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**Background** The prevalence of peripheral neuropathy in patients with Sjögren syndrome remains unclear owing to conflicting results in the published series, with numbers ranging from 2% to over 60% of Sjögren syndrome patients. Whether peripheral neuropathy is a feature of the systemic or glandular disease or whether it is related to a circulating antineuronal antibody remains also uncertain. **Methods** The authors reviewed the records of patients with primary Sjögren syndrome (pSS), fulfilling the Revised European-American Classification Criteria, seen in their department from 1992 to 2009. The patients with previously recorded neuropathic features were re-examined clinically and electrophysiologically. Other causes of polyneuropathy were excluded. The authors also searched for circulating antineuronal antibodies using immunofluorescence and western blot and for antibodies against muscarinic and nicotinic acetylcholine receptors as potential biomarkers. **Results** 509 cases met the diagnostic criteria for pSS. Among these, 44 patients were recorded as having neuropathic symptoms. After completing the evaluation, however, only nine (1.8%) had polyneuropathy with objective clinical signs and abnormal electrophysiological findings. The neuropathy was axonal in all, in five pure sensory and in four sensorimotor. The patients with peripheral neuropathy had extraglandular manifestations such as palpable purpura and vasculitis. No evidence of antineuronal autoimmunity was found, and no candidate biomarkers were identified. **Conclusion** Polyneuropathy is a rare manifestation of pSS occurring in 1.8% of patients. In the majority of patients, it is a late event and frequently associated with systemic disease or risk factors for lymphoma development.

# Peripheral neuropathies in Sjögren syndrome: a new reappraisal

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## ABSTRACT

**Background** The prevalence of peripheral neuropathy in patients with Sjögren syndrome remains unclear owing to conflicting results in the published series, with numbers ranging from 2% to over 60% of Sjögren syndrome patients. Whether peripheral neuropathy is a feature of the systemic or glandular disease or whether it is related to a circulating antineuronal antibody remains also uncertain.

**Methods** The authors reviewed the records of patients with primary Sjögren syndrome (pSS), fulfilling the Revised European—American Classification Criteria, seen in their department from 1992 to 2009. The patients with previously recorded neuropathic features were re-examined clinically and electrophysiologically. Other causes of polyneuropathy were excluded. The authors also searched for circulating antineuronal antibodies using immunofluorescence and western blot and for antibodies against muscarinic and nicotinic acetylcholine receptors as potential biomarkers.

**Results** 509 cases met the diagnostic criteria for pSS. Among these, 44 patients were recorded as having neuropathic symptoms. After completing the evaluation, however, only nine (1.8%) had polyneuropathy with objective clinical signs and abnormal electrophysiological findings. The neuropathy was axonal in all, in five pure sensory and in four sensorimotor. The patients with peripheral neuropathy had extraglandular manifestations such as palpable purpura and vasculitis. No evidence of antineuronal autoimmunity was found, and no candidate biomarkers were identified.

**Conclusion** Polyneuropathy is a rare manifestation of pSS occurring in 1.8% of patients. In the majority of patients, it is a late event and frequently associated with systemic disease or risk factors for lymphoma development.

## INTRODUCTION

Sjögren syndrome is a systemic autoimmune disease that affects 0.5 to 1% of the general population.<sup>1,2</sup> It usually presents as an isolated glandular disease affecting exocrine glands, typically manifested with xerostomia and xerophthalmia. Extraglandular manifestations are due to involvement of virtually every organ including the musculoskeletal system, skin, kidneys, lungs, liver and the central or peripheral nervous system (PNS).<sup>1–3</sup> The most serious complication of Sjögren syndrome is lymphoma, which affects 3–6% of patients and is 44 times more frequent than in the general population.<sup>4,5</sup>

The clinical spectrum of peripheral neuropathies encountered in Sjögren syndrome patients is

wide,<sup>6–9</sup> with sensory neuropathies being the most common.<sup>8,9</sup> The sensory neuropathies are of three distinct subtypes: distal (length-dependent) affecting sensory fibres with electrodiagnostic features of axonal involvement; painful, due to small-fibre involvement<sup>10–14</sup>; and sensory ataxic, a disabling neuropathy involving the dorsal root ganglia (ganglionopathy)<sup>15,16</sup> resulting in deaf-ferentation.<sup>17</sup> Axonal sensorimotor polyneuropathy, cranial neuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy and autonomic neuropathy are other less frequently encountered types.<sup>8,9</sup>

Although several studies have focused on the peripheral nerve manifestations of Sjögren syndrome, two issues remain contentious: the prevalence of peripheral neuropathy, with a reported range between 2 and 60%,<sup>6,13,18–29</sup> and the stage of the disease in which peripheral neuropathy is most commonly manifested. Some studies claim that peripheral neuropathy is a late event, presenting in patients with manifestations of severe systemic disease such as palpable purpura, low C4 complement factor, mixed monoclonal cryoglobulinaemia, glomerulonephritis and increased risk of lymphoma development.<sup>23</sup> Other studies, however, suggest that peripheral neuropathy is the presenting feature of an isolated glandular disease that has a benign course.<sup>8,9</sup> The pathogenesis of these neuropathies is also poorly investigated. Because Sjögren syndrome is a systemic autoimmune disease engulfing many autoimmune processes, correlating the temporal profile and clinical patterns of the neuropathy with the type of Sjögren syndrome's manifestations will help us understand the pathogenesis for each neuropathy subtype. Our study was therefore designed to assess the frequency of neuropathy diagnosed by means of objective clinical signs and abnormal electrophysiology, in the various stages of the disease. We also sought to examine whether the neuropathy is immune-mediated by searching for antibodies against a variety of peripheral nerve tissue antigens and for antibodies against muscarinic and ganglionic acetylcholine receptors, which have been implicated in both Sjögren syndrome and various peripheral neuropathies.<sup>30,31</sup>

## PATIENTS AND METHODS

### Patients

Clinical information was obtained retrospectively from the records of patients who met the diagnostic criteria of primary Sjögren syndrome, according to the Revised European—American

diagnostic criteria.<sup>32</sup> These patients had been followed from 1992 to 2009 at the Pathophysiology Clinic of the University of Athens Medical School, which serves as a national referral centre for systemic autoimmune diseases. All patients with previously recorded manifestations indicative of peripheral neuropathy (after providing written informed consent) were invited to participate in the current study that took place from 2008 to 2010. These patients were re-examined by a certified neurologist (MLK). The sensory examination was based on an assessment of pinprick, light touch, position and vibratory sensation. Patients with objective clinical signs of neuropathy underwent electromyography and nerve-conduction studies of the sural, peroneal and median nerve (ES). Normal values, defined as the mean  $\pm$  2SD, were determined from 100 normal individuals from different age groups. Skin temperature was measured to be greater than 32°C when all electrophysiological studies were conducted. The cut-off amplitude of the sural SNAP (sensory nerve action potential) was 10  $\mu$ V for ages younger than 65, and 8  $\mu$ V for ages 65 to 75; for people older than 85, the sural nerve amplitude was considered abnormal only when it was not elicited. The mean normal sural conduction velocity was determined at 48 m/s. The peroneal CMAP (compound muscle action potential) amplitude cut-off was 4 mV and conduction velocity 46 m/s. The median nerve SNAP was 20  $\mu$ V, and the sensory conduction velocity (from digit to wrist) was 47 m/s. The median nerve CMAP was 5 mV and conduction velocity 50 m/s. MRI or CT of the brain and/or spine was performed on a case-by-case basis to exclude spinal or cranial abnormalities as a possible cause for the clinical manifestations. New patients diagnosed during the study period were also included. Patients with other causes of peripheral neuropathy were excluded. Serum samples were obtained from all peripheral neuropathy patients and stored at -20°C for immunological studies (see below). The study was approved by the University of Athens' Medical School Ethics Committee.

### Antineural antibody screening

We searched for antineural antibodies in eight patients with clinically and electrophysiologically confirmed neuropathy, from eight controls with Sjögren syndrome without neurological involvement and from eight healthy controls using indirect immunofluorescence and western blot on a variety of nerve tissues. As positive controls, we used sera with known reactivities to brain and nerve antigens, namely Aquaporin-4 and MAG. Primate cerebellum and sciatic nerve sections were obtained from Euroimmun (Nerve Mosaic, No 1111-1003-2 Euroimmun, Lübeck, Germany). Human dorsal root ganglia were obtained from the Netherlands Brain Bank (Netherlands Institute for Neuroscience, Amsterdam) and sectioned in a Leica cryostat. Briefly, sections were fixed in 4% paraformaldehyde and incubated with 1% CHAPS. After blocking with 10% goat serum, they were incubated with the patients' sera diluted 1:100 in 1% goat serum followed by AlexaFluor 488 goat antihuman IgG or IgM (Invitrogen, Carlsbad, California) diluted 1:250 in 1% goat serum. Western blot experiments were carried out as previously described,<sup>33</sup> with the only modification being the use of the AEC peroxidase substrate kit (Vector Laboratories, Burlingame, California) for development.

### Anti-M1 and M3 receptor antibodies

Peptides corresponding to the second extracellular loop of M1 muscarinic acetylcholine receptor (165–185) and M3 muscarinic receptor in dimer form (213–237) were synthesised (Biosynthesis, Lewisville, Texas), and ELISA experiments were carried

out as previously described,<sup>34</sup> with the only modification being that a control well corresponding to each sample was coated only with blocking solution. The optical density (OD) of the control well was subtracted from each sample's OD. Samples were deemed positive for antimuscarinic antibodies when the final OD was greater than the mean plus three SDs of normal samples tested in the same manner.

### Ganglionic acetylcholine receptor antibody radioimmunoprecipitation assay

Solubilised membrane fractions from IMR32 cells<sup>31</sup> were labelled with <sup>125</sup>I-epibatidine and incubated with 5  $\mu$ l of patient's serum overnight at 4°C in duplicates. Following incubation for 2 h with goat antihuman IgG (RSR, Cardiff, UK) and precipitation, the pellets were washed with 0.5% Triton-X 100 in phosphate buffer, and radioactivity was measured. The value 10 arbitrary units was defined as the mean counts per minute value of healthy controls, and samples with values greater than 25 Units were deemed positive. mAb 198, which binds to muscle acetylcholine receptor  $\alpha$ -1 subunit and cross-reacts with the ganglionic  $\alpha$ -3 subunit, was used as a positive control.

## RESULTS

### Patients

The records of 509 patients with primary Sjögren syndrome were reviewed.<sup>32</sup> Forty-four patients were recorded as having neuropathic symptoms or signs including paraesthesias, pain, gait unsteadiness, Romberg sign, superficial or deep sensory deficits, diminished deep tendon reflexes or muscle weakness. Two of the 44 patients were excluded from further analysis because they were found to have secondary Sjögren syndrome or did not meet the criteria for Sjögren syndrome. Of the remaining 42 patients, originally recorded as having neuropathic symptoms, 11 were excluded from further analysis because their symptoms were caused by various musculoskeletal problems; two others with a history of trigeminal neuralgia were asymptomatic and were also excluded. Among the remaining 29 patients, three had clinical and electrodiagnostic findings of carpal tunnel syndrome; one other was diagnosed as having motor neuron disease and another with spinal stenosis. Among the remaining 24 patients, 15 complained for neuropathic symptoms such as pain and paraesthesias, but the clinical and electrophysiological evaluation were normal. These patients are suspected of having a small fibre neuropathy, but they did not undergo quantitative sensory testing or skin biopsy. Accordingly, only nine patients from the initial cohort of 509 patients (1.8%) fulfilled the clinical and electrophysiological criteria of polyneuropathy; five of them were diagnosed as having sensory and four as having sensorimotor polyneuropathy (table 1).

These patients with bona fide neuropathy were female, with a mean age of 65 years (range 54–84 years) at the time of the last evaluation. All complained of distal paraesthesias and had distal (length-dependent) neurological findings in the lower limbs; the upper limbs were affected in only two. In the majority of patients (6/9) the neurological findings were symmetrical. Among the patients with sensory polyneuropathy, two had position and vibratory sensation deficits, two had pinprick and light touch sensory deficits, and one had sensory deficits in all tested modalities; the patients with sensorimotor polyneuropathy had mostly light touch and pinprick sensory deficits. Deep tendon reflexes were diminished or absent in eight of the nine patients. The neuropathy was mild, and all patients were ambulatory; only one needed a cane for ambulation. All patients had the electrophysiological pattern of

**Table 1** Overview of peripheral neuropathy (PN) patients

Patient no	Clinical manifestations	Main laboratory findings	PN present at SS diagnosis	Neurological findings			Neuropathy
				Motor	Sensory	Deep tendon reflexes	
7	Mild sicca only	ANA, anti-Ro, anti-La, RF	+	Normal	PP, LT deficits, of the upper digits and soles, POS, Vib deficits of the distal lower limbs	Absent globally	Axonal sensory
24	Mild sicca only	ANA, anti-Ro, RF, low C4	–	Normal	PP, LT LL deficits distally	Triceps, Achilles diminished	Axonal sensory
10	Sicca, Raynaud phenomenon, vasculitis, purpura, PGE, atrophic gastritis	ANA, anti-Ro, anti-La, RF, anaemia, low C4, cryoglobulinaemia	+	Distal right UL muscle weakness (4/5)	PP, LT deficits in UL and LL	Left triceps and bilateral Achilles reflexes absent	Axonal sensorimotor
28	Sicca, arthritis, Raynaud phenomenon, purpura, PGE	ANA, anti-Ro, AMA, anti-U1RNP, anaemia	–	Normal	Vib, POS deficits globally	Absent in LL	Axonal sensory
30	Sicca, arthritis	ANA, anti-Ro, RF	–	Proximal and distal bilateral UL and LL muscle weakness (4/5)	Normal	Absent in right UL and LL bilaterally	Axonal sensorimotor
32	Sicca, arthralgias, PGE, lymphadenopathy	ANA, anti-Ro, anaemia, low C4	–	Normal	LT, PP deficits in right distal LL	Achilles tendon reflexes absent bilaterally	Axonal sensory
33	Sicca, purpura, vasculitis	ANA, anti-Ro, cryoglobulinaemia, low C4	–	Right LL distal muscle weakness (4/5)	Vib deficits in LL bilaterally	Absent Achilles deep tendon reflexes	Axonal sensory with superimposed acute mononeuropathy
34	Sicca, Arthralgias, Raynaud phenomenon, purpura, PGE, glomerulonephritis	ANA, anaemia	–	Proximal and distal muscle weakness in all limbs (4/5, except distal right LL 2/5)	PP, LT deficits in distal right LL	Bilaterally absent Achilles reflexes	Axonal sensorimotor
43	Sicca, Arthralgias, Raynaud phenomenon, vasculitis, purpura, lymphadenopathy	ANA, anti-Ro, RF, anaemia, cryoglobulinaemia, low C4	+	Distal symmetrical LL muscle weakness	PP and LT deficits in distal LL	Normal	Axonal sensorimotor

ANA, antinuclear antibodies; LL, lower limbs; LT, light touch; Pos, position sensation deep tendon reflexes, deep; PP, pinprick; RF, rheumatoid factor; SS, Sjögren syndrome; UL, upper limbs; Vib, vibration sensation.

axonal dysfunction. One patient with sensory polyneuropathy developed an acute mononeuropathy, in the setting of generalised vasculitis, confirmed by intestinal biopsy (see table 1 for a detailed description of the patients).

In six of nine patients, the neuropathy was a late event in the course of the disease with a median of 6 years (range of 2–24) from the time of the initial diagnosis of Sjögren syndrome; in one, the neuropathy was the presenting manifestation of Sjögren syndrome, confirmed soon thereafter; and in the remaining two the neuropathy was present at the time of Sjögren syndrome diagnosis, but the temporal relationship between the two could not be ascertained. One of the latter three patients had no extraglandular manifestations; this is in contrast to the other two who had prominent extraglandular manifestations as described below.

The majority of patients with neuropathy had active systemic disease. Extraglandular manifestations were present in seven of nine and included palpable purpura in five patients, Raynaud phenomenon in four, arthralgias in three, biopsy-documented vasculitis (in organs other than the nerves) in three, arthritis in two and lymphadenopathy in two. Glomerulonephritis and atrophic gastritis were present in two others. Six patients (three with sensory and three with sensorimotor polyneuropathy) were classified as type I Sjögren syndrome, which confers a higher risk for lymphoma development.<sup>35</sup> Type I Sjögren syndrome is defined based on the presence of at least two of the following manifestations: parotid enlargement, low C4 complement factor at the time of Sjögren syndrome diagnosis or palpable purpura.<sup>35</sup>

All patients with peripheral neuropathy had antinuclear antibodies; eight had anti-Ro antibodies, and two had anti-La antibodies. Rheumatoid factor was found in five. Three patients had cryoglobulinaemia. Low C4 complement factor at the time of Sjögren syndrome diagnosis was found in five patients.

#### Antineural antibody screening Immunofluorescence and western blot

Eight of nine polyneuropathy patients were screened for the presence of antineural antibodies with immunofluorescence and western blot.

#### Brain and dorsal root ganglion immunofluorescence

No consistent IgG or IgM immunostaining pattern on neuronal structures was observed with the patient's sera, with the exception of occasional antinuclear staining, as expected.

#### Peripheral nerve immunofluorescence

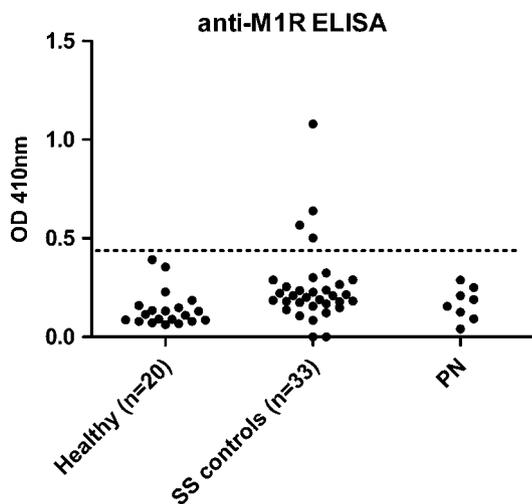
Staining primate nerve using an IgG and IgM secondary antibodies yielded no specific staining.

Western blot experiments of mouse brain extracts probed with patients and healthy control sera also revealed no specific bands.

#### Screening for putative peripheral neuropathy biomarkers

##### Muscarinic receptor autoantibodies

**ELISA for anti-M1 muscarinic receptor autoantibodies.** We tested eight polyneuropathy patients, 33 Sjögren syndrome patients without neurological involvement and 20 healthy controls. Antibodies against M1 muscarinic acetylcholine receptor were



**Figure 1** Anti-M1 muscarinic antibodies ELISA. Four patients with Sjögren syndrome (SS) were tested positive for anti-M1R antibodies, as opposed to peripheral neuropathy patients (PN) and healthy controls. OD, optical density.

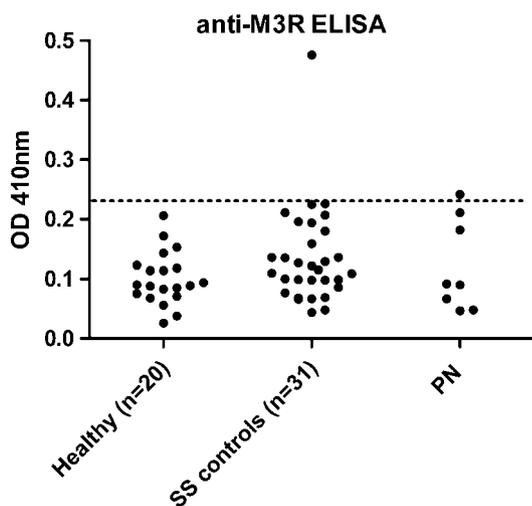
not found in any of the polyneuropathy patients or healthy controls. Four of 33 Sjögren controls were positive for anti-M1 muscarinic receptor antibodies (figure 1).

**ELISA for anti-M3 muscarinic receptor autoantibodies.** One of eight polyneuropathy patients was positive for antibodies against M3, as was one of 31 Sjögren syndrome patients without neurological involvement. None of the 20 healthy controls was positive (figure 2). This patient was diagnosed as having axonal sensorimotor polyneuropathy.

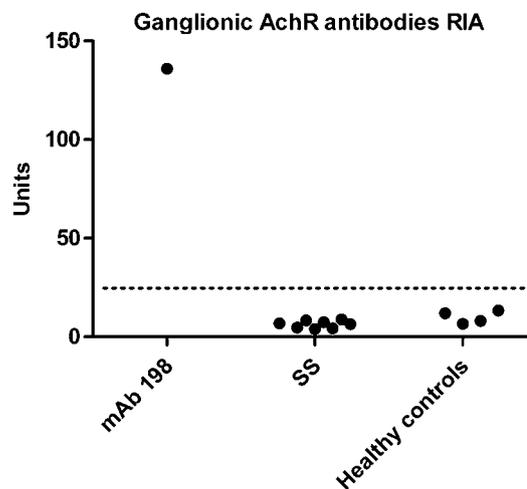
**Ganglionic ( $\alpha 3$ ) acetylcholine receptor autoantibodies.** None of the eight polyneuropathy patients and none of the four healthy controls was tested positive for ganglionic acetylcholine receptor antibodies (figure 3).

**DISCUSSION**

The study found a surprisingly low (1.8%) prevalence of polyneuropathy, diagnosed by means of objective signs and abnormal



**Figure 2** One patient with Sjögren syndrome and peripheral neuropathy (PN) was tested positive for anti-M3R antibodies, as was one patient with Sjögren syndrome (SS). None of the healthy controls was positive for these antibodies.



**Figure 3** Antiganglionic ( $\alpha 3$ ) acetylcholine receptor antibodies radioimmunoassay. None of the eight peripheral neuropathy patients (SS) or healthy controls screened was positive for the tested antibodies.

electrophysiology, among a large number of patients with bona fide Sjögren syndrome. This is in contrast to previous studies which have shown a much higher prevalence ranging from 2% to 60%.<sup>6 13 18–29</sup> Such a wide discrepancy can be explained on several factors. First, most of the other studies were published during the time when the diagnostic criteria for Sjögren syndrome were still evolving, and the diagnosis was at times questionable. Second, many studies have been retrospective and included contemporaneous neurological or electrophysiological assessments in a relatively small number of patients. Third, the definition of neuropathic symptoms varied greatly between series, and the electrophysiological parameters, especially among patients with sensory polyneuropathy, were quite variable. Fourth, the screen samples of pSS patients were generally small. Our study has attempted to address these issues by assessing peripheral neurological involvement in the largest ever cohort of primary Sjögren syndrome patients, while applying the latest criteria for diagnosis. Although its retrospective design is a limitation, the study was strengthened by re-evaluating all the patients with previously recorded neuropathic symptoms clinically and electrophysiologically. Further, on account of objectivity, we relied more on electrodiagnostic techniques rather than patient history or neurological examination alone.

One notable finding was the absence of ataxic neuropathy from our study cohort. This may be linked to a referral bias, as most of such cases are referred directly to neurologists or are misdiagnosed as ataxias related to other causes. Another interesting finding was the types of neuropathy; we noted an equal frequency of sensory (n=5) and sensorimotor (n=4) polyneuropathy patterns. Sensory polyneuropathy has, according to previous series, been considered a frequent manifestation compared with sensorimotor polyneuropathy.<sup>8 9</sup> The highly subjective nature of sensory examination or the lack of consensus on the diagnosis may account for some of these discrepancies. Although we found a low frequency of polyneuropathy among Sjögren syndrome patients, a much greater number of patients presented with painful neuropathic symptoms had normal clinical and electrophysiological evaluation. It is highly likely that these patients suffer from small fibre sensory neuropathy, which has been also observed but never systematically studied in Sjögren syndrome.<sup>10–14</sup> As this appears to be the commonest

pattern, the prevalence of small fibre neuropathy among Sjögren syndrome patients merits further investigation.

The timing of the manifestation of peripheral neuropathy during the course of Sjögren syndrome has also been debated.<sup>17–9 23</sup> In the majority of our patients (6/9), peripheral neuropathy was a late event. Studies suggesting the contrary may reflect the referral pattern, as such patients are referred first to neurologists. The majority of our patients with polyneuropathy had active, systemic Sjögren syndrome, especially Type I Sjögren's, a subset prone to developing lymphoma.<sup>35</sup> Although none of them had a lymphoproliferative disorder at the time of evaluation, the majority of them had risk factors, such as low C4 complement factor, parotid gland enlargement and purpura. Whether those factors are responsible for the neuropathy remains unclear.

Because Sjögren syndrome is a systemic autoimmune disease, we hypothesised that the neuropathy may have an autoimmune pathogenesis. Because ganglionic acetylcholine receptor autoantibodies have been recently found in a variety of peripheral neuropathies,<sup>30 31</sup> and muscarinic acetylcholine receptor antibodies have been found in patients with primary Sjögren syndrome,<sup>36</sup> we screened our neuropathy patients for these autoantibodies as candidate biomarkers. No immunoreactivity was noted, however. Alas, no evidence of antineural tissue autoimmunity was observed based on our immunofluorescence and western blot screening. It is likely that examination of tissues such as nerve biopsies might have been more informative to exclude or confirm the autoimmune pathogenesis. Such studies are in process in our ongoing prospective study.

**Competing interests** None.

**Ethics approval** Ethics approval was provided by the University of Athens Medical School Ethics Committee.

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