Neuropathy with Predominant Small Fiber Involvement Associated with Abnormal Anti-MAG Titer

Marco Luigetti¹, Francesca Madia¹, Amelia Conte¹, Pietro Tonali¹,² and Mario Sabatelli¹

Abstract

We describe a patient with painful neuropathy associated with an abnormal anti-MAG titer in which predominant involvement of intra-epidermal nerve fiber was documented. Electrophysiological studies revealed low-borderline amplitude of sensory and compound motor action potentials registering from lower limbs and normal conduction velocity. Sural nerve biopsy disclosed only a slight loss of myelinated fiber. Skin biopsy performed at the proximal thigh and at the distal leg was consistent with a non-length-dependent small fiber neuropathy. It is likely that in this case anti-MAG antibodies played a role in the pathogenesis of small fiber neuropathy.

Key words: neuropathy, anti-MAG, sural nerve biopsy, skin biopsy

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Introduction

Myelin-associated glycoprotein (MAG) is a major component of non-compact myelin and plays an important role in myelin-axon interactions (1). Monoclonal IgM antibodies against MAG are implicated in the pathogenesis of an acquired, late-onset demyelinating polyneuropathy characterized by sensory loss and ataxia, caused by predominant impairment of large myelinated sensory nerve fibers (2). Neurophysiological examination typically shows a widespread slowing of sensori-motor nerve conduction velocity with prolonged distal latencies (3). However, also the involvement of intra-epidermal nerve fiber has been well reported in anti-MAG neuropathy (4).

Herein we describe a patient presenting with painful neuropathy and an abnormal anti-MAG titer in which a predominant involvement of intra-epidermal nerve fibers was documented.

Case Report

A 60-year-old woman patient with a two-year history of shooting pain and burning in her lower limbs and hands was admitted to our department for the relevant investigations. She reported receiving liver transplantation fifteen years earlier due to autoimmune hepatitis followed by immunosuppressive therapy (azathioprine and cyclosporine, actually suspended; methylprednisolone gradually tapered up to 12.5 mg on alternate days) and being affected for ten years by a very mild form of ulcerative colitis treated occasionally with budesonide enemas. Three years earlier she also received a diagnosis of Waldenström macroglobulinaemia (WM), which was successfully treated with a complete cycle of Rituximab; after this therapy she presented a mild hypogammaglobulinemia currently treated with monthly administration of IVIg.

Neurological examination was unremarkable. The intensity of her pain was scored 6 on the 10 cm visual analogue scale. Extensive laboratory studies proved normal, including fasting glucose, glucose tolerance test, glycosalated hemoglobin, FT3, FT4, TSH, anti-thyroid antibodies, serum vitamin B12 and folate, hepatic enzymes, creatinine, urinalysis, antinuclear antibody (ANA), anti-extractible nuclear antigens, anti-DNA antibody, antineutrophil cytoplasmic antibodies (ANCA), circulating C3 and C4, titers of anti-GM1 and anti-GM2 and anti-Hu antibodies. Serologic tests for HBV, HCV, syphilis and HIV were all negative. Immunofixation electrophoresis confirmed the presence of IgMk and an anti-MAG essay showed 9,568 BTU (normal...
value <1,000); two years before, after rituximab therapy, these had been measured at 12,435 BTU.

Nerve conduction studies revealed low-borderline amplitude of sensory and compound motor action potentials registering from the lower limbs and normal conduction velocities (Table 1). Rectal mucosa biopsy and periumbilical fat needle aspiration ruled out amyloidosis. The patient underwent a 3-mm punch skin biopsy at the proximal thigh and at the distal leg, which showed a non-length-dependent small fiber neuropathy. Intra-epidermal nerve fiber (IENF) density was 4.69/mm at the proximal thigh and 2.6/mm at the distal leg, which showed a non-length-dependent small fiber neuropathy (Fig. 1). Intra-epidermal nerve fiber (IENF) density was 4.69/mm at the proximal thigh and 2.6/mm at the distal leg, which showed a non-length-dependent small fiber neuropathy (Fig. 1).

Table 1. Electrophysiological Studies of the Patient

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Right side</th>
<th></th>
<th>Left side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MCV (m/s)</td>
<td>dl (ms)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>55 (±45)</td>
<td>3.8 (±54)</td>
</tr>
<tr>
<td>W-APB</td>
<td></td>
<td>50 (±45)</td>
<td>57 (±45)</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td>50 (±45)</td>
<td>57 (±45)</td>
</tr>
<tr>
<td>Ab. E- Bel. E</td>
<td></td>
<td>47 (±42)</td>
<td>45 (±42)</td>
</tr>
<tr>
<td>W- ADM</td>
<td></td>
<td>47 (±42)</td>
<td>45 (±42)</td>
</tr>
<tr>
<td>Peroneal</td>
<td></td>
<td>48.2 (±50)</td>
<td></td>
</tr>
<tr>
<td>Tibialis</td>
<td></td>
<td>54 (±40)</td>
<td>14.3 (±25)</td>
</tr>
<tr>
<td>IF-W</td>
<td></td>
<td>48 (±45)</td>
<td>58 (±45)</td>
</tr>
<tr>
<td>IIIIF-W</td>
<td></td>
<td>46 (±45)</td>
<td>58 (±45)</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td>46 (±45)</td>
<td>58 (±45)</td>
</tr>
<tr>
<td>Radial</td>
<td></td>
<td>46 (±45)</td>
<td>58 (±45)</td>
</tr>
<tr>
<td>Sural</td>
<td></td>
<td>46 (±45)</td>
<td>58 (±45)</td>
</tr>
<tr>
<td>A-SURA</td>
<td></td>
<td>46 (±45)</td>
<td>58 (±45)</td>
</tr>
</tbody>
</table>

Legend: NE, not examined; MCV, motor conduction velocity; dl, distal latency; CMAP, compound muscle action potential; ml, median latency; SCV, sensory conduction velocity; SAP, sensory action potential; R, right; L, left; Ax, axilla; E, elbow; W, wrist; Ab. E- Bel. E, above elbow-below elbow; APB, abductor pollicis brevis; ADM, abductor digiti minimi; PF, popliteal fossa; A, ankle; FH, fibula head; EDB, extensor digitorum brevis; LM, lateral malleolus; AH, abductor hallucis; IF, first finger; IHF, third finger; VF, fifth finger. Normal values are given in brackets.

Congo-red staining was negative for amyloid deposits. Semithin section disclosed only a slight loss of myelinated fibers. No immunoreactivity was observed after incubation with anti-IgM antibodies.

Discussion

Our patient presented with painful neuropathy and an abnormal anti-MAG titer. However clinical and electrophysiological findings were not typical for an IgM-related neuropathy (3). The clinical history of our patient included three other significant conditions, which may be associated with peripheral neuropathy: ulcerative colitis, autoimmune hepatitis and WM (6-8). The connection of last two with small fiber neuropathy seems to be excluded by the liver transplantation fifteen years earlier without any signs of reject on and by the fact that symptoms of neuropathy manifested after successful immunotherapy for WM, respectively. We cannot exclude with certainty an association between ulcerative colitis and SFN, however colitis occurred many years before neuropathy and presented a very mild clinical course.

Sural nerve biopsy ruled out amyloidosis and vasculitis, two conditions that may complicate autoimmune or chronic inflammatory disorders. Skin biopsy showed a non-length-dependent small fiber neuropathy.

Anti-MAG related neuropathy may present an IENF involvement. In a recently described series, all anti-MAG pa-
The authors concluded that IENF involvement may be secondary to the autoimmune attack on dermal fibers, rather than directly on IENFs, which are naked axons without Schwann cell ensheathment (4). Another paper focused on possible mechanisms by which the presence of anti-MAG may cause axonal degeneration, concluding that axonal degeneration is probably not only a consequence of structural myelin damage, but may also result from inappropriate signalling cascades and impaired homeostasis, as they interfere with axonal maintenance (9). In both reported series, electrophysiological studies were consistent with anti-MAG associated neuropathy (4, 9).

It is also likely in the present patient that anti-MAG antibodies played a role in the pathogenesis of small fibers neuropathy but, considering the complex clinical history, a coincidental association can not be excluded. A possible mechanism of nerve damage in our case can be the presence of immunoglobulin deposition in spinal ganglia; this pattern has been already described in amyloidotic neuropathy in which clinical picture resembles that of our patient (10). On the other hand we cannot exclude an autoimmune attack by anti-MAG autoantibodies on myelinated dermal fibers, which results in damage of their epidermal terminals, or direct damage to epidermal unmyelinated axons deprived of MAG-related protective effects by the antibodies themselves (4, 9, 11). Further studies are necessary to clarify the complex pathogenesis of this neuropathy.

Disclosure: The authors report no conflicts of interest.

References


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