Primary Sjögren's Syndrome Associated Neuropathy

Svein Ivar Mellgren, Lasse G Göransson, Roald Omdal

ABSTRACT: Primary Sjögren’s syndrome (PSS) mainly affects exocrine glands and is clinically characterized by keratoconjunctivitis sicca and xerostomia. Among several possible extraglandular manifestations, involvement of the peripheral nervous system may occur with reported frequencies from 10% to 60%. Peripheral nerve manifestations constitute sensory neuropathy, including sensory ganglioneuropathy, sensorimotor, including polyradiculoneuropathy and demyelinating neuropathy, motor neuropathy, multiple mononeuropathy, trigeminal and other cranial neuropathies, autonomic neuropathy, and mixed patterns of neuropathy. Knowledge of the neurological manifestations of PSS is hampered by evolving classification criteria of PSS over the years, and by use of highly selected patient populations on the basis of a primary neurological diagnosis. Sural nerve biopsy may show vascular or perivascular inflammation of small epineural vessels (both arterioles and venules) and in some cases necrotizing vasculitis. Loss of myelinated nerve fibers is common and loss of small diameter nerve fibers occurs. Pathology in cases of sensory ganglioneuropathy consists of loss of neuronal cell bodies and infiltration of T cells. Peripheral neuropathy in PSS often is refractory to treatment although newer biological agents may provide more effective treatment options. Current treatment strategies used in autoimmune neuropathies may be tried depending upon characteristics of the neuropathy and results obtained by a thorough clinical and laboratory investigation.

Primary Sjögren’s syndrome (PSS) is an autoimmune disease that mainly affects exocrine glands and is clinically characterized by dryness of the eyes and mouth (keratoconjunctivitis sicca and xerostomia). These phenomena may be more objectively evaluated as a function of time by measuring production of tear fluid by the Schirmer’s test and unstimulated or stimulated saliva flow by sampling of saliva. Histologically there is focal infiltration of the salivary glands by mononuclear lymphoid cells and destruction of glandular epithelium. Onset is usually insidious, and many patients develop extraglandular manifestations like myalgias, arthralgias, and involvement of the pulmonary and gastrointestinal systems. General and nonspecific phenomena like fatigue are common. There are numerous reports on neurological manifestations in patients with PSS. In the series of Delalande et al the central and peripheral nervous systems were involved with approximately equal frequency. Prevalence of peripheral neuropathy in Sjögren’s syndrome may vary between 10% and 60%, depending on study population as

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well as definition and methods by which neuropathy may be
detected. Mellgren et al\(^2\) and Delalande et al\(^3\) reported that
distal sensorimotor polyneuropathy and distal sensory polyneuropathy
were the most common manifestations of peripheral nerve
disease. Neuropathic symptoms preceded sicca symptoms in
about 40% and in an equivalent proportion of patients sicca
symptoms came first.\(^5\) In a more recent study neuropathic
symptoms appeared before the diagnosis of PSS was made in
93%.\(^8\) However, these studies were biased by selecting patients
with neuropathy and were in most instances shown to have PSS
at a later stage. The fact that the reported prevalence of
neurological manifestations varies across studies, probably
depends on the changing PSS criteria the last few years, but is
also likely due to selection bias.

Several studies and case reports indicate that in some patients
with PSS the cell bodies of sensory neurons located in the dorsal
root ganglia are affected.\(^8\)-\(^11\) In these patients T-lymphocyte
infiltration of the dorsal root ganglia has been reported.\(^8\)\(^,\)\(^9\) Dorsal
root ganglionitis is thus a well-known phenomenon that may
occur in PSS.

Among other neuropathic varieties that have been reported in
Sjögren’s syndrome are multiple mononeuropathy, demyel-
inating neuropathy, motor neuropathy, and cranial neuropathy,
including trigeminal neuropathy. Following some comments of
diagnosis of PSS we herewith review in some more detail the
different peripheral neuropathic features that may occur in PSS.

### Diagnosis of Primary Sjögren’s syndrome

The diagnosis of PSS has in clinical practice often been based
on a pragmatic use of symptoms, signs, laboratory, and
histological features. For research purposes classification criteria
have been published, but until recently several sets of criteria
during the years and in different regions of the world have
resulted in con-comparable findings in different studies.\(^12\)\(^-\)\(^15\)
The American-European classification criteria for PSS are now
widely accepted.\(^16\) Having PSS according to this classification
requires four of six criteria including positive lip biopsy and/or
positive SSA- and/or SSB antibodies. The diagnosis can also be
achieved if three of the four objective criteria are present (Table 1).

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<th>Table 1: Revised international classification criteria for Sjögren’s syndrome(^16)</th>
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<td>I. Ocular symptoms: a positive response to at least one of the following questions:</td>
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<td>1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?</td>
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<td>2. Do you have a recurrent sensation of sand or gravel in the eyes?</td>
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<tr>
<td>3. Do you use tear substitutes more than 3 times a day?</td>
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<td>II. Oral symptoms: a positive response to at least one of the following questions:</td>
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<tr>
<td>1. Have you had a daily feeling of dry mouth for more than 3 months?</td>
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<tr>
<td>2. Have you had recurrently or persistently swollen salivary glands as an adult?</td>
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<tr>
<td>3. Do you frequently drink liquids to aid in swallowing dry food?</td>
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<td>III. Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:</td>
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<td>1. Schirmer’s test, performed without anaesthesia (&lt; 5 mm in 5 minutes).</td>
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<td>2. Rose bengal score or other ocular dye score ≥ 4 according to van Bijsterveld’s scoring system).</td>
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| IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert
histopathologist, with a focus score ≥ 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more
than 50 lymphocytes) per 4 mm\(^2\) of glandular tissue. |
| V. Salivary gland involvement: objective evidence of salivary gland involvement defined as a positive result for at least one of the following diagnostic test: |
| 1. Unstimulated whole salivary flow ≤ 1.5 ml in 15 minutes. |
| 2. Parotid sialography showing the presence of diffuse sialectasis (punctate, caviatory or destructive pattern), without evidence of obstruction in the major ducts. |
| 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion tracer. |
| VI. Autoantibodies: presence in the serum of the following autoantibodies: Antibodies to Ro (SSA) or La (SSB) antigens, or both. |
| For primary SS in 7 patients without any potentially associated disease, primary SS may be defined as follows: |
| a) The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive. |
| b) The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI). |
| c) The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological
survey. |
| Exclusion criteria |
| a) Past head and neck radiation treatment |
| b) Hepatitis C infection |
| c) Acquired immunodeficiency disease (AIDS) |
| d) Pre-existing lymphoma |
| e) Sarcoidosis |
| f) Graft versus host disease |
| g) Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug) |
As the criteria used in the different reports have not been the same, this may certainly account for some of the varying frequencies of peripheral neuropathy reported in PSS. Even more important is the selection of patients in the different studies, where most were retrospective.\textsuperscript{5,7} The recent study by Mori et al.\textsuperscript{8} comprehensively dealing with the spectrum of clinical manifestations of Sjögren’s syndrome associated neuropathy, consisted of 92 patients referred from 1986 to 2004 with neuropathic symptoms, but the majority of these patients were diagnosed with PSS after the symptoms of neuropathy appeared. Göransson et al.\textsuperscript{17} performed a study to investigate the involvement of the peripheral nervous system in PSS in an unselected cohort of patients and applying the new American-European classification criteria for the disease.\textsuperscript{16} This classification ensures that patients with “true” autoimmune PSS are optimally selected. It also excludes patients with sicca syndromes due to other causes (such as age, drugs, etc.). Primary Sjögren’s syndrome diagnosed according to these criteria makes sicca symptoms and signs likely to be associated with this disease, but it may be difficult to exclude an autonomic neuropathy with a concomitant cause.

Using this classification for PSS and applying fairly objective clinical, electrophysiological, and morphometric criteria, neuropathic features have been observed in a considerable proportion of the PSS patients.

**Categories of peripheral nerve manifestations in Primary Sjögren’s syndrome**

Since the data on prevalence of different types of peripheral neuropathy summarized in Table 2 are conflicting, the following description is not rated according to frequencies of occurrence of neuropathy in Sjögren’s syndrome.

**Sensory neuropathy**

Most of the previous reports on PSS associated neuropathy claim that neuropathy with sensory symptoms and signs are predominant. Mellgren et al.\textsuperscript{2} reviewed 33 cases of primary Sjögren’s syndrome and peripheral neuropathy evaluated by neurological examinations as well as EMG and nerve conduction studies (NCS) at the Mayo Clinic from 1976 to 1988, and studied sural nerve biopsy specimens in 11 of them. Thirty-two percent had sensory neuropathy. In a recent study of 92 patients with PSS, 36 patients had sensory ataxic neuropathy while 18 had painful sensory neuropathy.\textsuperscript{8} Chai et al.\textsuperscript{18} found that in 20 consecutive patients with Sjögren’s syndrome neuropathy 16 (60%) had burning feet and 12 of these (80%) non-length-dependent sensory symptoms. Leg and thigh skin biopsies from 13 patients showed all depletion of fibres or abnormalities in intraepidermal nerve fibres (IENFs). Seven of these had normal NCS. In an outpatient cohort of patients with Sjögren’s syndrome of 29 patients, and comparing with 11 controls, 45% were considered to have isolated small-fiber neuropathy.\textsuperscript{19} Large-fiber dysfunction after measuring vibration, deep tendon reflexes, and NCS was similar in patients and controls. In the study of Göransson et al.\textsuperscript{17} on an unselected cohort of 62 PSS patients, only 8 (13%) had evidence of sensory neuropathy by nerve conduction studies (NCS). A comparison with normal individuals showed that those with PSS on average had a significantly reduced IENF density as part of a neuropathy involving nerve fibers of all diameters.\textsuperscript{20} Only two cases had IENF densities below normal limits (Figures 1 and 2). These two had normal NCS.

Sensory ganglioneuronopathy may be regarded as a subgroup of sensory neuropathy in PSS. Malinow et al.\textsuperscript{21} and Griffin et al.\textsuperscript{9} showed infiltration of mononuclear cells without vasculitis and degeneration of dorsal root ganglion neuronal cell bodies. These manifestations were associated with sensory ataxia and the condition was considered to express that the ganglion neurons themselves were targeted in Sjögren’s syndrome. Since then several papers have reported on ganglioneuronopathy with sensory ataxia in Sjögren’s syndrome. Among nine patients with pure sensory neuropathy in the series of Delalande et al.\textsuperscript{7} four had clinical and electrophysiological features of sensory ganglioneuronopathy with severe ataxia. Mori et al.\textsuperscript{8} describe 36 out of 92 patients with sensory ataxia. Asymmetrical paresthesias in the feet or hands were the most frequent initial symptom. The paresthesias spread gradually in the limbs and to the trunk and face. Sensory findings were mostly detected as impairment of proprioception with Romberg’s sign and pseudoathetosis and the cases that had reached the most advanced stages were unable to walk. Most of the patients with sensory ataxic neuropathy had evidence of both central and peripheral rami lesions, expressed by low or absent sensory amplitudes or unelicitable sensory evoked potentials. Magnetic resonance imaging showed high signal intensity on T2 in the dorsal spinal columns. One autopsied patient had severe depletion of large-sized sensory ganglion cell bodies and T-cell invasion. Sural biopsy, performed in 31 of the 36 patients with sensory axiatic neuropathy, revealed variable reduction of myelinated fibers and lack of axonal sprouting. Vasculitis in epineurial arterioles was observed in six and mild perivascular infiltration in small vessels in nine patients. Mild perivascular T-cell infiltrations were also observed in peripheral nerve trunks of the patient where ganglionitis had been verified histologically. Mori et al.\textsuperscript{8} hypothesize that there may be a continuous spectrum of pathological processes among the different forms of neuropathy and that most of the patients with sensory ataxia had some evidence of ganglioneuronopathy. Even in the cases with painful sensory neuropathy there were...

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**Table 2: Main neuropathic categories in Primary Sjögren’s syndrome**

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<td>Sensory neuropathy including sensory ganglioneuronopathy</td>
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<td>Sensorimotor, including polyradiculoneuropathy and demyelinating neuropathy</td>
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<td>Motor neuropathy</td>
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<td>Multiple mononeuropathy</td>
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<tr>
<td>Trigeminal and other cranial neuropathies</td>
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<tr>
<td>Autonomic neuropathy</td>
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<td>Mixed patterns of neuropathy</td>
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some characteristics of ganglioneuronopathy (high T2 lesion intensity in the dorsal columns, although less than in the group with sensory ataxia, and lack of axonal sprouts in the sural nerve biopsies). There are no other studies reporting such a high prevalence of sensory atactic neuropathy (sensory ganglioneuronopathy). This may partly be explained by the selection of patients. Other studies are case reports with only a few patients with such features. In the cohorts of Sjögren’s syndrome patients published by Lopate et al.\textsuperscript{19} and Göransson et al.\textsuperscript{17} up to 55\% had clinical or neurophysiological abnormalities reflecting peripheral neuropathy. These studies also showed different profiles of neuropathy when comparing them (more small-diameter neuropathy in the first mentioned Missouri population,\textsuperscript{19} and predominance of F-response abnormalities in the Norwegian cohort\textsuperscript{17}), but features of sensory ganglioneuronopathy with ataxia were not reported.

**Sensorimotor and motor neuropathy**

A mixed sensorimotor neuropathy, involving large diameter fibres has been observed in many studies, most commonly axonal, but also demyelinating polyradiculoneuropathy\textsuperscript{8} has been described. In the retrospective study of Mellgren et al.\textsuperscript{5} symmetric sensorimotor polyneuropathy occurred most frequently (68\%), followed by symmetric sensory neuropathy (32\%). In the series of Delalande et al.\textsuperscript{7} with 82 patients, 19 had a distal axonal sensorimotor neuropathy, while 9 had pure sensory neuropathy. There are several case reports of neuropathy in Sjögren’s syndrome with characteristics of chronic inflammatory demyelinating neuropathy (CIDP).\textsuperscript{22,23} Subacute demyelinating neuropathy has also been reported,\textsuperscript{24} Mochizuki et al.\textsuperscript{25} presented two cases of motor dominant neuropathy. One showed signs similar to those of Guillain-Barré syndrome and the other had characteristics of CIDP. These patients received IV immunoglobulin therapy. In three patients with Sjögren’s syndrome associated neuropathy treated with interferon alfa, one

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**Figure 1:** 50 micron skin section from patient with PSS. Staining for intraepidermal nerve fibers (IENFs) with antibodies against PGP 9.5. The number of separate IENFs penetrating the basal lamina in at least three sections from each of the biopsies was counted, and the total length of epidermis was measured using the NIH image 1.61 morphometry program, according to guidelines in Lauria et al.\textsuperscript{49} Counterstained with hematoxylin and eosin. Shows relatively few fibers (arrows) entering into epidermis.

**Figure 2:** Comparison of our own data on intraepidermal nerve fiber densities in normal individuals, rheumatoid arthritis, primary Sjögren’s syndrome, and systemic lupus erythematosus.\textsuperscript{20} Mean number (± 95 \% confidence interval) of IENFs per mm in 50 micron sections from punch biopsy specimens of the lower leg. * p<0.0001. Reproduction with permission based on data from Göransson et al (Arch Neurol. 2006 Oct;63(10):1410-3. Copyright © (2006) American Medical Association).
had mainly demyelinating features. Guennoc et al found the coexistence of PSS and CMT 1A in a Sjögren patient and suggest that an inherited affection should be searched for before considering that demyelinating neuropathy might be a form of peripheral neuropathy caused by PSS. Sixty three unselected consecutive patients with PSS were prospectively evaluated for evidence of neurological manifestations. One had pure motor neuropathy, whereas another eight are described to have had a latent motor neuropathy. Cases with mild sensory or mixed neuropathy (N=17) predominated though. In the recent study of 62 patients with PSS not having been evaluated for neuropathic symptoms or signs before, it was observed that 19 (31%) had NCS recordings indicative of motor neuropathy. In 15 of these patients abnormally increased F-wave latency in ≥ 2 nerves was the only abnormal NCS finding.

**Multiple mononeuropathy**

Multiple mononeuropathy, a well recognized condition in other systemic autoimmune diseases have been reported in several case series and studies on larger populations of patients with PSS, but has been considered to be relatively uncommon in PSS. In the series of Mori et al of 11 of the 92 patients (12%) were classified with multiple mononeuropathy. Symptomatology and clinical deficits were rather typical for this condition with both sensory and motor manifestations, and were mostly restricted to the limbs, although trigeminal neuropathy and intercostal neuropathy also occurred in 2 of these 11 patients.

**Trigeminal and other cranial neuropathies**

Trigeminal neuropathy has been notified in patients with PSS for many years and occurs also in other systemic autoimmune diseases. Mori et al found that 15 (16%) of their patients had trigeminal neuropathy with sensory impairment. None exhibited motor trigeminal involvement. The prevalence of sensory trigeminal neuropathy in non-selected populations of PSS, however, seems to be less frequent. Function of proprioceptive trigeminal afferents in patients with Sjögren’s syndrome and sensory ganglioneuropathy has also been shown to be normal. Other cranial neuropathies or multiple neuropathies occur in some cases of PSS and may involve all relevant cranial nerves (II-XII) including the facial nerve bilaterally.

**Autonomic neuropathy**

Different patterns of autonomic nerve fibre involvement have been established in a series of publications. Most of the patients with ataxic sensory neuropathy and ganglioneuropathy described by Griffin et al had evidence of autonomic insufficiency. In some cases it was severe, with Adie’s pupils, fixed tachycardia, and orthostatic hypotension, but in most cases with PSS autonomic symptoms have been reported to be mild. Mori et al found that 3 of their 92 patients had severe autonomic neuropathy with prominent symptoms, including orthostatic hypotension, anhidrosis, bowel dysfunction, and loss of cardiac 123I-MIBG accumulation. Autonomic symptoms may be caused by both ganglioneuropathy and vasculitic lesions in peripheral nerves affecting autonomic fibers. Adie’s pupil, frequently observed in patients with Sjögren’s syndrome associated

neuropathy, is presumably caused by neuronitis in the ciliary ganglion cells. Interestingly Klein et al reported that among 18 patients with autoimmune autonomic neuropathies, 4 had a high ganglionic acetylcholine receptor antibody titer, sicca symptoms, abnormal pupils, and other autonomic abnormalities as part of severe autonomic failure. Dyck recently discussed autonomic neuropathy in patients with and without sicca phenomena. The sicca symptoms may occur as part of the autoimmune neuropathy, but this does not exclude that autoimmune mechanisms causing PSS also involve the peripheral nervous system including autonomic ganglia and nerves. Nevertheless the results in controlled studies have been contradictory, varying from normal to significant sympathetic or parasympathetic dysfunction in PSS. Niemela et al performed a conventional cardiovascular reflex test battery (Valsalva maneuver, deep breathing test, active orthostatic test and measurements of baroreflex sensitivity with phenylephrine and 24 hour heart rate variability) on 30 patients with PSS and 30 healthy age and sex matched controls. They found no significant differences between the PSS patients and the healthy controls in any of the tests and concluded that the prevalence of autonomic dysfunction is not increased in patients with PSS compared to the general population. In a similar study on the occurrence and clinical significance of a cardiovascular autonomic nervous system dysfunction in 51 patients with PSS, signs of autonomic nervous system dysfunction involving the cardiovascular system could be demonstrated in the majority of the patients.

**Mixed patterns of neuropathy in Sjögren’s syndrome**

Several of the specific neuropathic patterns mentioned above may occur in combination or may eventually emerge together with a specific type of neuropathy that was present from the onset. These “overlapping clinical features” have been reported in several of the previously mentioned studies.

**Histopathological findings in nerve biopsies, sensory dorsal root ganglions and skin biopsies of patients with peripheral neuropathy and Primary Sjögren’s syndrome**

Most nerve biopsy studies in primary Sjögren’s syndrome associated neuropathy have been performed on sural nerve material. Vascular or perivascular inflammation of small epineurial vessels (arterioles and venules) were observed in all 11 biopsies analyzed in a series from Mayo Clinic. In two patients vessel wall inflammation and necrosis was diagnostic of necrotizing vasculitis. In another six nerves there were various degrees of intimal proliferation, recanalization, and perivascular hemosiderin in macrophages. There was varying loss of myelinated fibers and teased preparations revealed that axonal degeneration predominated. These findings were observed in cases with both sensorimotor and sensory neuropathies. Griffin et al reported pathological sural nerve findings in patients with PSS and sensory ganglioneuropathy. Most of the 12 biopsies had varying degrees of myelinated fiber loss with no marked variation in fiber densities among or within fascicles, six had inflammatory cells around epineurial vessels, but none had necrotizing vasculitis.

Vasculitis in small arteries and arterioles of the sural nerve has been demonstrated in several PSS patients with multiple mononeuropathy. Axonal degeneration caused by vasculitis may
be the aetiology of multiple mononeuropathy and possibly of cranial neuropathy, but this constellation has also been reported in sensory and sensorimotor symmetrical neuropathies in Sjögren’s syndrome. Myelinated nerve fiber loss and inflammatory vasculopathy from a patient with PSS are shown in Figures 3 and 4. Vasculitis is a process with heavy inflammatory cell infiltrates throughout the vessel wall and accompanied by fibrinoid necrosis eventually leading to mononeuropathy if involving the vasa nervorum. The term “vasculopathy” implies a less serious histological picture with some inflammatory cells in the vessel wall and in the close vicinity, an activated epithelium.

Figure 3: Sural nerve from the same patient as in Figure 1 with epineurial vessel inflammation (arrows). Transverse semithin 2 micron section stained with toluidine. Bar 50 microns.

Figure 4: Part of the same section as in Figure 3 showing loss of myelinated nerve fibers.

Aspects of clinical features and possible pathogenetic mechanisms of Primary Sjögren’s syndrome associated neuropathy

The clinical spectrum of Sjögren’s syndrome associated neuropathy seems to reflect various pathogenetic mechanisms of peripheral nerve involvement. Sensory neuropathy often occurs and may in some cases present as predominant small-fiber neuropathy with pain. Göransson et al found, however, that in an unselected cohort of patients with PSS a significant loss of IENFs occurred only in 2 out of 62 patients. This was also less frequent than in patients with SLE. Mori et al found that their patients with painful sensory neuropathy without sensory ataxia had predominantly superficial sensory impairment, with well preserved motor nerve function, and small diameter axon loss with relative preservation of large axons. T2-high intensity signal lesions were observed in the dorsal column of the spinal cord although not to the same extent as in sensory ataxic neuropathy. They propose that absence of axonal sprouts in the sural nerve biopsy argues against primary axonal lesions and speculate that sensory painful neuropathy also is a form of sensory ganglionneuronopathy that affects small ganglion neurons. It is further suggested that overlapping symptoms in some of the patients indicate that these two varieties are part of a spectrum of disorders with the same underlying pathology involving the sensory ganglion neurons. Involvement of sensory ganglion cells in some patients with Sjögren’s syndrome is also supported by the demonstration of autoantibodies specific to ganglion neurons and cross-reacting with salivary gland tissue.

In the series of Mori et al there was a low prevalence of anti SS-A and SS-B antibodies. This deviates from other materials. Anti-alpha-fodrin antibody was elevated in patients with Sjögren’s syndrome associated neuropathy, but also in patients with predominantly autonomic neuropathy and sicca complex (marked dry eyes and dry mouth) high levels of ganglionic acetylcholine receptor autoantibodies may also occur.

and no fibrinoid necrosis or occlusion of the vessel. This is commonly seen in patients with for example systemic lupus erythematosus (SLE), and may be regarded as a morphological evidence of ongoing immune processes. It is possible that vasculopathy in some instances may have been interpreted or reported as vasculitis for example in PSS.

In skin biopsies from patients with PSS reduction of IENF densities has been demonstrated, as well as morphological changes, in particular IENF axonal swellings. Non length dependent IENF loss (with similar absolute densities in leg and thigh) has been considered to be a feature of possible small-fiber sensory neuronopathy.

In cases of Sjögren’s syndrome with sensory ganglionneuronopathy, infiltration of mononuclear cells without vasculitis and degeneration and loss of dorsal root ganglion neuronal cell bodies were demonstrated. The infiltrating CD8+ T cells were shown to cluster around individual degenerating neurons.
The pathological basis of sensory trigeminal neuropathy in PSS is unknown. It can manifest itself as a pure sensory neuropathy in the trigeminal area, but may also occur in combination with the sensory ataxic form of neuropathy or painful sensory neuropathies. It may represent a cranial variety of sensory gangliononeuropathy although further evidence is needed to confirm this.9

Therapy of peripheral neuropathy and neuronopathy in Sjögren’s syndrome

Reports on therapy in primary Sjögren’s syndrome associated neuropathy are anecdotal or based only on small series of patients. The therapeutic response likely differs among the neuropathic forms. Most of the patients of Griffin et al9 received prednisone and many of these were also treated with azathioprine, intravenous cyclophosphamide infusions or other immunosuppressants as well as plasma exchange. Only in one patient with relapsing course a clear response of corticosteroid treatment was observed. Based on the experience with treatment of their patients, Mori et al9 suggest that corticosteroids are suitable for multiple mononeuropathy and multiple cranial neuropathy. Improvement may also be obtained in painful dysesthesias of the painful sensory neuropathy41 and in radiculoneuropathy forms8 with IV immunoglobulin (IVIG) therapy. Therapeutic responses were seen in some patients, but in most the neuropathic as well as non-neuropathic symptoms of Sjögren’s syndrome progressed. Favourable responses were only seen in certain subpopulations of patients treated with corticosteroids or IVIG. There are also other, anecdotal reports on IV immunoglobulin treatment.42,43 Takahashi et al44 administered IVIG to five patients with severe disabilities of sensory gangliononeuropathy for an average of 12 years. Four patients showed remarkable improvement, two of whom responded after the first course. Primary Sjögren’s syndrome patients with sensory gangliononeuropathy have also been treated with plasma exchange.45 Two, receiving treatment within two weeks of onset, showed marked and sustained response, while the other two patients of four had no detectable effect. Caroyer et al46 demonstrated improvement of clinical and neurophysiologic deficits in sensory gangliononeuropathy associated with PSS by treatment with infliximab. However, no controlled trials have proved the effectiveness of plasma exchange, IVIG or infliximab in these conditions. In our own clinical practice IVIG, infliximab and other TNF-alfa inhibitors have so far been disappointing for treatment of neuropathy in PSS. B-cell depletion by biological agents like Rituximab may offer a new therapeutic possibility based on the preliminary observations of effect on the clinical manifestations in PSS.47,48

Randomized controlled studies to assess the efficacy of treatments for Sjögren’s syndrome associated neuropathy are still lacking, but obviously some of the patients may obtain a response by regimens used in other immune mediated neuropathies as outlined above.

FINAL COMMENTS

Sjögren’s syndrome is associated with a heterogeneous group of peripheral nerve disorders. There are great differences in the reported distribution of neuropathic categories in studies collecting patients with established neuropathy and often subsequently diagnosed with PSS versus population based materials with only PSS being the inclusion criterion. Future studies should therefore be controlled and population based. Also, extensive clinical, laboratory, electrophysiological, and biopsy studies should be performed to characterize the disease processes and the true pattern and prevalence of neurological manifestations in PSS. This may be fundamental for developing efficacious therapy.

REFERENCES