Neuropathy, amyloidosis, and monoclonal gammopathy

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SUMMARY Three cases of neuropathy with monoclonal gammopathy and amyloid deposits in peripheral nerves are described. They appeared to present a benign gammopathy because of the duration of the neuropathy in the absence of any clinical or biological sign of myeloma or macroglobulinaemia. The pathological abnormality found in the sural nerves of the three patients was characterised by a marked loss of myelinated and unmyelinated nerve fibres because of active axonal degeneration with Wallerian degeneration. The most striking feature in all three cases was the finding of deposits identified as an accumulation of microfibrils.

Peripheral neuropathy is often associated with malignant gammopathies, such as multiple myeloma and Waldenström's macroglobulinaemia. The association between neuropathy and generalised amyloidosis, in the familial or sporadic form, is also well known. We recently observed three cases of neuropathy with monoclonal gammopathy and amyloid deposits in peripheral nerve.

Case reports

CASE 1 (PB)

In 1967, at the age of 60 years, this patient first noticed plantar paraesthesiae and slight weakness of both legs. In 1968, an examination showed distal sensory loss in both legs and arms, and moderate weakness in both legs. In 1969, a monoclonal IgM was found. In 1974, an examination showed distal sensory loss and weakness in upper and lower limbs. Sternal marrow was normal. Treatment with prednisone 60 mg/day, and later 15 mg/day was given from May 1974 and stopped in November 1974, without any clinical modification. In 1977, the patient complained of generalised weakness, pain in the legs, and tremor in action. He noticed no impotence, no orthostatic symptoms, but irregular bowel movements, and absence of perspiration in the hands and feet.

Examination showed total areflexia, wasting and

weakness of distal muscles in upper and lower limbs, and sensory loss in a glove and stocking distribution. There was postural tremor of both hands, exaggerated on movement, and ataxia of gait. The skin was dry and there was no orthostatic hypotension.

Electromyography in 1976 showed a median nerve conduction velocity of 15 m/s. The lateral and medial popliteal nerves were inexcitable. All the muscles examined showed marked denervation.

The ESR was 36 mm/hr, Hb 15.3 g/dl, white blood cells 5500/mm³. Serum electrolytes, glucose, urea, creatinine, uric acid, alkaline phosphatase, cholesterol, total proteins, and bilirubin were in the normal range. Electrophoresis showed a monoclonal immunoglobulin component, shown to be IgM kappa by immunoelectrophoresis. The immunoglobulin levels were: IgM 1045 mg/dl, IgG 690 mg/dl, IgA 71 mg/dl (March, 1976) and IgM 1400 mg/dl, IgG 800 mg/dl, IgA 70 mg/dl (November, 1977). Serum viscosity was 1.58. CSF protein level was 0.47 g/l. The urine was normal. Sternal marrow was normal, with 23% lymphocytes.

A sural nerve biopsy was performed and specimens prepared for light and electronmicroscopic examination. Segments of the nerve were also stained with Congo red, thioflavin T, and periodic acid-Schiff reagent (PAS)—in the Department of Neurology, Berne University.

Light microscopy on 1 µm thick transverse sections stained with methylene blue showed a

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severe reduction in the number of the myelinated nerve fibres with virtually complete loss of myelinated nerve fibres of large diameter. The endoneurial intercellular space appeared of increased density, and around two of the endoneurial vessels a cuff of a dark amorphous substance was very striking (Fig. 1). The nerve did not react with the Congo red and thioflavine techniques.

Electron microscopy showed that most of the preserved myelin sheaths had a normal lamellar structure. Some features of myelin sheath breakdown indicative of Wallerian degeneration were also present. In about 20% of the axons, including those of unmyelinated nerve fibres, axonal degeneration was obvious. Many Schwann cell pro-

cesses depleted of axons showed a budded appearance. No onion bulb formation was discernible. In the extracellular space, disseminated accumulations of microfibrils, 10 nm in width, were seen. They were particularly striking in relation to endoneurial vessels, where they were condensed to a felt-like mass (Fig. 2).

CASE 2 (MB)

In 1969, at the age of 66 years, this patient noticed loss of sensation in his left hand and cramps and paraesthesiae in both hands. Neurological examination was normal. In 1974, he began to complain of difficulties in walking, and pain and weakness of the legs. In 1975 physical examination disclosed

Fig. 1 Case 1. Left: sural nerve from IgM gammopathy, stained with methylene blue. In the transverse section severe loss of myelinated nerve fibres is apparent. Two intraneurial vessels show a cuff of an amorphous (dark) mass (arrows). Right: normal sural nerve. Original magnification $\times 207$.

Fig. 2 Case 1. Electron micrograph of a cross-sectioned intrafascicular vessel. There is a cuff of a dense substance around the endothelial cells representing microfibrillar masses (right) indicated by arrows. Original magnification $\times 3900$ (right) $\times 36\,500$.

almost total areflexia and diffuse weakness and sensory loss in the legs. During the next two years, the patient complained of progressive weakness, with inability to walk from April 1977. He noticed constipation, impotence, and hoarseness of voice.

Examination showed total areflexia and muscle wasting of both hands and legs. There was moderate weakness in upper limbs, marked weakness of the proximal muscles and almost total loss of function of the distal muscles in lower limbs. Touch and pinprick sensation were impaired in glove and stocking distribution. Temperature sensation was absent in hands and legs. Vibratory sensation was reduced in the hands and absent at the ankles. The skin was dry. There was no orthostatic hypotension on rising from supine to sitting position. Six months later, examination showed further loss of function of proximal muscles of the legs.

At electromyography in 1975 conduction velocity of various nerves were: median 48 m/s, ulnar 49 m/s, right lateral popliteal 35 m/s, left lateral popliteal 38 m/s. Subacute denervation of muscles of right leg and left hand was observed. In 1977 the conduction velocities were: median nerve 32 m/s, ulnar nerve 49 m/s. Both lateral popliteal nerves were inexcitable. Subacute to chronic denervation was detected in muscles of the right leg and left hand.

The ESR was 20 mm/hr, Hb 13.1 g/dl, white cells 4,500/mm³. Serum electrolytes, urea, creatinine, uric acid, alkaline phosphatase, and cholesterol were in the normal range. Fasting blood glucose level was 104 mg/dl (5.2 mmol/l). Provoked hyperglycaemia was in the normal range. Total serum proteins were 5.6 g/dl. Electrophoresis disclosed a monoclonal immunoglobulin component, shown to be IgG lambda by immunoelectrophoresis. Immunoglobulin levels were IgG 1900 mg/dl, IgA

100 mg/dl, IgM 90 mg/dl. Serum viscosity was 1.52. The CSF contained 1 white cell per mm³. The level of protein was 0.94 g/l with monoclonal IgG. No Bence-Jones protein was found in the urine. Porphobilinogen was elevated, uroporphyrin absent, and coproporphyrin was in the normal range. Sternal marrow was hypocellular, with normal cells of all series; 20% were plasma cells, slightly polymorphic.

Sural nerve biopsy was performed and prepared as in case 1. Histological examination showed a severe defect with almost complete loss of myelinated nerve fibres. Endoneurial vessels also showed striking changes with the presence of a poorly defined homogeneous clear substance extending from the vessel wall into the adjacent neural tissue, where the normal fascicular structure appeared more or less effaced (Fig. 3).

Electron microscopy clearly displayed the severe loss of myelinated and unmyelinated nerve fibres, with a reduction in number of Schwann cell processes. Many Schwann cell processes appeared budded. Multiple deposits of a material consisting of accumulations of microfibrils typical of amyloid were recognisable within the expanded intercellular spaces (Fig. 4).

CASE 3 (HF)

In 1974, at the age of 47 years, this patient began to complain of paraesthesiae and dysaesthesiae in both legs. He noticed fatigue and cramps in the legs during walking. These symptoms increased progressively until 1977. He complained also of decreased sexual potency.

Examination showed a depressed left ankle reflex; other reflexes were present and symmetrical. There was wasting of distal muscles of lower limbs, predominantly on the left side. Muscular function was preserved in the upper limbs but reduced in

Fig. 3 Case 2. Sural nerve from IgG gammopathy showing the almost complete loss of myelinated nerve fibres. In the centre a homogeneous clear mass represents a diseased vessel (*) from which clear material is infiltrating the neural tissue. Methylene blue. Original magnification $\times 720$.

Fig. 4 Case 2. Electron micrograph exhibiting the complete loss of myelinated and unmyelinated axons. Schwann cell processes appear budded. There are four deposits of microfibrillar masses representing amyloid (arrows). Original magnification $\times 5900$.

the lower limbs, predominantly on the left side. Touch, pinprick, and temperature sensation were normal in upper and lower limbs. Vibratory sensation was reduced at both ankles, predominantly on the left side.

At electromyography conduction velocities of nerves were: median 62 m/s, right lateral popliteal 59 m/s (with irregular potential, 0.5 mV), left lateral popliteal 66 m/s (with prolonged potential, 1 mV, 30 ms), left medial popliteal 48 m/s (with irregular potential, 0.5 mV). Chronic denervation was observed in muscles of the lower limbs, predominantly in the left tibialis anterior.

The ESR was 6 mm/hr, Hb 16.3 g/dl, white cells 8700/mm³. Serum electrolytes, glucose, urea, creatinine, uric acid, total proteins, cholesterol, bilirubin, alkaline phosphatase, T3 and T4 were in the normal range. Electrophoresis disclosed a monoclonal immunoglobulin component, shown to be IgG kappa by immunoelectrophoresis. Immunoglobulin levels were: IgG 1200 mg/dl, IgA 210 mg/dl, IgM 110 mg/dl. Serum viscosity was 1.54. The urine was normal. Sternal marrow was normal, with 20% lymphocytes and 10% well differentiated plasma cells.

Sural nerve biopsy showed a virtually complete absence of myelinated nerve fibres. In a small number of nerve fascicles a loosely structured material of moderate density was accumulated circumferentially in a subperineurial location.

Electron microscopic analysis revealed the preservation of only a few myelinated nerve fibres of

small calibre with a myelin sheath of normal ultrastructure (Fig. 5). Axonal degeneration was present in myelinated and unmyelinated nerve fibres. The Schwann cells were markedly reduced in number. The intercellular space appeared distended and filled with accumulations of microfibrils in a patchy distribution (Figs. 5 and 6). This material was collected predominantly in the subperineurial space (Fig. 7).

Discussion

MALIGNANT AND BENIGN MONOCLONAL GAMMOPATHIES

Apart from multiple myeloma and Waldenström's macroglobulinaemia, production of monoclonal immunoglobulin has been described in healthy subjects and in chronic inflammatory disease. This condition was termed "benign monoclonal hyperglobulinaemia" and considered as a stable non-premyelomatous state by Waldenström (1964).

During recent years, malignant and benign monoclonal gammopathies have been classified under the same name as "plasma cell dyscrasias", on the basis of several observations. Monoclonal immunoglobulins of benign gammopathies may belong to any of the immunoglobulin classes, and cannot be distinguished from immunoglobulins of malignant gammopathies (Wintrobe, 1974). Several cases of apparently benign monoclonal gammopathies evolved to multiple myeloma or macroglobulinaemia after a number of years, even after

Fig. 5 Case 3. Electron micrograph of the transverse sectioned sural nerve showing a severe depletion of nerve fibres and Schwann cells. In the extracellular space, a flaky infiltration by a poorly defined structure is visible. Original magnification $\times 5900$.

Fig. 6 Case 3. With high resolution there appear patchy accumulations of microfibrils consistent with amyloid. Original magnification $\times 178\,000$.

Fig. 7 Case 3. Electron micrograph of the subperineurial region displaying a finely dispersed infiltration by amyloid fibrils between some thin fibroblastic processes. Original magnification $\times 13\,500$.

18 years of observation (Kyle and Bayrd, 1966; Wintrobe, 1974; Osserman, 1975).

However, it is evident that not every benign monoclonal gammopathy progresses to a malignant gammopathy, as the incidence of these two forms is different. The yearly incidence of multiple myeloma is 0.002–0.004%, the incidence of benign monoclonal gammopathies has been estimated from 0.15–1.0% in adults, and at 3% in subjects over the age of 70 (Wintrobe, 1974; Ameis and Pruzanski, 1976).

It is not known whether benign monoclonal gammopathies are precursors of myeloma, which would all progress in this direction if they had enough time, or if these conditions are distinct. For this reason Osserman (1975) does not speak of benign monoclonal gammopathy, but of "plasma cell dyscrasia of unknown significance."

We are at the moment unable to predict the evolution of individual cases of benign monoclonal gammopathy. Indeed, if malignant monoclonal gammopathies differ from benign forms in a series of parameters such as a higher level of the monoclonal immunoglobulin, reduced level of other immunoglobulins, serum hyperviscosity, reduced haemoglobin level, and an increased number of plasma cells in the marrow, none of these criteria is absolute and of predictive value in an isolated case (Clauvel *et al.*, 1971; Ritzmann *et al.*, 1975).

AMYLOIDOSIS AND MONOCLONAL GAMMOPATHIES

Amyloid substance is well known for Congo red staining, polarisation birefringence, and its fibrillar aspect at electron microscopy. The different forms of amyloidosis were first classified according to the presence or absence of associated pathology, and the distribution of amyloid in the organism. In the non-familial forms, amyloidosis may be either "primary" or "secondary" to another disease, such as multiple myeloma, macroglobulinaemia, neoplasms, chronic inflammatory and autoimmune diseases. Primary amyloidoses, and those associated with a myeloma or a macroglobulinaemia, have a predominantly mesenchymatous, or "pericollagen" distribution: heart, tongue, muscles, gastrointestinal tract, nerves, skin (pattern 1). The other secondary forms have a predominantly parenchymatous, or "perireticular" distribution: liver, spleen, kidney, adrenals (pattern 2) (Wintrobe, 1974; Osserman, 1975).

Biochemical studies have shown that there are at least two types of amyloid: one of immunoglobulin origin, with a pattern 1 distribution, and one of non-immunoglobulin origin with a pattern 2 distribution. Analysis of amino-acid sequences showed that pattern 1 amyloid is composed of im-

munoglobulin light chains, and particularly of their variable fragment (Wintrobe, 1974; Glenner, 1975). This amyloid appears to be the result of production of monoclonal immunoglobulin or immunoglobulin light chains for three reasons. The amino-acid sequence was found to be homogeneous in different amyloid deposits in a given individual (Wintrobe, 1974). An M component, immunoglobulin or immunoglobulin light chain, was found in serum or urine of almost all cases of pattern 1 amyloidosis (Pruzanski and Katz, 1976). In contrast to the usual predominance of kappa light chains, a predominance of lambda light chains was found in monoclonal immunoglobulins associated with amyloidosis, corresponding to a predominance of lambda-type fibrils in amyloid (Glenner, 1975; Ameis and Pruzanski, 1976).

Bone marrow examination showed another analogy between "primary" amyloidosis and monoclonal gammopathies. A moderate bone marrow plasma cell infiltration was found in more than 90% of cases of "primary" amyloidosis. These plasma cells even had an immature character in some cases (Pruzanski and Katz, 1976). Thus, pattern 1 (or "primary") amyloidosis is now considered as a particular manifestation of plasma cell dyscrasias such as benign and malignant gammopathies (Wintrobe, 1974; Osserman, 1975).

PERIPHERAL NEUROPATHY AND MALIGNANT MONOCLONAL GAMMOPATHIES

The first case of peripheral neuropathy associated with a myeloma was described by Davison and Balser (1937). This sensorimotor neuropathy was predominant in the upper limbs, and was characterised by intense pain, hypaesthesia, and distal muscle wasting. Examination of the brachial plexuses showed swollen axons and disintegration of myelin. In the absence of nerve compression or infiltration, the neuropathy was considered to be secondary either to anaemia or to an unknown toxic factor.

Many similar observations were reported, and a review of the literature mentioned a total of 44 cases of neuropathy associated with myeloma, excluding the cases with cellular infiltrate or amyloid deposits (Davis and Drachman, 1972). Among 23 cases of myeloma, Walsh (1971) found three neuropathies on clinical examination (13%), and nine on electrophysiological study (39%). The association between peripheral neuropathy and Waldenström's macroglobulinaemia is also well known, and more than 20 cases have been described (McLeod and Walsh, 1975).

The onset of clinical manifestations is generally progressive but may be acute. This sensorimotor

neuropathy begins in most cases in the lower limbs, is sometimes asymmetrical in macroglobulinaemia, and can progress to quadriplegia. Pain is a complaint frequently found in myeloma neuropathy—it is mentioned in 59% of cases in a review of the literature. The signs of neuropathy generally precede the diagnosis of myeloma, sometimes for several months, but may appear either before or after the systemic manifestations of macroglobulinaemia (Davis and Drachman, 1972; McLeod and Walsh, 1975).

Most studies indicate an axonal degeneration as the primary process with secondary segmental demyelination. Hesselvik (1969), on the other hand, found that demyelination was more important than axonal degeneration, and another case of diffuse demyelination without axonal degeneration, but with a plasma cell infiltration has been described (Walsh, 1971; McLeod and Walsh, 1975).

Though amyloidosis is often associated with myeloma and macroglobulinaemia, deposits of amyloid in peripheral nerves were rarely found when neuropathy accompanied these conditions. In a pathological study of myeloma neuropathy Hesselvik (1969) found amyloid deposits in peripheral nerves in two cases from 17 necropsies and in none from 17 biopsies. Campbell and Halford (1964) described amyloid in the vasa nervorum in a myeloma case and Dayan *et al.* (1971) and Davies-Jones and Esiri (1971) reported the presence of amyloid not only in vasa nervorum but in nerve interstitium. Nevertheless, these observations remain isolated, and in most cases no amyloid has been found in peripheral nerves in myeloma neuropathy. Likewise, in macroglobulinaemia only four cases of amyloid deposits in peripheral nerves are known (McLeod and Walsh, 1975).

According to a review of the literature concerning 30 cases of myeloma, the neuropathy may decrease under treatment, particularly in isolated plasmocytoma if treated with radiotherapy. Improvement of neuropathy after radiotherapy was reported in two cases of plasmocytoma with a follow-up of one and a half and 10 years. Other treatments, steroids and antimetabolites, have no effect on neuropathy (Davis and Drachman, 1972). A therapeutic effect on macroglobulinaemia neuropathy has been described in some rare cases (McLeod and Walsh, 1975).

PERIPHERAL NEUROPATHY AND AMYLOIDOSIS

A hereditary neuropathy associated with familial amyloidosis was first described by Andrade (1952) in Portugal. The onset consists of autonomic and sensory dysfunction and is followed by loss of

motor function. The mode of transmission is autosomal dominant. Several classes of hereditary neuropathies were described with particular characters in each group.

In the non-familial forms of amyloidosis, neuropathy is found only in pattern 1 amyloidosis. An M component was found in serum or urine in most cases of neuropathy associated with pattern 1 amyloidosis (Benson *et al.*, 1973; Engel and Askanas, 1976; Trotter *et al.*, 1977).

The lower limbs are generally affected first with hypaesthesiae, paraesthesiae, or constant pain. The sensory loss is distributed in a glove and stocking pattern. Loss of pain and temperature discrimination with preservation of touch has been noted in the hereditary form and in some cases of sporadic amyloid neuropathy. Loss of motor function develops later, and frequently oedema and ulceration in the lower limbs.

Autonomic dysfunction is important and is sometimes the sole manifestation in amyloid neuropathy. It is characterised by orthostatic hypotension, bowel dysfunction, loss of sweating, and impotence. The carpal tunnel syndrome is frequent, and is caused by extrinsic compression of nerve (Cohen and Benson, 1975).

Cohen and Benson (1975) have described four patterns of amyloid deposits. Amyloid substance may be situated outside of the nerve and provoke a compression neuropathy, particularly a carpal tunnel syndrome. Amyloid is also intravascular and can obstruct the vasa nervorum. Lastly, it is found in the neural interstitial space, forming globular deposits and diffuse infiltration.

By electron microscopy, amyloid appears as nodular masses extending tongues into the intrafascicular space. Amyloid substance is composed of microfibrils with a diameter of 100 to 150 Å (Bischoff, 1973).

Several authors have found a preferential loss of unmyelinated and small myelinated axons, which correlates well with the pain and temperature sensory loss and the autonomic disturbances (Thomas and King, 1974). However, one group mentioned a preferential degeneration of myelinated fibres (Coimbra and Andrade, 1971). Biopsy samples from cases of amyloid neuropathy, however, show loss of both myelinated and unmyelinated fibres.

At present, no treatment is effective in amyloid neuropathy. Because of the relationship between pattern 1 amyloid and other plasma cell dyscrasias, amyloid neuropathies were treated as for myeloma with melphalan and prednisone, but without benefit (Cohen and Benson, 1975; Trotter *et al.*, 1977).

PERIPHERAL NEUROPATHY AND BENIGN MONOCLONAL GAMMOPATHY WITHOUT AMYLOIDOSIS

Apart from neuropathy associated with a malignant gammopathy, almost always without amyloid, and apart from amyloid neuropathy, mostly associated with a benign gammopathy, two cases were reported concerning a neuropathy associated with benign monoclonal gammopathy without amyloid at nerve biopsy.

The patient of Forssman *et al.* (1973) complained of subjective sensory disturbances in the lower limbs, without sensory loss at clinical examination. A monoclonal IgM was found, which was considered a benign gammopathy in the absence of other signs of Waldenström's macroglobulinaemia during six years. The nerve biopsy did not show amyloid, but revealed lymphocytic infiltrates, and immunofluorescence showed IgM in connection with these infiltrates. With treatment by chlorambucil, the symptoms disappeared within three weeks and a second nerve biopsy was normal six months later.

The case of Contamin *et al.* (1976) presented a symmetrical sensorimotor neuropathy associated with a benign IgG monoclonal gammopathy. Nerve biopsy showed no amyloid deposits.

These two isolated cases present unusual features for plasma cell dyscrasia neuropathies—the absence of plasma cell infiltration of bone marrow, and the favourable effect of treatment.

RELATIONSHIP BETWEEN AMYLOID NEUROPATHY AND NEUROPATHY ASSOCIATED WITH MALIGNANT MONOCLONAL GAMMOPATHIES

There are two main classes of neuropathy associated with a monoclonal gammopathy: the neuropathy of myeloma and macroglobulinaemia, associated with a malignant monoclonal gammopathy, and amyloid neuropathy associated with a benign monoclonal gammopathy. At present, malignant and benign monoclonal gammopathies and pattern 1 amyloidosis are considered to be different manifestations of plasma cell dyscrasia. A possible common cause for the neuropathies which accompany these conditions may be invoked.

The pathogenesis of nerve damage is unknown in these two types of neuropathy. In the case of amyloid neuropathy, an ischaemic process has been postulated, caused by the intravascular deposits of amyloid. However, the obstruction of vasa nervorum with amyloid is often confined to a minority of vessels and does not explain the diffuse degeneration of nerve fibres. Similarly, the hypothesis of nerve damage through amyloid nodule compression cannot be retained, because these nodular deposits are frequently absent. As

electron microscopy showed dissolution of basement membrane by amyloid (Coimbra and Andrade, 1971; Bischoff, 1973), it is possible that the loss of this diffusion barrier causes damage to Schwann cells of metabolic origin. The extensive and symmetrical character of amyloid neuropathy suggested a "remote effect" of plasma cell dyscrasia through the associated M component, either immunoglobulin or immunoglobulin fragment (Engel and Askanas, 1976; Trotter *et al.*, 1977). Thus amyloid infiltration would represent the visible manifestation of an immune mechanism by an abnormal monoclonal IgM or IgG.

The hypothesis of a "remote effect" through the M component has also been applied to the neuropathy associated with myeloma and macroglobulinaemia (Dayan *et al.*, 1971; Davis and Drachman, 1972; Trotter *et al.*, 1977). Indeed, amyloid deposits in peripheral nerves cannot be incriminated, as they are absent in most cases. Similarly, the plasma cell or lymphocytic infiltrates are rare. Serum hyperviscosity was also invoked, particularly in macroglobulinaemia neuropathy, but this hypothesis cannot be retained because several series of macroglobulinaemia neuropathies have been described without hyperviscosity (Bigner *et al.*, 1971).

Immunofluorescence studies provide supplementary arguments for participation of M component in peripheral nerve damage. Forssman *et al.* (1973) described the presence of IgM in nerve biopsy sample in a case of neuropathy associated with IgM monoclonal gammopathy. The nerve biopsy showed a lymphocytic infiltrate, but no amyloid. Chazot *et al.* (1976) found monoclonal immunoglobulin in nerve biopsy samples in eight of 10 cases of peripheral neuropathy associated with monoclonal gammopathy. In the two negative cases there was another possible cause for neuropathy—alcoholism and diabetes. Finally, in three cases of monoclonal gammopathy without neuropathy the nerve biopsy did not show any fluorescence. Using the serum of three cases of neuropathy with benign monoclonal gammopathy, Read *et al.* (1978) did not demonstrate any antibody binding to peripheral nerves. However, this observation does not eliminate an immunological origin, as these authors did not use autologous nerves, but homologous post-mortem nerves. Indeed a serum IgM M component has been demonstrated on the myelin of sural nerve in a case of macroglobulinaemia neuropathy, but this serum did not show any binding to homologous control nerve (Propp *et al.*, 1975).

It is, therefore, possible that amyloid neuropathy and neuropathy associated with malignant mono-

clonal gammopathies originate from a related or common immunological process. However, the role of the M component remains unclear, and it is not known whether the monoclonal immunoglobulin found in peripheral nerve is responsible for nerve damage, or if it is only a bystander.

PRESENT CASES

Our three cases presented a progressive sensorimotor neuropathy, with autonomic dysfunction (loss of sweating and irregular bowel movements in two cases, partial or total loss of potency in two cases), in association with monoclonal gammopathy (IgM kappa, IgG lambda, IgG kappa). Though no absolute criterion distinguishes the malignant from the benign forms, we think that these three cases present a benign gammopathy because of the duration of the neuropathy in the absence of any clinical or biological sign of myeloma or macroglobulinaemia (10 years in case 1, at least three years in case 2, three years in case 3). In case 1, the bone marrow was normal at the first examination and showed 23% well-differentiated lymphocytes at the second. It revealed 20% slightly polymorphic plasma cells in case 2, and 10% well differentiated plasma cells in case 3.

The pathological abnormality found in the sural nerves of these three cases was characterised by a marked loss of myelinated and unmyelinated nerve fibres because of active axonal degeneration with Wallerian degeneration. The defect was particularly confined to the myelinated nerve fibres of large size in the case of IgM monoclonal gammopathy, whereas in the two cases with IgG monoclonal gammopathy it was much more pronounced, comprising also many unmyelinated nerve fibres and resulting in a remarkable decrease in Schwann cells. There was no significant evidence of primary demyelination as suggested by Propp *et al.* (1975), and in no case was lymphoid infiltration of the nerve fascicle observed, in contrast to the findings of Chazot *et al.* (1976) and Contamin *et al.* (1976).

The most striking feature in all three cases was the finding of deposits of a material which by high resolution was identifiable as an accumulation of microfibrils. In the case of IgM gammopathy, the microfibrillar infiltration was most prominent in relation to the endoneurial blood vessels, but it was apparently unrelated to blood vessels in the third case where it gave the intercellular intrafascicular space a patchy appearance. In all three cases the microfibrils were consistent with the ultrastructural appearance of amyloid deposits. Since in the two cases with IgG gammopathy, the severe defect of the neural structures is attributable to direct infiltration by amyloid, an effect of a specific

antibody directed against neural tissue might be suggested.

These cases appear similar to another recently described by Neundörfer *et al.* (1977). Their case presented a sensory, motor, and autonomic neuropathy with loss of pain discrimination and relative preservation of touch sensation. There was an IgG monoclonal gammopathy, and amyloid was discovered in a peripheral nerve biopsy. In spite of these features of amyloid neuropathy, the authors labelled this case as myeloma because of a plasma cell infiltration of bone marrow. However, in most cases of pattern 1 amyloidosis, a plasma cell infiltration is found in bone marrow, sometimes exceeding 50% and occasionally presenting atypical forms (Pruzanski and Katz, 1976).

In the presence of amyloid in peripheral nerve in association with an apparently benign monoclonal gammopathy and moderate infiltration of the bone marrow with differentiated plasma cells or lymphocytes, there is a strong argument to consider these three cases as pattern 1 amyloidosis neuropathy.

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