Pure sensory neuropathy in patients with primary Sjögren’s syndrome: clinical, immunological, and electromyographic findings

J Font, J Valls, R Cervera, A Pou, M Ingelmo, F Graus

Abstract
A pure sensory neuropathy caused by lymphocytic infiltration of the dorsal root ganglia has been reported in a few patients with Sjögren’s syndrome. The clinical, immunological, and electromyographic findings of five patients with this type of neuropathy and primary Sjögren’s syndrome were reviewed. Typical clinical indications were the presence of a chronic asymmetrical sensory deficit, initial disease in the hands with a predominant loss of the vibratory and joint position senses, and an association with Adie’s pupil syndrome or trigeminal sensory neuropathy. The simultaneous impairment of the central and peripheral evoked cortical potentials suggested that there was a lesion of the neuronal cell body. The neuropathy preceded the diagnosis of Sjögren’s syndrome in four patients. Four patients were positive for Ro antibodies, but systemic vasculitis or malignancy was not found after a mean follow up of six years. These findings indicate that in patients with a sensory neuropathy the diagnosis of Sjögren’s syndrome has to be considered, even if the patient denies the presence of sicca symptoms, and that appropriate tests must be carried out.

Sjögren’s syndrome is a chronic, multisystem immunological disorder that is characterised by progressive destruction of the exocrine glands, accompanied by a variety of autoimmune phenomena. This syndrome can present either as a primary disorder or as a component of other autoimmune diseases, such as rheumatoid arthritis, scleroderma, or systemic lupus erythematosus. Virtually any organ system of the body can be affected. The most characteristic symptoms are keratoconjunctivitis sicca and xerostomia, resulting from a destructive mononuclear infiltration of the lachrymal and salivary glands, respectively. Similar mononuclear infiltrates invading visceral organs can give rise to such extraglandular manifestations as interstitial pulmonary fibrosis, renal tubular acidosis, and Hashimoto’s thyroiditis. Neurological features are well documented in primary Sjögren’s syndrome, and peripheral nervous system disease is reported in 10–32% of patients with this disorder: mixed polyneuropathy confined to the lower extremities and mononeuritis multiplex are the most commonly observed. These neuropathies occur after the diagnosis of Sjögren’s syndrome is well established and they are usually associated with systemic vasculitis. There have recently been reports of a few patients with primary Sjögren’s syndrome and a new type of sensory neuropathy due to lymphocytic infiltration of the dorsal root ganglia. In some of these case reports the clinical setting of this neuropathy was not completely defined, and the description of isolated cases prevented identification of the main clinical and neurophysiological features that would have been helpful in its diagnosis. The recognition of this sensory neuropathy, however, is important because it usually precedes the diagnosis of Sjögren’s syndrome, it is not associated with systemic vasculitis, and treatment with corticosteroids may not be appropriate.

The purpose of this study was to analyse the clinical, immunological, and electromyographic findings of a series of five patients with primary Sjögren’s syndrome and pure sensory neuropathy to determine the most characteristic features which distinguish this neuropathy from the more common neuropathies observed in primary Sjögren’s syndrome.

Patients and methods

Patients
The clinical, immunological, and electromyographic features of five women with pure sensory neuropathy associated with primary Sjögren’s syndrome, and diagnosed in our hospital were reviewed. Two of them (patients 4 and 5; table 1) have already been reported. The median age was 44-4 years (range 28–75 years). All but one patient were first seen because of the neurological deficit. The onset of neurological symptoms was asymmetrical, insidious, and in the arms in all the patients. Presenting clinical manifestations were numbness, paraesthesias, and difficulty in identifying objects with the affected hand. The symptoms slowly progressed over the ensuing years to affect asymmetrically both upper and lower extremities. All patients had had long periods (years) during which the neuropathy seemed to have stabilised.

All patients had Sjögren’s syndrome defined according to the more commonly used criteria. Keratoconjunctivitis sicca was confirmed by a positive Schirmer’s test and characteristic rose bengal staining. Xerostomia was confirmed by an abnormal salivary gland scintigram and a positive minor salivary gland biopsy specimen. A work-up to identify an occult malignancy yielded negative results in all the patients, and other causes of keratoconjunctivitis sicca, xerostomia, and sensory neuropathy were excluded. All the patients were prospectively studied by the authors after sensory neuropathy...
Mild=Symptoms do not interfere with daily activities; moderate=clinical symptoms cause some limitations in daily activities; severe=extremity practically useless because of the proprioceptive deficit.

had been diagnosed, with a follow up ranging from two to 13 years.

ELECTROMYOGRAPHIC STUDIES
Needle electromyography (EMG) was performed in the distal muscles of the hands and feet. Conventional neuropathic studies of motor and sensory conduction velocity and compound action potential amplitude were carried out in the common peroneal, posterior tibial, sural, median, and ulnar nerves. Long latency reflex responses were studied in the arms and legs: H reflex was tested in soleus muscles, T’ wave was tested in soleus and biceps brachii muscles, and F wave was examined in posterior tibial and median nerves. Somatosensory evoked cortical potentials recorded on the scalp were tested bilaterally by the stimulation of the median nerve at the wrist and the posterior tibial nerve at the ankle. Blink reflex was studied in both eyes by the electrical stimulation of the supraorbital nerve. The electromyograph used in the study was an MS8 MEDELEC (Old Woking, Surrey, England). All tests were performed using routine techniques and standard equipment and electrodes.

IMMUNOLOGICAL STUDIES
Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using mouse liver as substrate. Rheumatoid factor was tested by latex fixation (positive titre >1/40). Anti-dsDNA antibodies were determined with Farr’s ammonium sulphate precipitation technique. Antibodies to extractable nuclear antigens (ENA) Ro (SS-A), La (SS-B), U1-rNP, and Sm were detected by counterimmunoelectrotophoresis using human spleen and calf thymus extracts. Antimitochondrial and anti-smooth muscle antibodies were detected by indirect immunofluorescence using rat kidney and stomach as substrates. The presence of antibodies against nuclear antigens was evaluated by indirect immunofluorescence on frozen sections of normal human dorsal root ganglia, as described previously. Circulating immune complexes were detected by Clq binding assay and cryoglobulins by immunoelectrophoresis. Complement components (C3 and C4) were estimated by radial immunodiffusion and CH50 by Lachmann’s haemolytic technique.

Results
Neurological findings are summarised in table 1. Pupils were poorly reactive to light and severely constricted in response to 0.1% pilocarpine (Adie’s pupil syndrome) in three patients; in two the defect was bilateral. Sensory trigeminal neuropathy was also present in two patients. All modalities of sensation were asymmetrically affected. The sensory loss affecting the vibratory and joint position senses was disproportionate to the loss of light touch or pinprick sensations, which was slightly impaired. Pseudoathetotic movements were observed in the hand where the deficit was severe. In the patient with the most severe neuropathy such movements were present in all four extremities. Deep tendon reflexes were absent in all patients. The rest of the neurological examination yielded normal results.

At the time of the neurological examination, only one patient (No 1) had had Sjögren’s syndrome diagnosed, nine years previously. Two patients spontaneously complained of symptoms suggestive of sicca syndrome. In one patient (No 5) only xerostomia was found at the time of diagnosis but keratoconjunctivitis sicca was present one year later. The remaining two denied the presence of such symptoms, but in one sicca syndrome was confirmed by Schirmer’s test, rose bengal staining, parotid scintigraphy, and minor salivary gland biopsy. The other patient was not specifically evaluated for xerostomia and keratoconjunctivitis sicca at the time of the initial presentation in 1976 but she developed full-blown sicca syndrome in 1987.

Electromyographic results are summarised in table 2. The needle biopsy study showed no signs of denervation. The results of the neurographic tests of motor nerves were normal. F wave was present in all nerves examined, but H wave was absent in all nerves tested.

Table 1: Sensory neuropathy and primary Sjögren’s syndrome: neurological manifestations

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age/sex</th>
<th>Duration of neuropathy (years)</th>
<th>Cranial nerves</th>
<th>Sensory disturbances*</th>
<th>Deep tendon reflexes</th>
<th>Muscle strength</th>
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<tr>
<td>1</td>
<td>33/F</td>
<td>6</td>
<td>Adie’s pupil</td>
<td>Moderate Mild Mild Mild</td>
<td>Abolished Normal</td>
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<td>2</td>
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<td>6</td>
<td>Adie’s pupil</td>
<td>Severe Mild Moderate Mild</td>
<td>Abolished Normal</td>
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<tr>
<td>3</td>
<td>28/F</td>
<td>13</td>
<td>Adie’s pupil</td>
<td>Moderate Normal Moderate Mild</td>
<td>Abolished Normal</td>
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<td>4</td>
<td>58/F</td>
<td>7</td>
<td>Trigeminal sensory neuropathy</td>
<td>Moderate Mild Mild Mild</td>
<td>Abolished Normal</td>
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<td>5</td>
<td>75/F</td>
<td>5</td>
<td>Trigeminal sensory neuropathy</td>
<td>Severe Severe Severe Severe</td>
<td>Abolished Normal</td>
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*Impairment of joint position and vibratory senses over other sensory modalities in all cases.
Mild=symptoms do not interfere with daily activities; moderate=clinical symptoms cause some limitations in daily activities; severe=extremity practically useless because of the proprioceptive deficit.

Table 2: Sensory neuropathy and primary Sjögren’s syndrome: electrophysiological results

<table>
<thead>
<tr>
<th>EMG</th>
<th>CMAP, F wave</th>
<th>SNAP</th>
<th>Right sural</th>
<th>Left sural</th>
<th>Right median</th>
<th>Left median</th>
<th>Right ulnar</th>
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<th>SEP</th>
<th>Right median</th>
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<th>Right tibial</th>
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<th>H reflex</th>
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N=normal; A=absent; L=low amplitude; D=delayed; ND=not done; EMG=needle electromyography; CMAP=compound muscle action potential; SNAP=sensory nerve action potentials; SEP=somatosensic evoked cortical potentials; BR=blink reflex.

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reflexes and T waves were absent in all patients. Most of the neurographic tests of sensory nerves showed abnormal results, often with absent responses. Nevertheless, in three patients some nerves had normal or low amplitude responses, reflecting asymmetrical clinical disease. Somatosensory evoked cortical potentials recorded on the scalp were not obtained when tested in those nerves with absent sensory action potentials. Blink reflexes were absent or delayed in the four patients examined.

Positive ANA tests were seen in two patients (Nos 1 and 3) up to a titre of 1/400. Rheumatoid factor was positive at 1/80 in two patients (Nos 2 and 3). Four patients were positive for Ro (SS-A) antibodies and three for La (SS-B). All patients were negative for DNA binding, RNP, Sm, antimitochondrial, and anti-smooth muscle antibodies. Circulating immune complexes were present in patient 1, and cryoglobulins were not detected. Complement components were normal in all patients. No patient showed the presence of specific antibodies against neural antigens. Nuclear or nucleolar staining of neurones was at the same titre as that seen in other nuclei, suggesting that the pattern was due to the presence of Ro or La antibodies.

To date, the mean duration of our patients' neuropathy has been 7·4 years (five to 13). All but one patient remain ambulatory in spite of the neurological symptoms. In these patients the principal impairment was usually the proprioceptive deficit present in the hand affected at the onset of the neuropathy. One patient (No 3) still has the sensory deficit confined to the arms 13 years after the onset of neuropathy (table 1). On the other hand, the neuropathy in patient No 5 took a severe progressive course two years after the onset of the disease in spite of treatment with high doses of prednisone (1 mg/kg daily). Two patients (Nos 1 and 3) received low doses of prednisone (5 mg daily) because of sicca syndrome without an apparent improvement in neuropathy. The other two patients received no treatment. During follow up none of the patients developed systemic vasculitis or lymphoma; patient No 2 developed Hashimoto's thyroiditis.

Discussion

Unlike previous case reports our study shows that not only can neuropathy precede the diagnosis of Sjögren's syndrome but it may be present even when a definite diagnosis of Sjögren's syndrome cannot be made. Therefore, appropriate tests must be repeated during follow up to confirm the diagnosis of Sjögren's syndrome. Moreover, the present series shows that these patients have remarkably similar clinical and electromyographic features to those described in patients with Sjögren's syndrome, with no significant differences in the level of sensory or motor dysfunction. The neuropathy remained asymmetrical even years after its onset. Although some patients had autonomic dysfunction, no patient was found to have autonomic neuropathy.

In conclusion, we believe that in patients with a sensory neuropathy, with the clinical and electromyographic features reported above, the diagnosis of Sjögren's syndrome has to be con-
We acknowledge the technical assistance of Ms Maria Jesús Iranzo.

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