospective study of the clinicopathologic features and response to therapy in 25 patients. *Am J Med* 1981;71:517-24.
- 49 Lightfoot RW, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088-93.
- 50 Churg J, Strauss L. Allergic granulomatosis, allergic angitis, and periarteritis nodosa. *Am J Pathol* 1951;27:277-301.
- 51 Chumbley LC, Harris EG, DeRemee RA. Allergic granulomatosis and angitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc* 1977;52:477-84.
- 52 Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angitis). *Arthritis Rheum* 1990;33:1094-100.
- 53 Lanham JG, Elkon KB, Pusey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 1984;63:65-81.
- 54 Chang Y, Karga S, Goates J, et al. Intraventricular and subarachnoid hemorrhage resulting from necrotizing vasculitis of the choroid plexus in a patient with Churg-Strauss syndrome. *Clin Neuropathol* 1993;12:84-7.
- 55 Kok J, Bosserey A, Brion J, et al. Chorea in a child with Churg Strauss syndrome. *Stroke* 1993;24:1263-4.
- 56 Weinstein JM, Chui H, Lane S, et al. Churg Strauss syndrome (allergic granulomatous angitis). Neuro-ophthalmologic manifestations. *Arch Ophthalmol* 1983;101:1217-20.
- 57 Acheson JF, Cockerell OC, Bentley CR, et al. Churg Strauss vasculitis presenting with severe visual loss due to bilateral sequential optic neuropathy. *Br J Ophthalmol* 1993;77:118-9.
- 58 Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101-7.
- 59 Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
- 60 Nishino H, Rubino FA, DeRemee RA, et al. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol* 1993;33:4-9.
- 61 Miller K, Miller K. Wegener's granulomatosis presenting as a primary seizure disorder with brain lesions demonstrated by magnetic resonance imaging. *Chest* 1993;103:316-8.
- 62 Bullen CL, Liesegang TJ, McDonald TJ, et al. Ocular complications of Wegener's granulomatosis. *Am J Ophthalmol* 1989;90:279-90.
- 63 Stern GM, Hoffbrand AV, Ulrich H. The peripheral nerves and skeletal muscles in Wegener's granulomatosis: a clinico-pathological study of four cases. *Brain* 1989;58:151-64.
- 64 Gross WL, Csernok E, Flesch BK. Classic anti-neutrophil cytoplasmic autoantibodies (cANCA), Wegener's autoantigen and their immunopathogenic role in Wegener's granulomatosis. *J Autoimmun* 1993;6:171-84.
- 65 Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
- 66 Hunder GG, Lie JT, Goronzy JJ, et al. Pathogenesis of giant cell arteritis. *Arthritis Rheum* 1993;36:757-61.
- 67 Huston KA, Hunder GG, Lie JT, et al. Temporal arteritis. A 25-year epidemiologic, clinical, and pathologic study. *Ann Intern Med* 1978;88:162-7.
- 68 Mertens JC, Willemsen G, Van Saase JL, et al. Polymyalgia rheumatica and temporal arteritis: a retrospective study of 111 patients. *Clin Rheumatol* 1995;14:650-5.
- 69 Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122-8.
- 70 Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. *Neurology* 1988;38:352-9.
- 71 Sanchez MC, Arenillas JIC, Guierrez DA. Cervical radiculopathy: a rare symptom of giant cell arteritis. *Arthritis Rheum* 1983;26:207-9.
- 72 Hunder GG, Sheps SG, Allen GL, et al. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann Intern Med* 1975;82:613-8.
- 73 Mehler MF, Rainowich L. The clinical neuro-ophthalmologic spectrum of temporal arteritis. *Am J Med* 1988;85:839-44.
- 74 Hall S, Hunder GG. Is temporal artery biopsy prudent? *Mayo Clin Proc* 1984;59:793-6.
- 75 Wise CM, Agudelo CA, Chmielewski WL, et al. Temporal arteritis with low erythrocyte sedimentation rate: a review of five cases. *Arthritis Rheum* 1991;34:1571-4.
- 76 Kyle V, Cawston TE, Hazleman BL. Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up. *Ann Rheum Dis* 1989;48:667-71.
- 77 Cupps TR, Moore PM, Fauci AS. Isolated angitis of the central nervous system. Prospective diagnostic and therapeutic experience. *Am J Med* 1983;74:97-105.
- 78 Moore PM. Diagnosis and management of isolated angitis of the central nervous system. *Neurology* 1989;39:167-73.
- 79 Kolodny EH, Rebeiz JJ, Caviness VS Jr, et al. Granulomatous angitis of the central nervous system. *Arch Neurol* 1968;19:510-24.
- 80 Crane R, Kerr LD, Spiera H. Clinical analysis of isolated angitis of the central nervous system. A report of 11 cases. *Arch Intern Med* 1991;151:2290-4.
- 81 Cravito H, Feigin I. Non-infectious granulomatous angitis with a predilection for the nervous system. *Neurology* 1959;9:599-609.
- 82 Alhalabi M, Moore PM. Serial angiography in isolated angitis of the central nervous system. *Neurology* 1994;44:1221-6.
- 83 Giang DW. Central nervous system vasculitis secondary to infections, toxins, and neoplasms. *Semin Neurol* 1994;14:313-9.
- 84 Igarashi M, Gilmartin RC, Gerald B, et al. Cerebral arteritis and bacterial meningitis. *Arch Neurol* 1984;41:531-5.
- 85 Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* 1985;18:574-82.
- 86 Tija D, Yeow UK, Tan CB. Cryptococcal meningitis. *J Neurol Neurosurg Psychiatry* 1985;48:853-8.
- 87 Williams PL, Johnson R, Pappagianis D. Vasculitic and encephalitic complications associated with *Coccidioides immitis* infection of the central nervous system in humans: report of 10 cases and review. *Clin Infect Dis* 1992;14:673-82.
- 88 Meurers B, Kohlepp W, Gold R, et al. Histopathologic findings of the central and peripheral nervous system in neuroborreliosis: a report of three cases. *J Neurol* 1990;237:113-6.
- 89 Koeppen AH, Lansing LS, Peng S, et al. Central nervous system vasculitis in cytomegalovirus infection. *J Neurosci* 1981;1:395-410.
- 90 Powers JM. Herpes zoster maxillaris with delayed occipital infarction. *Journal of Clinical Neuroophthalmology* 1986;6:113-5.
- 91 Hilt DC, Buchholz D, Krumholz A, et al. Herpes zoster ophthalmicus and delayed contralateral hemiparesis caused by cerebral angitis: diagnosis and management approaches. *Ann Neurol* 1983;14:543-53.
- 92 Citron BP, Halpern M, McCarron M, et al. Necrotizing angitis with drug abuse. *N Engl J Med* 1970;283:1003-11.
- 93 Rumbaugh CL, Bergeron RT, Fang HC, et al. Cerebral angiographic changes in the drug abuse patient. *Radiology* 1971;101:335-44.

- 94 Mullick FG, McAllister HA, Wagner BM, *et al.* Drug related vasculitis. Clinicopathologic correlations in 30 patients. *Hum Pathol* 1979;10:313-25.
- 95 Krendel DA, Ditter SM, Frankel MR, *et al.* Biopsy-proven cerebral vasculitis associated with cocaine abuse. *Neurology* 1990;40:1092-4.
- 96 Johnson PC, Rolak LA, Hamilton RH, *et al.* Paraneoplastic vasculitis of nerve: a remote effect of cancer. *Ann Neurol* 1979;5:437-44.
- 97 Petito CK, Gottlieb GJ, Dougherty JH, *et al.* Neoplastic angioendotheliosis: Ultrastructural study and review of the literature. *Ann Neurol* 1978;3:393-9.
- 98 Greer JM, Longley S, Edwards NL, *et al.* Vasculitis associated with malignancy. Experience with 13 patients and literature review. *Medicine* 1988;67:220-30.
- 99 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- 100 Moreland LW, Heck LWJ, Koopman WJ. Biologic agents for treating rheumatoid arthritis. Concepts and progress. *Arthritis Rheum* 1997;40:397-409.
- 101 Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.
- 102 Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. *Cell* 1996;85:307-10.
- 103 Feldmann M, Brennan FM, Williams RO, *et al.* Cytokine expression and networks in rheumatoid arthritis: rationale for anti-TNF alpha antibody therapy and its mechanism of action. *J Inflamm* 1995;47:90-6.
- 104 Weller RO, Bruckner FE, Chamberlain MA. Rheumatoid neuropathy: a histological and electrophysiological study. *J Neurol Neurosurg Psychiatry* 1970;33:592-604.
- 105 Pallis CP, Scott JT. Peripheral neuropathy in rheumatoid arthritis. *BMJ* 1965;1:1141-7.
- 106 Conn DL, McDuffie FC, Dyck PJ. Immunopathologic study of sural nerves in rheumatoid arthritis. *Arthritis Rheum* 1972;15:135-43.
- 107 Casey AT, Bland JM, Crockard HA. Development of a functional scoring system for rheumatoid arthritis patients with cervical myelopathy. *Ann Rheum Dis* 1996;55:901-6.
- 108 Kauppi M, Sakaguchi M, Kontinen YT, *et al.* Pathogenetic mechanism and prevalence of the stable atlantoaxial subluxation in rheumatoid arthritis. *J Rheumatol* 1996;23:831-4.
- 109 Clark CR. Rheumatoid involvement of the cervical spine. An overview. *Spine* 1994;19:2257-8.
- 110 Frei K, Malipiero UV, Leist TP, *et al.* On the cellular source and function of interleukin 6 produced in the central nervous system in viral diseases. *Eur J Immunol* 1989;19:689-94.
- 111 Moore PM, Lisak RP. Systemic lupus erythematosus: immunopathogenesis of neurologic dysfunction. *Springer Semin Immunopathol* 1995;17:43-60.
- 112 Moore PM. Stress, stroke, and seizures: neuropsychiatric SLE. *Ann N Y Acad Sci* 1997;823:1-17.
- 113 Kuroe K, Kurahashi K, Nakano I, *et al.* A neuropathological study of a case of lupus erythematosus with chorea. *J Neurol Sci* 1994;123:59-63.
- 114 McNicholl JM, Glynn D, Mongey A, *et al.* A prospective study of neurophysiologic, neurologic and immunologic abnormalities in systemic lupus erythematosus. *J Rheumatol* 1994;21:1061-6.
- 115 Hietaharju A, Jantti V, Korpela M, *et al.* Nervous system involvement in systemic lupus erythematosus, Sjogren syndrome and scleroderma. *Acta Med Scand* 1993;88:299-308.
- 116 Provenzale J, Bouldin TW. Lupus-related myelopathy: report of three cases and review of the literature. *J Neurol Neurosurg Psychiatry* 1992;55:830-5.
- 117 Tola MR, Granieri E, Caniatti L, *et al.* Systematic lupus erythematosus presenting with neurological disorders. *J Neurol* 1992;239:61-4.
- 118 Smith RW, Ellison DW, Jenkins EA, *et al.* Cerebellum and brainstem vasculopathy in systemic lupus erythematosus: two clinico-pathological cases. *Ann Rheum Dis* 1994;53:327-30.
- 119 Wong KL, Woo EK, Yu YL, *et al.* Neurological manifestations of systemic lupus erythematosus: a prospective study. *Q J Med* 1991;81:857-0.
- 120 Fox RI. Clinical features, pathogenesis, and treatment of Sjogren's syndrome. *Curr Opin Rheumatol* 1996;8:438-45.
- 121 Alexander EL, Arnett FC, Provost TT, *et al.* Sjogren's syndrome: association of anti-Ro (SS-A) antibodies with vasculitis, hematological abnormalities, and serologic hyperreactivity. *Ann Intern Med* 1983;98:155-9.
- 122 Malinow K, Yannakakis GD, Glusman SM. Subacute sensory neuropathy secondary to dorsal root ganglionitis in primary Sjogren's syndrome. *Ann Neurol* 1986;20:535-7.
- 123 Griffin JW, Cornblath DR, Alexander E, *et al.* Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. *Ann Neurol* 1990;27:304-15.
- 124 Tumiati B, Casoli P, Parmeggiani A. Hearing loss in the Sjogren syndrome. *Ann Intern Med* 1997;126:450-3.
- 125 Creange A, Sedel F, Brugieres P, *et al.* Primary Sjogren's syndrome presenting as progressive parkinsonian syndrome. *Mov Disord* 1997;12:121-3.
- 126 Bragoni M, Di PV, Priori R, *et al.* Sjogren's syndrome presenting as ischemic stroke. *Stroke* 1994;25:2276-9.