Peripheral Neuropathy in Primary Sjögren Syndrome

A Population-Based Study

Lasse G. Gøransson, MD; Anita Herigstad, MD; Anne B. Tjensvoll, MD; Erna Harboe, MD; Svein I. Mellgren, MD, PhD; Roald Omdal, MD, PhD

Background: Neurological manifestations appear to be frequently involved in patients with primary Sjögren syndrome (PSS).

Objective: To investigate the involvement of the peripheral nervous system, including small-diameter nerve fibers, in an unselected cohort of patients who fulfilled the new international criteria for PSS.

Design: Cross-sectional study.

Setting: Stavanger University Hospital.

Patients: Sixty-two patients with PSS (mean±SD age, 57.1±14.6 years).

Interventions: Clinical neurologic examinations, conventional nerve conduction studies, and skin punch biopsies.

Main Outcome Measures: Signs of large-diameter and small-diameter peripheral nerve fiber neuropathy as determined by clinical examination, nerve conduction studies, and densities of intraepidermal nerve fibers in skin punch biopsy specimens.

Results: Seventeen patients (27%) were diagnosed as having neuropathy after clinical examination. The results of nerve conduction studies were abnormal in 34 patients (55%): 19 patients (31%) had motor neuropathy, 8 (13%) had sensory neuropathy, and 7 (11%) had sensorimotor neuropathy. Two patients had intraepidermal nerve fiber densities less than 3.4 fibers per millimeter, fitting the morphologic criteria for small-diameter nerve fiber neuropathy.

Conclusions: Peripheral neuropathy occurs in a large proportion of patients with PSS, in most cases as a subclinical demyelinating neuropathy. Small-diameter nerve fiber neuropathy is not a frequent finding in these patients.

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DISEASE MANIFESTATIONS OF chronic immunopathies (connective tissue diseases) in the central and peripheral nervous system are well recognized. In the peripheral nervous system, the prevalence and pattern of involvement varies across disorders, likely reflecting differences in pathogenesis. Primary Sjögren syndrome (PSS) is an autoimmune disease that mainly affects the exocrine glands; it is clinically characterized by keratoconjunctivitis sicca and xerostomia. The histologic hallmark is focal infiltration of the salivary glands by mononuclear lymphoid cells, replacing the glandular epithelium. Onset of the disease is usually insidious, and more than half of patients develop extraglandular manifestations, such as myalgias, arthralgias, and involvement of the pulmonary and gastrointestinal systems. General and unspecific phenomena such as fatigue are also frequent in PSS.

Several authors have explored the neurologic manifestations of the central and peripheral nervous system in patients with PSS. The most commonly reported conditions of the peripheral nerves are symmetric sensorimotor peripheral neuropathy (PN) and symmetric pure-sensory PN. Infrequently, the proximal region of sensory neurons located in the dorsal root ganglia are affected, and ganglionitis may occur. Studies of PN in patients with PSS have in general been performed on highly selected patients or have not used the new PSS criteria. In light of this, we sought to further investigate the prevalence and pattern of PN in PSS using an unbiased sample of patients, stringent PSS criteria, and neurologic approaches that focused on both small- and large-diameter nerve fibers.

METHODS

Stavanger University Hospital, as the only hospital in the southern part of Rogaland County, Norway, offers local service to approximately 290,000 inhabitants. We reviewed the medical records of all hospital inpatients and outpatients with a diagnosis of PSS from 1980 through 2004. In addition, we identified all salivary gland biopsy specimens from 1990 through 2004 (N = 410) that revealed a focus score of 1 or higher and had been analyzed in the hospital’s Department of Pathology. Sixty-seven patients ful-
filled the revised international classification criteria for PSS,13 and 63 gave informed consent to be included in the study, which was approved by the regional research ethics committee. One patient withdrew her consent; thus, a total of 62 patients, 8 men (13%) and 54 women (87%), participated (Table). One patient refused to undergo a skin biopsy.

The mean ± SD age of the patients was 57.1 ± 14.6 years (range, 20.0-85.0 years), and the mean ± SD disease duration was 12.1 ± 9.6 years (range, 0-48.0 years). Of the 62 patients, 28 (45%) were not receiving medication for PSS. Among those receiving medication for PSS, 24 (39%) were taking antimalarial medication, 14 (23%) were taking corticosteroids, 4 (6%) were taking azathioprine, 1 was taking cyclophosphamide, and 1 was receiving anti–tumor necrosis factor α therapy. Twenty-two patients (35%) were using tear substitution. Thirty-two patients (52%) were taking medication for concomitant conditions: 19 (31%) were receiving cardiovascular therapy (antihypertensives, diuretics, and statins), 10 (16%) were receiving nonsteroidal anti-inflammatory drugs, 10 (16%) were receiving thyroxin substitution therapy, 10 (16%) were taking antidepressants, 8 (13%) were taking low-dose acetylsalicylic acid, 2 (3%) were taking proton pump inhibitors, and 3 (5%) were receiving bronchodilator therapy. Bisphosphonate therapy, warfarin sodium, hormone therapy, and antiepileptic drugs were each being taken by 1 patient.

Concomitant diseases included well-regulated thyroid disease in 10 patients (16%), hypertension in 8 (13%), cardiovascular disease in 5 (8%), migraine in 5 (8%), psoriasis in 5 (8%), obstructive lung disease in 3 (5%), osteoporosis in 2 (3%), cervical disease in 2 (3%), epilepsy in 2 (3%), and urolithiasis in 2 (3%). Five patients (8%) had been treated for malignant diseases (rectal cancer, colon cancer, lymphoma, uterine cervix cancer, and tonsil cancer) without relapse. Hip osteoarthritis, anemia, essential thrombocytosis, and Meniere disease were each present in 1 patient.

All participants underwent a standardized general and neurologic examination, nerve conduction studies (NCSs), skin biopsies, and blood and urinary tests. An experienced internist (L.G.G.) recorded the history of concomitant diseases. An experienced internist (A.B.T.) performed the neurologic examination. Nerve conduction studies, skin biopsies, and blood and urinary tests were each being taken by 1 patient.

A hematologic test results; plasma glucose, cobalamin, and folate acid measurements; and thyroid function test results were analyzed in the hospital's laboratory. Antinuclear antibodies were detected with the HEp-2000 assay (Immune Concepts, Sacramento, Calif), and antibodies to double-stranded DNA were verified using the Nova Lite dsDNA Cribitidula lucilae 7082000 indirect immunoassay assay (NOVA Diagnostics, San Diego, Calif). Screening for antibodies to SS-A/Ro and SS-B/La was performed using QUANTA Lite ENA 6, and positive test results were confirmed by QUANTA Lite SS-A and SS-B (INOVA Diagnostics, San Diego, Calif). All analyses, including tests for the complement factors C3 and C4, were performed in the hospital's immunologic laboratory.

Seventeen patients (27%) had PN according to the neurologist's standards of conventional neurologic examination (Figure 1). For 19 patients (31%), NCS results
were indicative of motor neuropathy. In 15 of these patients, abnormally increased F-wave latency in 2 or more nerves was the only abnormal NCS finding. The NCS results indicated that 8 patients (13%) had sensory neuropathy and 7 (11%) had sensorimotor neuropathy. Three patients (5%) had abnormal NCS findings after local injuries unrelated to PSS, and 7 (11%) had carpal tunnel syndrome; 2 of these cases were bilateral. The mean conduction velocities were significantly lower for patients with abnormally increased F-wave latencies vs normal F-wave latencies (Figure 2A). Amplitudes of the motor responses tended to be lower in the group with abnormal F-wave latencies, but these differences did not reach statistical significance (Figure 2B).

Eight patients (13%) were classified as having PN based on both clinical examination and the NCSs. Of these 8, 3 (5%) had sensorimotor neuropathy, 3 (5%) had motor neuropathy, and 2 (3%) had sensory neuropathy. The mean±SD IENF density in patients with PSS was 9.2±3.8 fibers per millimeter in the leg vs 9.6±3.1 fibers per millimeter in the proximal thigh (P=.37, Figure 3). The mean IENF densities in the leg were significantly lower in patients with PSS vs patients without PSS (P=.004). A considerable proportion of the patients with PSS, and morphometric criteria, we identified a neuropathy in a considerable proportion of the patients with PSS. The classification excludes patients with sicca syndromes attributable to other causes. Using this classification and applying fairly objective clinical, electrophysiologic, and morphometric criteria, we identified a neuropathy in a considerable proportion of the patients with PSS.

In contrast to previous reports,7,8,10 many patients in this study had a subclinical demyelinating motor neuropathy. This determination was based on abnormally increased F-wave latencies in 2 or more nerves accompanied by normal motor amplitudes. The nerve conduction velocity between knee and ankle was significantly lower in patients with prolonged vs normal F-wave latency. Notably, the increased F-wave latencies were bilateral in all 15 patients, strongly in favor of a generalized demyelinating process. However, for both groups of patients the conduction velocities were within the reference range. The more pronounced abnormalities in F-wave latency vs distal conduction velocity could theoretically be explained by more proximal than distal involvement. However, in our opinion, this is unlikely and is supported by similar findings in other distal neuropathies.20 The F-wave latency is often regarded as the single most sensitive neurophysiologic parameter for detection of generalized motor nerve abnormalities.20,21 The long distance used for F-wave registrations improves the detection of slight changes in the whole nerve as opposed to more pronounced focal processes detected by abnormalities in conduction velocities. In addition, the F-wave latency ref-

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**Figure 2.** Nerve conduction velocities and motor response amplitudes. A, Nerve conduction velocities (mean±95% confidence interval [CI]) in the peroneal and tibial nerves. P values are Bonferroni corrected. •P < .001. †P = .004, ‡P = .03. B, Motor response amplitudes (mean±95% CI) in the peroneal and tibial nerves.

**Figure 3.** Intraepidermal small-diameter nerve fiber (IENF) densities in the lower limb of patients with primary Sjögren syndrome (N = 62). The lines represent the IENF densities in the thigh and corresponding leg of each patient.

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**COMMENT**
densities were found in the proximal part of the thigh biopsy specimens in some studies but not in others. This finding suggests that the abnormal F-wave latencies observed in patients with PSS were not accidental and that the pathogenesis for PN in the 2 diseases is different.

Small-diameter nerve fiber neuropathy was an infrequent finding. Furthermore, no significant differences were found between the IENF densities in the leg and thigh. This pattern has been reported in patients with sensory ganglionopathies but contrasts the findings in healthy subjects, in whom significantly higher IENF densities were found in the proximal part of the thigh compared with the distal part of the leg. However, in a small group of healthy subjects (N = 13), we recently identified the same IENF pattern as in PSS: no proximal-to-distal gradient (L.G.G., S.I.M., and R.O., unpublished data, 2005). This discrepancy may be methodologically related and should be investigated in future studies.

Several mechanisms likely underlie the involvement of the peripheral nervous system in patients with PSS. Vascular or perivascular inflammatory infiltrates with or without necrosis have been observed in peripheral nerve biopsy specimens in some studies but not in others. On a more general basis, neurons could be affected secondary to an inflammatory process involving the vasa nervorum. In several other clinical conditions, such as patients with anti-Hu or antisulfatide antibodies, an immunopathogenesis for PN is well documented. Therefore, several antibodies with reactivity against the proximal regions of sensory and motor neurons are candidate factors in the PN of patients with PSS.

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