Vasculitis

Vasculitis, primary or secondary, is the cause of many acquired neuropathies. Peripheral nerves are at high risk of ischaemic lesions in primary vasculitis, which predominantly affect small arteries of the size of the vasa nervorum present in the epineurium of nerve trunks. Thus primary necrotizing vasculitis is the key manifestation of connective tissue disorders and related conditions that include polyarteritis nodosa (PAN) and the Churg Strauss syndrome variant, rheumatoid arthritis, systemic lupus and Wegener’s granulomatosis. In these conditions ischaemic focal and multifocal neuropathy results from destruction of the arterial wall and occlusion of the lumen of small epineurial arteries. Vasculitis also occurs as a secondary phenomenon in other conditions including infection with HIV and hepatitis B and C as well as in diabetes mellitus and sarcoidosis. In all these settings the neuropathy is often curable after treatment of the vasculitis with corticosteroids, often with the adjunct of immunosuppressive drugs.

Different patterns of vasculitis

Primary vasculitis and connective tissue disorders (CTD)

Primary vasculitides are often classified according to the size of vessels predominantly affected but overlaps are common. In the medium-sized vessel vasculitis, neuropathy occurs in patients with PAN. Small vessel vasculitides includes Wegener’s granulomatosis (WG), the Churg-Strauss syndrome (CSS), and microscopic polyangiitis with involvement of capillaries often overlaps with PAN.

Necrotising arteritis (NA) of the type observed in PAN is related to the formation of soluble, circulating immune complexes, which is a consequence of the large-scale synthesis of antibodies by plasma cells. Wegener granulomatosis (WG) is an antibody-mediated autoimmune, granulomatous vasculitis, in which antibodies against proteinase 3 and myeloperoxidase are demonstrable in the serum of patients. Serologic demonstration of these ANCs is a sensitive and specific means by which to confirm WG and monitor patients with WG.

Secondary vasculitis

In vasculitis secondary to inflammatory disorders, the role of cellular factors is often prominent. In such conditions macrophages and cytotoxic T lymphocytes seem to play a major role in vessel wall damage.

The Peripheral Neuropathy of Primary vasculitis

The consequences of vascular inflammation and occlusion depend on the size and number of blood vessels affected. Clinical neuropathy occurs in more than 75% of the patients with systemic vasculitis of the PAN group.

Typically the clinical picture is that of an acute or subacute mononeuropathic, multiplex, with successive or simultaneous involvement of multiple nerve trunk territories over days, weeks or months. Distal symmetrical sensory or sensorimotor neuropathy also occurs. The peroneal nerve, which is the most commonly affected nerve, is involved uni- or bilaterally in 27%, bilaterally in 30% of the patients. In the upper extremities the ulnar is the most commonly affected (one side, 16%; both sides in 9%). In typical cases, the onset of the neuropathy is abrupt and the deficit severe; but in many cases only partial deficit in a nerve territory is observed. A slowly progressive course is observed in some cases, especially in the elderly. The CSF is usually normal. Recovery from a motor deficit due to an ischaemic neuropathy takes months, because of the axonal pattern of nerve lesions. Residual pains are common and may be difficult to differentiate from relapses of the neuropathy.

Polyarteritis nodosa

In PAN the ischaemic neuropathy induced by NA can be observed as an isolated manifestation, or in the context of a multisystemic disorder. In classic PAN, which was the most common disorder encountered in our series, cutaneous vasculitis was the most common non-neurological manifestation with livedo, cutaneous necrosis and nodules. Non specific focal oedema, usually affecting one limb extremity, often preceded the onset of neuropathy. Arthritis, renal involvement and asthma were present in 10% of the patients on average. Biological markers of inflammation including CRP and ESR, increased platelet and white blood cell count with eosinophilia are often seen. However, they remain normal in nearly 30% of the patients seen in neurology.

Churg and Strauss variant of polyarteritis nodosa

In 1951, Churg and Strauss reported a study of 14 cases of a form of disseminated necrotising vasculitis occurring frequently among asthmatic patients, with fever, eosinophilia, and a fulminant multisystem disease with pathology of NA, eosinophilic infiltration and extravascular granulomas. The vascular and nerve lesions observed in nerve biopsies from patients with this syndrome are responsive to treatment and are similar to those observed in PAN, with occasional elevated ANCA.

Necrotizing arteritis and neuropathy in patients with rheumatoid arthritis

The occurrence of NA in the context of rheumatoid arthritis is associated with a poor outcome. In our series patients with rheumatoid arthritis and neuropathy due to histologically proven necrotizing vasculitis in muscle and/or in nerve biopsy specimens, 15 had a sensory and motor neuropathy, the others a purely sensory neuropathy. Low CH50, C3 and C4 complement levels were associated with a poorer outcome.

Wegener’s granulomatosis

Wegener’s granulomatosis (WG) is characterised by granulomatous vasculitis of the upper and lower respiratory tract with or without glomerulonephritis. Peripheral neuropathy has been observed in
Necrotising arteritis and isolated neuropathy

In many instances peripheral neuropathy is the presenting and only manifestation of necrotising arteritis, but silent involvement of other organs is common in such patients, as shown by the frequent finding of specific arterial lesions in muscle biopsy specimens.

General signs or symptoms, usually minor, including fever and loss of weight are present in half of them. From a neurological standpoint, approximately a quarter of the patients present with a distal symmetrical sensory or sensorimotor neuropathy; and the diagnosis of NA is seldom considered before the results of the nerve and muscle biopsies.

One third of patients with the so-called non-systemic vasculitis subsequently develop systemic manifestations within an average of six years, but the overall outcome remains better than in classic PAN.

Vasculitic neuropathy in the elderly

Neuropathy is an important factor in the disability of the elderly. In a series of 100 patients over 65 years of age referred for a disabling neuropathy, we found that 25% had a vasculitic neuropathy.

Morphological aspects

Demonstration of NA in nerve and muscle biopsy specimens

The diagnosis of NA needs histological confirmation, which can sometimes be achieved by biopsy of a specific skin lesion. If not, nerve and/or muscle biopsies are advised in the search of the characteristic lesions of muscular or epineurial arteries.

The specific lesion can be found in the muscle, in the nerve, or both in the nerve and the muscle specimens, which must often be studied on serial sections because NA is segmental.

The diagnostic criteria include transmural infiltration of small arteries with polymorphonuclear cells, leukocytoclasia, fibrinoid necrosis and usually sparing of adjacent venules. These lesions result in arterial occlusion that are followed after days or weeks by spontaneous recanalization of the artery.

Lesions of nerve fibres - The ischaemic neuropathy

Nerve ischaemia due to a vasculitic neuropathy induces acute axonal degeneration, often with asymmetry of lesions between, and within, fascicles which may predominate in the centrofascicular area. Large myelinated fibers are affected. The nerve lesions appear to result from the summation of lesions of different ages involving the nerve blood vessels.

Secondary vasculitic neuropathy

Vasculitis can complicate the course of different conditions including an inflammatory immune reaction triggered by an infective agent, a delayed type hypersensitivity reaction, diabetes mellitus or malignancy.

Necrotising vasculitis and viral infection

Symptomatic viral infection, including HIV infection, cytomegalovirus (CMV infection at a late stage of HIV infection); hepatitis B and C and HTLV-I infection can be associated with neuropathy and necrotising vasculitis. In HIV patients, necrotising arteritis is usually associated with marked inflammatory infiltrates affecting the endoneurium and capillaries.

Sarcoidosis

Angitis has been recognized at autopsy in the CNS and occasionally in patients with sarcoid neuropathy.

Vasculitis in focal and multifocal diabetic neuropathy

A small proportion of diabetic patients over the age of 50, may present with proximal neuropathy of the lower limbs characterised by a variable degree of pain and sensory loss associated with uni- or bilateral proximal muscle weakness and atrophy. Others develop a subacute multifocal nerve trunk involvement, with pains and weakness.

Treatment

Prednisone is usually started at 1mg/Kg/day. Simultaneous treatment with cyclophosphamide, 2mg/Kg/day, or azathioprine may help reduce the doses of corticosteroids. We usually give a full dose of steroids for approximately 6-8 weeks and then taper prednisone over 6-10 months, or more. It is necessary to control the ESR and other markers of disease activity, including CRP and eosinophilic polymorphonuclear cell levels, which may vary from one patient to another, and to adjust the doses of prednisone accordingly. In our experience, up to half of the patients relapse during tapering of the prednisone or after treatment has been stopped. In some patients treatment with low dose prednisone must be pursued indefinitely.

In the evaluation of the efficacy of treatments of vasculitic neuropathies, it must be remembered that there is a wide range of modalities of evolution in NA, and that spontaneous remissions after several years duration can occur. Sensormotor deficit resulting from nerve ischaemia will take months to recover, because of the underlying axonal lesions. Motor recovery will be helped by physiotherapy, but residual pains are common.

REFERENCES