Survey of progress

Polyneuropathy in paraproteinaemia

Claus Meier

Department of Neurology, University of Berne, Inselspital, CH-3010 Berne, Switzerland

Summary. Paraproteinaemias are frequently associated with peripheral neuropathies. "Benign" paraproteinaemia, myeloma and Waldenström's macroglobulinaemia may present clinically as polyneuropathy. Therefore immunoelectrophoresis is strongly recommended in the routine diagnosis of polyneuropathies of unknown origin. Peripheral neuropathies associated with paraproteinaemia are clinically, electrophysiologically, pathologically and probably also pathogenetically heterogeneous. There are subgroups such as demyelinating neuropathy associated with IgM paraproteinaemia, which show quite distinctive features. This survey describes the different types of paraproteinaemia and their associated peripheral neuropathies. The incidence, pathogenesis and therapy of peripheral neuropathy associated with monoclonal gammapathies are discussed.

Key words: Paraproteinaemia – Polyneuropathy

Introduction

Paraproteinaemias are a group of disorders caused by an uncontrolled proliferation of a single clone of plasma cells that gives rise to a pathological increase in a homogeneous monoclonal immunoglobulin. Because of its restricted electrophoretic mobility, a paraprotein can be demonstrated by serum electrophoresis as a tall, narrow (M-) peak. In older subjects, the detection of a monoclonal serum protein is quite frequent. Monoclonal gammapathies have been found in 1% of normal populations above the age of 50 years and in 3% above the age of 70 years in Sweden and the USA [3, 36].

In systematic studies of hospital populations in London [30] and in Berne [34], paraproteinaemia was discovered in 154 (0.6%) of 27,100 sera. In 20 (12%) of these 154 cases, a malignant plasma cell dyscrasia (myeloma, Waldenström's macroglobulinaemia, or lymphoproliferative disorder) was diagnosed.

In the majority of cases monoclonal gammapathies are clinically asymptomatic. It was recognized, however, that a certain proportion of these cases with "benign gammopathy" may develop a malignant plasma cell dyscrasia. In a 5-year follow-up, Kyle [35] found that 11% of 241 patients with asymptomatic monoclonal gammapathy had developed myeloma, Waldenström's macroglobulinaemia, amyloidosis or lymphoma. He therefore proposed the term "monoclonal gammopathy of undetermined significance".

Peripheral neuropathies associated with paraproteinaemia are clinically, electrophysiologically, pathologically and probably also pathogenetically heterogeneous. There may even be heterogeneity within the different types of paraproteinaemia. Nevertheless, there are features which allow for some further nosological distinction. Also, the management of the different types of paraproteinaemia may warrant some separation. We therefore describe the different types of paraproteinaemia and their associated peripheral neuropathies separately.

Myeloma

Radiologically three types of myeloma may be distinguished: multiple osteolytic myeloma, osteosclerotic myeloma (multiple or solitary) and plasmocytoma (solitary myeloma with osteolytic lesion). Polyneuropathies occur in all types. They may antedate the diagnosis of myeloma, particularly in osteosclerotic and solitary myeloma, or develop with or after the general symptoms of the malignant disease, as in most cases of multiple osteolytic myeloma.

Multiple osteolytic myeloma, the most frequent type of myeloma, is characterized by a tumorous growth of plasma cells, replacing bone marrow and infiltrating bone and soft tissues. Anaemia and renal failure are common. Because of a secondary antibody deficiency syndrome, the patients are frequently susceptible to infection. Lymphadenopathy and hepatosplenomegaly are found in about 50% of cases. By immunoelectrophoresis a monoclonal gamma globulin (M-band) has been demonstrated in 80% of the patients [18, 20]. The paraproteins are IgG in 50% and IgA in 20%. IgD, IgM or IgE paraproteins have rarely been described. In about 20% of patients an M-band is not detectable in the serum, but electrophoresis of concentrated urine shows the presence of monoclonal light chains (Bence-Jones protein). The median survival time is 18 months after diagnosis, but may be shorter in cases complicated by systemic amyloidosis [31, 32]. Neurological complications in multiple myeloma are frequently caused by compression of nervous tissues. Collapsed vertebrae may cause paraplegia and endodural or extradural tumour may cause orbital syndromes or other cranial nerve palsies as well as spinal root, plexus or peripheral nerve compression. In large series, polyneuropathies were found in about 5% of patients [66]. In a prospective study the incidence of peripheral neuropathy was 13% and increased to about 50% when patients with subclinical neuropathy, based on abnormal nerve conduction velocity or histopathology were included [79]. The clinical picture of peripheral neuropathy in multiple myeloma is heterogeneous. Cases with pure motor and pure sensory neuropathy have been described as well as mixed...
types [31]. An asymmetrical type of presentation is always suggestive of a root or nerve compression, which can be ascertained by electrophysiological or radiological investigations. Complaints of pain by some patients may result from bone or soft tissue involvement. Cases with multiple myeloma complicated by systemic amyloidosis may present with a typical carpal tunnel syndrome, which responds to surgery, before symptoms of generalized peripheral neuropathy become readily evident [31]. Some degree of autonomic involvement also has been described in these cases. The clinical picture of neuropathy associated with plasmocytoma is not significantly different from multiple osteolytic myeloma.

**Osteosclerotic myeloma.** Only about 3% of patients with myeloma show multiple or solitary osteosclerotic lesions radiologically. The frequent association of osteosclerotic myeloma and peripheral neuropathy has been emphasized by Aguayo et al. [1], and is now well established [31, 43, 51, 60]. In nine of ten patients reported by Kelly et al. [31] the polyneuropathy antedated the diagnosis by about 2 years. The age of onset was earlier than in typical myeloma, and the clinical picture was characterized by predominantly motor disturbances in a relatively homogeneous manner.

Rousseau et al. [61] described a patient with osteosclerotic myeloma with peripheral neuropathy and ectopic secretion of calcitonin. These authors advanced a hypothesis about the secretion of calcitonin by neoplastic plasma cells and its potential role in the pathogenesis of myeloma osteosclerosis. Other similar cases have not yet been described.

A remarkable percentage of cases of osteosclerotic myeloma and peripheral neuropathy are associated with a multisystem disorder that includes skin changes (hyperpigmentation, thickened skin), oedema (peripheral and generalized type), endocrinopathy ( amenorrhoea, gynaecomastia, impotence, diabetes mellitus, hypertrichosis, hypothyroidism, adrenal insufficiency, hyperprolactinemia), clubbed fingers, and hepatosplenomegaly [28]. Early observations of such cases were reported by Scheinker [62] and Crow [14]. Numerous case reports have now been published, mainly from Japan. A recent review includes 102 Japanese patients [53]. The pathogenesis of this syndrome is obscure. It seems most likely that an antibody-mediated process could be the cause, based on the assumption that the IgG lambda antibodies produced by the myeloma are able to recognize multiple antigenic determinants. This combination of symptoms has also appeared in the literature under the terms POEMS syndrome [6] and Crow-Fukase syndrome [53].

**Electrophysiological studies** in patients with myeloma suggest axonal degeneration rather than a demyelinating lesion [31, 45]. Walsh [80] performed neurography in 23 patients with multiple myeloma and found mild slowing of conduction velocity in 39%, while only 13% had clinical evidence of peripheral neuropathy.

**Pathological findings** (Fig. 1a, b). Victor et al. [75] described autopsy findings from three patients with peripheral neuropathy and multiple myeloma. In these cases, the most striking feature was a degeneration of the peripheral nerves and to a lesser extent of the anterior and posterior roots, always more in the distal than in the proximal segments. Only a moderate number of dorsal root and anterior horn cells were lost. There was also fibre loss and secondary gliosis in the dorsal columns in those cases in which spinal cord compression due to collapsed vertebrae could be excluded. Walsh [80] studied five cases of myeloma neuropathy. He found fibres undergoing axonal degeneration, loss of myelinated and unmyelinated fibres, but little evidence of axonal regeneration. Hesselvik [26] examined sural nerve biopsy specimens from 26 patients with multiple myeloma, 3 of whom had clinical signs of peripheral neuropathy. Axonal degeneration and myelin abnormalities were seen in 17 patients, while in 1 patient plasma cell infiltration was present in the perineurium. Only in a minority of patients with multiple myeloma has amyloid been found [76]. Segmental demyelination, noted by some authors, might be secondary [19, 75, 80], although in single cases a predominantly demyelinating process has been reported [45].

**Waldenström's macroglobulinaemia**

Waldenström's macroglobulinaemia [78] is now recognized as a non-Hodgkin lymphoplasmoid lymphoma of low malignancy [40]. The general clinical features of Waldenström's macroglobulinaemia are malaise, fatigue, weakness, weight loss, hepatosplenomegaly, lymphadenopathy and bleeding diathesis. A proliferation of lymphocytoid cells is present in the bone marrow, lymph nodes and other tissues. On immunoelectrophoresis of the serum, a markedly increased 19s IgM-band is present in the beta-gamma region. About 50% of cases may show secondary deficiency of other immunoglobulins (IgG < 8.0 g/l, IgA < 0.6 g/l). Neurological complications are common in Waldenström's macroglobulinaemia and in addition to peripheral neuropathy include strokes, subarachnoid haemorrhage, parkinsonism and diffuse encephalopathy [41]. The association between Waldenström's macroglobulinaemia and peripheral neuropathy was first mentioned by Waldenström [79] and emphasized by Garein et al. [23]. Subsequently, a number of reports of peripheral neuropathy associated with Waldenström's macroglobulinaemia have been published, indicating that sensory phenomena consisting of distal numbness, painful dysesthesia and muscle cramps predominate as presenting symptoms in most cases. Raynaud's phenomenon can also occur in the initial phase. These symptoms commence insidiously in the feet or hands, sometimes asymmetrically, but gradually a distal symmetrical sensory-motor neuropathy develops. Although sensory deficits predominate in the majority of cases, there are reports in which muscle wasting and pareses lead to disabling weakness [2, 19, 27, 41, 55].

In a few cases, a multiple mononeuropathy type of presentation including cranial nerves has been reported [5, 44]. A single case of acute onset with Guillain-Barré syndrome has been observed, but poorly documented [41], and there are two reports of a cauda equina syndrome [41, 74]. In the majority of cases the symptoms of peripheral neuropathy develop after the systemic manifestations, although peripheral neuropathy may also antedate the general symptoms of Waldenström's macroglobulinaemia [2, 27, 29, 49, 57]. The cerebrospinal fluid (CSF) may be normal or show a moderate elevation of the protein level. An IgM-band has been demonstrated in a few cases [25]. We recently observed an IgM-band in the CSF which showed antibody activity against myelin-associated glycoprotein by immunoelectroblotting [49]. A pleocytosis is unusual.

In the majority of cases of Waldenström's macroglobulinaemia plasma viscosity is elevated. In a series of 23 patients, which included 12 with polyneuropathy, Arfmann et al. [2] did