Current Concepts

Neuropathies Associated with Paraproteinemias

Allan H. Ropper, M.D., and Kenneth C. Gorson, M.D.

A number of common disorders of the peripheral nervous system, termed paraproteinemias, are closely connected with the presence of excessive amounts of an abnormal immunoglobulin in the blood. These immunoglobulins can be detected by immunelectrophoresis or the more sensitive immunofixation test. An estimated 10 percent of idiopathic polynuropathies are of this type.1,2 The anomalous blood proteins are usually monoclonal (termed M protein or M spike) and are the product of a single clone of plasma cells. They are clinically important because some of them have the properties of antibodies directed at components of the myelin or the axolemma. Others have an uncertain pathophysiologic role intermediate between that of proteins associated with neuropathies and that of proteins associated with lymphoproliferative disorders. The nerves may also be damaged by deposition of the amyloid byproduct of the circulating paraprotein.

These neuropathies may precede a number of systemic disorders. They are typically associated with a monoclonal gammopathy of nonneoplastic origin, multiple myeloma, Waldenström's macroglobulinemia, osteosclerotic myeloma, primary amyloidosis, cryoglobulinemia, non-Hodgkin's lymphoma, Castleman's disease and related lymphatic diseases, and chronic leukemias (Table 1). Since the first of these is the most common, we discuss it in detail and list only the broad features of the others.

Glycoconjugates and the Immune Pathogenesis of Paraproteinemic Neuropathies

Although much attention has been directed toward the protein antigens of myelin, most of the dry weight of nerves consists of lipids. The principal lipids in nerves are cholesterol, phospholipids, galactocerebroside, galactosylceramide-3-O-sulfate (sulfatide), and, in lesser amounts, glycosphingolipids, including gangliosides (Fig. 1). Gangliosides are complex glycosphingolipids with a sialic acid group bound to an oligosaccharide. They are situated in the membranes of neurons and supporting cells where they participate in a number of regulatory functions.4 The complex gangliosides (GM1, GM2, GD1a, GD1b, GT1b, GQ1b, and LM1) and the sulfated glycosphingolipids (sulfate-3-glucuronyl paragloboside [SGPG] and sulfatide) are all implicated as antigens in immune-mediated peripheral neuropathy. Their regional distribution is consistent with certain clinical features. For example, purely motor neuropathy is often associated with antibodies against GM1, which is located predominantly on motor nerves, whereas sensory neuropathy is associated with antibodies to gangliosides with disialosyl moieties, such as GD1b, which is thought to be overrepresented on sensory nerves.

Myelin-associated glycoprotein (MAG) is a minor protein (glycoconjugate) component of nerve but is central to understanding the paraproteinemic neuropathies. It is concentrated in periaxial Schwann-cell membranes and paranodal loops of myelin and apparently acts as an adhesion molecule for interactions between the Schwann cells and the axons. Its unique structure consists of five immunoglobulin-like domains and a carbohydrate epitope (Fig. 1). The carbohydrate epitope reacts with the HNK-1 adhesion molecule that is shared by the nervous and immune systems. Additional shared antigens include the main $P_o$ protein of myelin, other adhesion molecules in the immunoglobulin superfamily, peripheral myelin protein-22 (PMP-22), and several complex glycosphingolipids. Of the complex glycosphingolipids with which it reacts, the best characterized and most relevant to neuropathy is SGPG (Fig. 1).5 The intercalation of anti-MAG antibodies between densely packed layers of myelin probably accounts for the characteristic wide spacing between the myelin lamellae in this disorder (Fig. 2) and the resultant neuropathy.6,7,9

The principal confirmation that antinerve antibodies that are a component of a paraprotein are linked to neural damage has been derived from the detection by direct immunofluorescent staining of endoneurial deposits of immunoglobulin and complement in nerve10 and the induction of a demyelinating neuropathy in animals by immunization with the aforementioned antigens, by transfer of serum from patients with the disease, and by intraneural injection.11,12 In all these instances the case for pathogenic activity of IgM antibodies directed against MAG, gangliosides, and other glycosphingolipids is better established than that for other antigens and for IgG and IgA antibodies.

Monoclonal Gammopathy of Undetermined Significance

Two thirds of patients with paraproteinemic neuropathy have what has been awkwardly termed “monoclonal gammopathy of undetermined signifi-
Lymphoma

Cryoglobulinemia

Amyloidosis

Osteosclerotic myeloma

Multiple myeloma

Waldenström’s macroglobulinemia

Table 1. Malignant and Special Paraproteinemias Disorders Associated with Neuropathy.*

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>NEUROPATHY</th>
<th>SYSTEMIC FEATURES</th>
<th>PARAPROTEIN</th>
<th>ELECTROMYOGRAPHIC CHANGES</th>
<th>PATHOLOGICAL FEATURES</th>
<th>TREATMENT FOR NEUROPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>Symmetric, distal sensory or sensorimotor; usually mild</td>
<td>Bone pain, fatigue, anemia, hypercalcemia, renal insufficiency</td>
<td>IgM–κ or IgG–κ (≥3 g/dl)</td>
<td>Axonal degeneration, with or without amyloid deposition</td>
<td>None</td>
<td></td>
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<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>Symmetric, distal sensory or sensorimotor, progressive; may simulate CIDP</td>
<td>Fatigue, weight loss, oronasal bleeding, visual blurring, encephalopathy</td>
<td>IgM–κ</td>
<td>Demyelinating</td>
<td>Plasma exchange, Prednisone, Melphalan</td>
<td></td>
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<tr>
<td>Osteosclerotic myeloma</td>
<td>Symmetric, proximal and distal sensorimotor, progressive areflexia; simulates CIDP</td>
<td>POEMS syndrome, Castleman’s disease</td>
<td>IgG–κ or IgA–κ</td>
<td>Demyelinating and axonal degeneration, with or without inflammation</td>
<td>Radiation therapy, Prednisone, Melphalan, Cyclophosphamide, Melphalan plus prednisone, Autologous stem-cell transplantation</td>
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<tr>
<td>Amyloidosis</td>
<td>Symmetric, distal, progressive, painful, sensorial, and autonomic symptoms</td>
<td>Congestive heart failure, renal failure, hepatosplenomegaly, macroglossia, weight loss</td>
<td>IgG–κ or IgA–κ</td>
<td>Axonal degeneration, with amyloid deposition</td>
<td>None</td>
<td></td>
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<tr>
<td>Cryoglobulinemia</td>
<td>Symmetric or multifocal, distal, painful, sensory or sensorimotor; multiple mononucleosis</td>
<td>Hepatoplenomegaly, purpura, arthralgias, leg ulcers, Raynaud’s phenomenon</td>
<td>IgM–κ or IgG–κ</td>
<td>Axonal degeneration, vasculitis, inflammatory infiltrate</td>
<td>Plasma exchange, Prednisone, Cyclophosphamide, Interferon alfa</td>
<td></td>
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<tr>
<td>Lymphoma (Castleman’s disease, hypersensitivity adenopathy, and chronic leukemia)</td>
<td>Variable: pure sensory or pure motor, sensory or sensorimotor, motor neuron disease; may simulate CIDP or Guillain–Barre syndrome</td>
<td>Lymphadenopathy, fatigue, weight loss, POEMS syndrome</td>
<td>IgM–κ or IgG–κ</td>
<td>Axonal degeneration, rarely with lymphomatous infiltrate</td>
<td>Plasma exchange, Prednisone, Chemotherapy for lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

*CIDP denotes chronic inflammatory demyelinating polyneuropathy, and POEMS polyneuropathy, organomegaly, endocrinopathy, M spike, and skin changes.

cance” (MGUS). In addition to the pathophysiologic mechanisms described above, M proteins and polyclonal paraproteins are linked by several lines of epidemiologic evidence: the prevalence of MGUS is higher in patients with idiopathic neuropathy than in those whose neuropathy has an identifiable cause, and the incidence of neuropathy is higher in patients with monoclonal gammopathy than in the general population of similar age. MGUS was once considered benign, but it is known that approximately 20 percent of patients will in time acquire a malignant plasma-cell disorder, usually myeloma. MGUS is distinguished from myeloma by the absence of the well-known systemic features of myeloma and by the smaller amount of paraprotein (usually 0.75 to 1.5 g per deciliter of serum and, in any case, less than 3 g per deciliter). Whereas IgG is the most common class of paraprotein in patients with MGUS, IgM is more frequent in those with neuropathy (60 percent), followed by IgG (30 percent) and IgA (10 percent). In contrast to patients with osteosclerotic myeloma or amyloidosis (discussed below), patients with MGUS predominantly have a kappa-light-chain component.

These polyneuropathies affect principally, but not exclusively, men over 50 years of age. Foot numbness, paresthesias, imbalance, and gait ataxia progress over a period of months. Sensation in the legs referable to conduction in large fibers is most affected (touch, joint position, and vibration). Half the patients have aching discomfort, dysesthesias, or lancinating pains. Weakness of the distal leg muscles with variable atrophy occurs as the illness advances. A few patients have a pure motor disorder resembling motor neuron disease.

The study of MGUS neuropathy has been confounded by its relation to an idiopathic condition well known to neurologists, chronic inflammatory demyelinating polyneuropathy. Probably one quarter of patients with the latter disorder also have a paraproteinaemia, but the meaning of this association is unclear. The cardinal electromyographic feature of chronic inflammatory demyelinating polyneuropathy, a focal block of electrical conduction in motor nerves, sometimes occurs in MGUS, and both neuropathies respond to immunomodulating treatments. The cerebrospinal fluid protein level is usually elevated in both conditions.

With limited success, correlations have been made between the immunoglobulin type (IgM, IgG, or IgA) and the clinical and electromyographic characteristics of the neuropathy. In patients with IgM neuropathy, tremor, sensory loss, and ataxia are more prominent; the demyelinating findings on electro-
myography may be more severe\textsuperscript{2,14,20,21}; and the disease may be less responsive to immune therapies. However, none of the differences between IgM and IgG neuropathies are consistent.\textsuperscript{22}

It is of greater importance regarding pathogenesis that half of patients with IgM neuropathy have a distinctive clinical syndrome that is associated with antibodies against MAG and also against other cross-reacting glycoproteins in myelin.\textsuperscript{5,7,9,23} The syndrome is slowly progressive and painless, with features of large-fiber sensory dysfunction foremost (ataxia, loss of joint position, and Romberg’s sign). Distal-limb weakness develops late and only then overshadows the sensory loss.

In contrast, a small number of patients, usually with IgG MGUS, have the electrophysiologic features of an axonal neuropathy.\textsuperscript{21,24,25} When the frequency of paraproteinemia in older patients is considered, it is never clear whether the presence of an “idiopathic” axonal neuropathy together with an M protein is coincidental. However, a few patients with a sensory form of axonal neuropathy have autoantibodies directed against sulfatide or chondroitin sulfate C, both of which are epitopes on the axon.\textsuperscript{26,27} A sural-nerve biopsy is generally advisable in cases of predominantly sensory axonal neuropathy in order to rule out amyloid deposition, as discussed below.

The optimal treatment for MGUS neuropathies has not been established, and the choice of initial therapy is somewhat arbitrary. The condition of one third or more of those with IgG or IgA MGUS improves within days or weeks of the administration of high-dose intravenous immune globulin (0.4 g per kilogram of body weight daily for five days), plasma exchange (a total of 220 ml per kilogram, given in four or five treatments), or therapy with corticosteroids, often in combination with immunosuppressants.\textsuperscript{3,16,17,22,24} Only the benefit of plasma exchange has been substantiated in a controlled trial.\textsuperscript{28} An alternative treatment is immunoadsorption, a simpler technique in which IgG and immune complexes are

\begin{figure}
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\includegraphics[width=\textwidth]{structure.png}
\caption{Structure and Location of Three Main Glycoconjugate Antigens on Peripheral Nerve Implicated in the Paraproteinemic Neuropathies.}
\end{figure}
removed by passing the patient’s blood through a plastic column containing covalently bound staphylococcal protein. These treatments generally produce only transient amelioration and require repetition every several months, as gauged by the patient’s clinical state. If one treatment fails, another is likely to succeed. The IgM neuropathies tend to be the most refractory, but some improvement can be expected with the same regimens, particularly if cyclophosphamide or chlorambucil is added in doses sufficient to reduce the amount of M protein. Patients with anti-MAG antibodies generally require prolonged therapy with monthly plasma exchange and continuous oral or pulsed intravenous cyclophosphamide. Interferon alfa was beneficial in one trial.

A special, purely motor disorder termed multifocal motor neuropathy occurs in middle-aged men; it is linked to high titers of IgM antibodies directed at the GM1 ganglioside on myelin membranes (Fig. 1). The circulating paraprotein is often polyclonal but is monoclonal in 20 percent of cases. The disease is characterized by slowly progressive, painless weakness that is asymmetric or confined to one limb and by normal or reduced reflexes, without sensory changes. The syndrome superficially resembles amyotrophic lateral sclerosis, since regional atrophy, cramps, and fasciculations occur, but the upper-motor-neuron findings of the latter disease (hyperreflexia, spasticity, Babinski signs, and dysarthria) are absent. The defining feature is an electrical conduction block in the middle or proximal segments of the motor nerves together with normal sensory conduction in the same nerves. The observed binding of GM1 antibodies at the nodes of Ranvier provides a plausible explanation for the block of electrical conduction. Immune globulin is effective in as many as 90 percent of patients, but repeated infusions are required; cyclophosphamide is used in patients who have a relapse or do not respond to treatment.

Figure 2. Electron Micrograph of a Sural-Nerve–Biopsy Specimen Demonstrating Separation of the Outer Myelin Lamellae Due to the Binding of IgM (×25,000).
A deposit of the paraprotein is seen (arrow), under a lamella of myelin. Reprinted from Jacobs with the permission of the publisher.
MULTIPLE MYELOMA

This disease has been reviewed recently in the Journal. One third of patients with multiple myeloma are found to have abnormalities on careful electrophysiologic examination. However, neuropathy is a dominant feature in only 10 percent of patients, and it commonly precedes the discovery of the blood dyscrasia. Weakness and numbness of the distal limbs appear over a period of weeks, occasionally beginning in the arms. In typical cases, electromyographic studies indicate axonal damage but pathological specimens show destruction of both axons and myelin, the first presumably being primary. Removing the paraprotein by plasma exchange has no consistent effect on the neuropathy. Amyloid deposition is a complication in 30 to 40 percent of cases but is by no means universal. Sensory neuropathy, a chronic inflammatory demyelinating polyneuropathy, and neoplastic root infiltration also rarely occur.

WALDENSTRÖM’S MACROGLOBULINEMIA

A paraproteinemic neuropathy was first observed in Waldenström’s macroglobulinemia. Systemic symptoms of fatigue, weight loss, and bleeding dominate. The IgM paraprotein is derived from lymphocytoid cells that proliferate in the marrow and lymph nodes, much the same as in IgM MGUS, from which Waldenström’s macroglobulinemia may arise. Paresthesias and numbness in the feet are followed by weakness and wasting of the lower legs, causing foot drop and a steppage gait, and months later, by arm weakness. In typical cases, electromyography demonstrates demyelination, but distal axonopathy and sensory neuropathy are rare associations. Plasma exchange is helpful in slowing the progress of the neuropathy, and there has been some success, albeit inconsistent, with prednisone, melphalan, and chlorambucil.

OSTEOSCLEROTIC MYELOMA, OR THE POEMS SYNDROME

Osteosclerotic myeloma is a rarer plasma-cell dyscrasia characterized by single or multiple plasmacytomas that manifest as sclerotic bone lesions. Although it accounts for only 3 to 5 percent of myelomas, 85 percent of patients present with polyneuropathy. The neuropathic symptoms are slowly progressive and have the features of demyelination. The M protein, which is usually IgG or IgA present at low concentration, is found in 90 percent of cases, and the light chain is virtually always of the lambda subtype. One helpful diagnostic feature is the almost invariable elevation of the cerebrospinal fluid protein level, often to more than 100 mg per deciliter. A constellation of systemic features may surface, referred to as the POEMS (polyneuropathy, organomegaly, endocrinopathy, M spike, and skin changes), or Crow–Fukase, syndrome, but the POEMS syndrome and osteosclerotic myeloma are essentially the same disease. The deposition of light chains in the endoneurium suggests that the paraprotein has a proximate role in nerve damage. Greatly elevated levels of proinflammatory cytokines, such as tumor necrosis factor, have also been implicated. With resection of solitary bone lesions, focused radiation, or chemotherapy, the neuropathy stabilizes or improves in half of patients, but the response may take many months. As in neuropathy associated with myeloma, plasma exchange is generally ineffective.

AMYLOID NEUROPATHY

The amyloid polyneuropathies are of two types — one associated with inherited amyloidosis and the other with primary (nonfamilial) systemic amyloidosis, as reviewed recently in the Journal. The latter is more often seen in practice and is relevant because an M spike is present in the serum or urine in 90 percent of patients, usually consisting of IgG with a lambda light chain or the light chain alone. The initial feature in 15 percent of patients is neuropathy manifesting as numbness in the feet, but the signature symptoms are burning and aching pains with lancinating electrical sensations and loss of pain and thermal sensation in the distal limbs. A predominant effect on small-diameter sensory fibers is consistent with these symptoms. Autonomic symptoms can be extreme, particularly postural hypotension, diarrhea (also from infiltration of the gut wall), impotence, and bladder dysfunction. The pathogenesis of the generalized sensory neuropathy is uncertain; both a direct toxic effect of amyloid and vascular insufficiency have been proposed. Carpal tunnel syndrome is also frequent because of amyloid concentration in the flexor retinaculum. The neuropathy may be eclipsed by weight loss and amyloid deposition in other organs, mainly the heart and kidneys, resulting in death in three to five years. Electrodiagnostic studies demonstrate a symmetric sensorimotor axonal disorder, and the diagnosis is established by detecting amyloid in biopsies of bone marrow (50 percent), abdominal fat pad (70 percent), rectal mucosa (80 percent), or sural nerve (90 percent).

Melphalan combined with prednisone prolongs survival in a small proportion of patients for several years, but the treatment has little effect on the neuropathy. Autologous stem-cell transplantation has improved or stabilized the condition of a few patients who have been studied for only one year.

CRYoglobulinemia

Cryoglobulins are proteins (usually IgG or IgM) that precipitate when cooled, redissolve after warming, and are deposited as immune complexes in blood vessels. Their detection requires that the blood specimen be transported to the laboratory in a warm-water bath. The immunoglobulin may be monoclonal-
al, both monoclonal and polyclonal (mixed essential cryoglobulinemia), or polyclonal. Neuropathy is quite common in patients who have mixed essential cryoglobulinemia, the type unassociated with lymphoproliferative diseases, chronic infections, or autoimmune disorders.26

There is almost always pain at the onset, and weakness may be generalized or multifocal. Paresthesias are precipitated by cold in some patients, as is the accompanying Raynaud’s phenomenon. The onset is acute in the one third of patients who have multiple mononeuritis, but more commonly there is a progressive, symmetric, distal sensorimotor pattern combined with one or two recognizable mononeuropathies (e.g., foot or wrist drop). The polyneuropathy represents a confluence of incomplete mononeuropathies caused by vasculitis in numerous nerve fascicles.

Corticosteroids, cyclophosphamide, and plasma exchange are variably successful in stabilizing the neuropathy, and interferon alfa has shown promise in cases associated with hepatitis C,26 although none of these treatments have been studied systematically.

NEUROPATHY IN OTHER LYMPHOPROLIFERATIVE DISORDERS

Subacute or chronic polyneuropathies in the presence of a paraprotein also occur in non-Hodgkin’s lymphoma, Castleman’s disease, hypersensitivity lymphadenopathy, and leukemia (Table 1). In some cases, the polyneuropathy is similar to one of the typical paraproteinemic conditions. It is uncertain whether the neuropathy is strictly related to the paraproteinemia or whether it represents a different type of paraneoplastic condition.

Several distinctive neurologic syndromes occur among the paraproteinemic neuropathies, and sometimes they may indicate a plasma-cell dyscrasia or a related disease. The neuropathies and some of the revealed systemic disorders are at least partially treatable, underscoring the need for immunoelectrophoresis or the more sensitive immunofixation test in the evaluation of any unexplained polyneuropathy.

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