SHORT REPORT

Peripheral neuropathy associated with primary Sjögren’s syndrome

Franco Gemignani, Adriana Marbini, Giovanni Pavesi, Stefano Di Vittorio, Paolo Manganelli, Giovanna Cenacchi, Domenico Mancia

Abstract
Clinical and electrophysiological signs of peripheral neuropathy were found in 10 of 46 patients (21.7%) with primary Sjögren’s syndrome, symmetric polyneuropathy in seven (mainly sensory in five, mainly autonomic in two), sensory neuropathy in two patients, and mononeuropathy multiplex in one patient. Peripheral neuropathy was the presenting manifestation in five patients (10.9%). Onset of the disease after 50 years was significantly more common in the polyneuropathy group (six of seven) than in non-neuropathic patients with primary Sjögren’s syndrome (14 of 36; p = 0.034). No other difference in clinical or laboratory variables between neuropathic and non-neuropathic patients with primary Sjögren’s syndrome was found. Neuropathological study showed variable findings predominantly suggesting an axonopathy. Nerve biopsy showed moderate remyelination and regeneration in four patients, and fibre loss, mainly of large size, in three. Necrotising vasculitis was not seen but alterations of the endoneurial microvessels were prominent.

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Various forms of peripheral neuropathy have been reported in primary and secondary Sjögren’s syndrome (SS),1–10 with prevalence ranging from 10% to 50%.11–13 A major problem in the assessment of the prevalence and of the spectrum of peripheral neuropathy in Sjögren’s syndrome is represented by the lack of universally accepted criteria for the diagnosis of Sjögren’s syndrome.14 Also, some studies investigated the prevalence of peripheral neuropathy on the basis of minimal neuropathological alterations, without elucidating the range of clinically manifest peripheral neuropathy.12 Finally, adequate separation between primary and secondary forms has not been made in some studies,18,11 raising the possibility that peripheral neuropathy was caused by the accompanying disease rather than by Sjögren’s syndrome. Therefore, the vasculitic pathogenesis advanced by some authors14 has to be critically evaluated in the light of the criteria for patients’ selection. The aim of the present study was to assess the prevalence of clinically significant peripheral neuropathy and its range in a series of patients with well characterised primary Sjögren’s syndrome, and to evaluate factors possibly related to its occurrence.

Patients and methods
Forty six consecutive patients (43 women, three men) with primary Sjögren’s syndrome were evaluated for symptoms and signs of peripheral neuropathy, and submitted to neurophysiological investigation according to previously reported methods15 when clinical examination suggested peripheral neuropathy.

The diagnosis was made according to the Copenhagen criteria16 with minor modifications, when at least two out of four criteria were met for both xerophthalmia (subjective complaint of dry eyes, abnormal Schirmer test, abnormal break up time, positive rose-bengal or fluorescein staining) and xerostomia (subjective complaint of dry mouth, history of parotid enlargement, abnormal salivary gland scintigraphy or sialography, positive lower lip biopsy showing focal sialoadenitis with more than one lymphocyte focus per 4 mm2, according to Greenspan et al.16 Primary Sjögren’s syndrome was diagnosed in the absence of any other autoimmune rheumatic disease, sarcoidosis, lymphoma, and other malignancies, and of medications known to reduce secretions. Patients with diabetes, cryoglobulinaemia, alcoholism, and other conditions possibly causing peripheral neuropathy were also excluded. Clinical and laboratory variables (including immunoglobulin, latex test for IgM rheumatoid factor, C3 and C4, anti-nuclear antibody, antiparietal cells, antimitochondria, antismooth muscle, antithyroid, anti-Ro and anti-La antibodies) of neuropathic patients were analysed with regard to their possible relevance for the pathogenesis of peripheral neuropathy compared with the patients without peripheral neuropathy as a control group. Fischer’s exact test was used for statistical comparison, and p < 0.05 was considered significant.

Sural nerve biopsy was performed on seven patients with peripheral neuropathy (five

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Copenhagen criteria:16

1. Symmetrical xerostomia
2. Symmetrical xerophthalmia
3. Clinical lymphadenopathy
4. Positive test for rheumatoid factors
5. Biopsy showing lymphocytic salivary gland inflammation
6. Biopsy showing lymphocytic lacrimal gland inflammation
7. Positive test for anti-Ro or anti-La antibodies
8. Positive test for anti-SS-A or anti-SS-B antibodies
9. Symmetrical peripheral neuropathy
10. Symmetrical joint pain
11. Symmetrical Raynaud’s phenomenon
12. Symmetrical fever
13. Symmetrical subcutaneous nodules
14. Symmetrical myalgia

The diagnosis was made according to the Copenhagen criteria16 with minor modifications, when at least two out of four criteria were met for both xerophthalmia (subjective complaint of dry eyes, abnormal Schirmer test, abnormal break up time, positive rose-bengal or fluorescein staining) and xerostomia (subjective complaint of dry mouth, history of parotid enlargement, abnormal salivary gland scintigraphy or sialography, positive lower lip biopsy showing focal sialoadenitis with more than one lymphocyte focus per 4 mm2, according to Greenspan et al.16 Primary Sjögren’s syndrome was diagnosed in the absence of any other autoimmune rheumatic disease, sarcoidosis, lymphoma, and other malignancies, and of medications known to reduce secretions. Patients with diabetes, cryoglobulinaemia, alcoholism, and other conditions possibly causing peripheral neuropathy were also excluded. Clinical and laboratory variables (including immunoglobulin, latex test for IgM rheumatoid factor, C3 and C4, anti-nuclear antibody, antiparietal cells, antimitochondria, antismooth muscle, antithyroid, anti-Ro and anti-La antibodies) of neuropathic patients were analysed with regard to their possible relevance for the pathogenesis of peripheral neuropathy compared with the patients without peripheral neuropathy as a control group. Fischer’s exact test was used for statistical comparison, and p < 0.05 was considered significant.

Sural nerve biopsy was performed on seven patients with peripheral neuropathy (five
patients with symmetric polyneuropathy and two with sensory neuroneuropathy), according to previously reported methods. 7

Results
Ten patients (nine women, one man) out of 46 had clinical and neurophysiological evidence of peripheral neuropathy (21.7%), including two patients previously described as case reports. 27 One patient had multiple mononeuropathy, seven patients had distal symmetric polyneuropathy with mainly sensory or autonomic features, and two patients had sensory neuropathy, as confirmed by neurophysiological investigation (see later), with ataxia and pseudoathetosis predominantly in the arms (table). Peripheral neuropathy was the presenting manifestation in five patients (10.9%), being the most common onset of the disease in neuropathic patients (50%), followed by sicca syndrome (30%), which was, conversely, the most common manifestation at onset in non-neuropathic patients (55.5%).

A comparison of the 10 patients with peripheral neuropathy and the remaining 36 without did not show any significant difference in clinical and laboratory variables. The median age was 56 years (range 26–76) in non-neuropathic patients and 66 years (range 25–76) in neuropathic patients, and median age at onset was, respectively, 47.5 years (range 25–76) years and 56 years (range 23 to 73) years. The occurrence of systemic involvement was similar in the two groups, arthritis, lymphadenopathy, and interstitial pulmonary fibrosis being the most common manifestations (respectively 50%, 33-3%, and 11-1% in non-neuropathic, and 60%, 50%, and 10% in neuropathic patients). Segregating seven patients with distal symmetric polyneuropathy, onset of the disease after 50 years was significantly more frequent in this group (six of seven) than in non-neuropathic patients with Sjögren’s syndrome (14 of 36; p = 0.034).

Neurophysiological study (table) showed variable abnormalities usually suggesting axonopathy in patients with distal symmetric polyneuropathy. Sympathetic skin response was absent in the two patients with autonomic neuropathy. Absent peripheral and central evoked responses in the upper extremities coupled with preserved motor responses
Peripheral neuropathy associated with primary Sjögren's syndrome

<table>
<thead>
<tr>
<th>Lip biopsy</th>
<th>Neurophysiological study</th>
<th>Nerve biopsy fibre density</th>
<th>Treatment (course duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>Marked denervation.</td>
<td>Axonal degeneration</td>
<td>Prednisone, slight improvement (14 months)</td>
</tr>
<tr>
<td></td>
<td>Peroneal nerve MCV 27 m/s</td>
<td>with poor regeneration,</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>diffuse fibre loss 2379/mm²</td>
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<tr>
<td>+</td>
<td>Moderate denervation.</td>
<td>Remyelination, clusters</td>
<td>Deflazacort, hydroxychloroquine, stabilisation (3 months)</td>
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<td></td>
<td>Median SAP 5 μV,</td>
<td>7091/mm²</td>
<td></td>
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<td></td>
<td>Sural nerve SCV 29 m/s</td>
<td></td>
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</tr>
<tr>
<td>+++</td>
<td>Moderate denervation.</td>
<td>Remyelination, pronounced</td>
<td>Spontaneous stabilisation (72 months)</td>
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<tr>
<td></td>
<td>SCV 35 m/s (borderline)</td>
<td>cluster formation 5740/mm²</td>
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<tr>
<td>+</td>
<td>Mild denervation.</td>
<td>Remyelination, sparse</td>
<td>Prednisone, stabilisation (96 months)</td>
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<td>Sural nerve SAP 5 μV,</td>
<td>clusters 5692/mm²</td>
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<td></td>
<td>SCV 31-6 m/s</td>
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<tr>
<td>+++</td>
<td>Mild denervation.</td>
<td>Remyelination, clusters.</td>
<td>Spontaneous stabilisation (60 months)</td>
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<td>ScV 30-6 m/s</td>
<td>Large fibre decrease</td>
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<td></td>
<td>Median SAP 4-5 μV,</td>
<td>6830/mm²</td>
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<td>Absent sympathetic skin</td>
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<tr>
<td>response</td>
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<tr>
<td>+++</td>
<td>Normal MCV, SCV,</td>
<td>Not done.</td>
<td>Chlorambucil, stabilisation (36 months)</td>
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<td>and SAP.</td>
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<td>Absent sympathetic skin</td>
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<td>response</td>
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<tr>
<td>+++</td>
<td>Absent SAPs in all limbs.</td>
<td>Large fibre loss (1.2%)</td>
<td>Prednisone, azathioprine, stabilisation (30 months)</td>
</tr>
<tr>
<td></td>
<td>Absent SEPs in the arms.</td>
<td>mononuclear perivascular</td>
<td></td>
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<tr>
<td>Normal MCV</td>
<td></td>
<td>infiltrates 5141/mm²</td>
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<tr>
<td>+++</td>
<td>Absent SAPs and SEPs in</td>
<td>Large fibre decrease</td>
<td>Prednisone, pulsed</td>
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<tr>
<td></td>
<td>the left upper limb,</td>
<td>(9-6%) 3346/mm²</td>
<td>cyclophosphamide, slight</td>
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<td></td>
<td>reduced in the right,</td>
<td></td>
<td>improvement (36 months)</td>
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<td>mildly abnormal in the</td>
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<tr>
<td>legs</td>
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<tr>
<td>+</td>
<td>Right median nerve SCV</td>
<td>Not done.</td>
<td>Methylprednisolone,</td>
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<td></td>
<td>35 m/s</td>
<td></td>
<td>stabilisation (12 months)</td>
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<td></td>
<td>Right ulnar nerve SCV</td>
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<tr>
<td></td>
<td>35 m/s</td>
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<tr>
<td></td>
<td>Left ulnar nerve SCV</td>
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<td></td>
<td>37 m/s</td>
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were seen in cases 8 and 9, consistent with sensory neuropathy.6

Nerve biopsy (table) showed moderate changes consisting of thinly myelinated fibres isolated or in clusters suggesting remyelination and regeneration, in patients with symmetric polyneuropathy (except in case 1 who showed active axonal degeneration and severe fibre loss with poor regeneration). In no case was there multifocal fibre loss. In one patient with sensory neuropathy (case 8) there was complete loss of large fibres and intense perivascular inflammatory infiltrates, whereas in the other (case 9) there were only non-specific alterations, probably reflecting milder involvement of the lower limbs. Electron microscopy showed prominent alterations of the endoneurial microvessels, with thickening and reduplication of the basal laminae in all patients. Necrotising vasculitis was not seen.

Discussion

We found a prevalence of 21·7 of peripheral neuropathy in primary Sjögren's syndrome, similar to other studies.411 Hietaharju et al13 reported an involvement of the peripheral nervous system in 18 of 48 patients, which was, however, in the form of entrapment neuropathy or radiculopathy in most cases. A higher prevalence of 50% was reported by Andonopoulous et al16 on the basis of neurophysiological studies, including asymptomatic patients with prolonged motor nerve terminal latency of uncertain relevance as the only abnormality; also, several patients had cryoglobulinemia, which represents an additional important factor for the development of peripheral neuropathy.15 In our study, patients with peripheral neuropathy seemed to represent a quite definite subset of Sjögren's syndrome, in that neurological involvement was often the presenting manifestation and the main feature of the disease, whereas onset with sicca syndrome was definitely less common than in other patients with Sjögren's syndrome.

In accord with Kaplan et al10 we considered three main forms of peripheral neuropathy in Sjögren's syndrome, possibly reflecting different pathogenic mechanisms.

(1) Mononeuropathy (multiplex) was under-represented in our series, and none of our patients had a cranial neuropathy as often reported in Sjögren's syndrome, especially in the form of trigeminal neuropathy.1 As trigeminal neuropathy and mononeuropathy multiplex are a known accompaniment of other connective tissue diseases and systemic vasculitis, it is possible that their low incidence in our series was a consequence of the use of restrictive inclusion criteria.

(2) Sensory neuropathy is a highly distinctive entity probably related to lymphocytic infiltration in the dorsal roots and ganglia.918 In our two patients, as in most previously reported cases,69101920 it was the presenting manifestation of Sjögren's syndrome, and was associated with especially intense infiltration on lip biopsy, and presence of perivascular inflammatory cells, but not necrotising vasculitis, in sural nerve biopsies.

(3) Distal symmetric polyneuropathy includes patients with distal sensory, sensorimotor, and autonomic polyneuropathies, assuming that these forms represent the ends of a continuum rather than distinct entities. In none of our patients did the sural nerve biopsy show necrotising vasculitis of the epineural arterioles, whereas alterations of the endoneurial small vessels were often seen. Mellgren et al9 suggested that symmetric polyneuropathy in Sjögren's syndrome could be related to necrotising vasculitis, but in some of their patients there were associated pathogenic factors not directly related to Sjögren's syndrome, such as systemic vasculitis, cutaneous vasculitis and cryoglobulinaemia, and association of myeloma and lymphoma. Indeed, they found evidence of necrotising vasculitis in only two of 11 nerve biopsies, whereas in the other patients there were non-diagnostic aspects of perivascular inflammation. We and others6 found similar aspects in patients with sensory neuropathy in whom nerve fibre degeneration was likely.
caused by damage to the dorsal root ganglia rather than by peripheral nerve ischaemia. In our study, patients of this group developed Sjögren's syndrome at a significantly older age than patients without neuropathy. Aging seems to be a critical factor for polyneuropathy in Sjögren's syndrome, possibly favouring microangiopathic changes in the endoneurial vessels.

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