Paper V

Peripheral neuropathy in primary Sjögren´s syndrome – a population based study

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Abstract

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

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

Design: Cross-sectional study.

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

Interventions: Clinical neurological 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 biopsies.

Results: Seventeen patients (27%) were diagnosed with neuropathy following clinical examination. 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 IENF densities less than 3.4 fibers/mm fitting the morphological 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.

Disease manifestations of chronic immunopathies (connective tissue diseases) in the central and peripheral nervous system are well recognized.[1] In the peripheral nervous system, the prevalence and pattern of involvement varies across disorders, likely reflecting differences in pathogenesis.

Primary Sjögren´s syndrome (PSS) is an autoimmune disease that mainly affects exocrine glands; it is clinically characterized by keratoconjunctivitis sicca and xerostomia.[2] The histological hallmark is focal infiltration of the salivary glands by mononuclear lymphoid cells, replacing glandular epithelium.[3] Onset of the disease is usually insidious, and more than half of patients develop extraglandular manifestations like myalgias, arthralgias, and involvement of the pulmonary and gastrointestinal systems. General and unspecific phenomena like fatigue are also frequent in PSS.[2]

Several authors have explored the neurological manifestations of the central and/or peripheral nervous system in patients with PSS.[4-10] The most commonly reported afflictions of the peripheral nerves are symmetric sensorimotor peripheral neuropathy (PN) and symmetric pure- sensory PN.[7,8] Infrequently, the proximal region of sensory neurons located in the dorsal root ganglia are affected, and ganglionitis may occur.[10-14] Studies of PN in patients with PSS have in general been performed on highly selected patients, or have not utilized the new PSS criteria.[15] 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,[15] and neurological approaches that focused on both small- and large diameter nerve fibers.

Patients and Methods

Stavanger University Hospital offers local hospital service to approximately 290,000 inhabitants of Rogaland county, Norway. 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 biopsies from 1990 through 2004 (N = 410) that revealed a focus

score ≥ 1 and had been analyzed in the hospital's Department of pathology. Sixty-seven patients fulfilled the revised international classification criteria for PSS,[15] 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 1). One patient refused to undergo a skin biopsy.

The mean age ± SD was 57.1 ± 14.6 years (range 20.0-85.0 years), and the mean disease duration was 12.1 ± 9.6 years (range 0.0-48.0 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 patients (32%) were using tear-substitution. Thirty-two patients (52%) were on 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, hormonal replacement therapy, and anti-epileptic drugs were each being taken by 1 patient.

Concomitant diseases were well-regulated thyroid disease in 10 patients (16%), hypertension 8 (13%), cardiovascular disease 5 (8%), migraine 5 (8%), psoriasis 3 (5%), obstructive lung disease 3 (5%), osteoporosis 2 (3%), celiac disease 2 (3%), epilepsy 2 (3%), and urolithiasis 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 Mb Meniere were each present in 1 patient.

All participants were subjected to a standardized general and neurological examination, nerve conduction studies (NCS), skin biopsies, and blood and urinary tests. An experienced internist (LGG) recorded the history of concomitant diseases and performed the general clinical examination, and an experienced neurologist (ABT) performed the neurological examination.

Hematological tests, plasma glucose, cobalamin, folic acid, and thyroid function tests were analyzed in the hospital's laboratory. Antinuclear antibodies (ANA) were detected by using the HEp-2000 assay (Immune Concepts, Sacramento, CA, USA), and antibodies to dsDNA verified using the Nova Lite dsDNA *Crithidia luciliae* 708200 indirect immunofluorescens assay (NOVA Diagnostics, San Diego, CA, USA). Screening for antibodies to SSA/Ro and SSB/La was performed using QUANTA Lite™ ENA 6, and positive tests were confirmed by QUANTA Lite™ SS-A and SS-B (INOVA Diagnostics, San Diego, CA, USA). All analyses, including tests for the complement factors C3 and C4 were analyzed in the hospital's immunological laboratory.

For nerve conduction studies (NCS), surface stimulating and recording electrodes were used at standard temperature. The amplitude, velocity, distal latency, and F-wave latency (expressed as F - distal motor latency) of motor fibers of the median, ulnar, peroneal, and tibial nerves were recorded, and the amplitude and conduction velocity of sensory fibers of the median, radial, ulnar, and sural nerves were recorded. Normal values for motor fibers are those provided by the manufacturer (Dantec Keypoint apparatus, Dantec Medical A/S, Skovlunde, Denmark), which are themselves based on data from the Department of Clinical Neurophysiology, University Hospital, Uppsala, Sweden. Normal values (mean $\pm$ 1.96 SD) for sensory fibers are based on data from healthy subjects in our neurophysiological laboratory. The neurophysiological criterion for PN was defined as abnormalities in two or more nerves.[16]

The skin biopsies were performed under local anesthesia (2% lidocaine and adrenaline) with a 3-mm disposable circular-punch needle (Biopsy Punch, Stiefel Laboratories Ltd., Sligo, Ireland) and sterile technique. Four biopsies were obtained from the same right extremity of each patient during the same procedure: two biopsies approximately 10 cm from above the lateral malleolus and two biopsies approximately 20 cm from the anterior iliac crest on the lateral part of the thigh. If the skin on the right limb was inflamed or had scars, the left limb was used. The biopsies were immediately fixed and prepared as previously described.[17] The density of intraepidermal nerve fibers (IENF, fibers/mm) was reported as the mean count in six sections, three from each of the biopsies. The IENF density in the leg was considered abnormal when it was below the lower limit of normative values (3.4 fibers/mm) previously determined by our group.[18]

Statistics.

The variables were normally distributed and subjected to parametric statistics. When appropriate, results are reported as the mean ± SD with the median and range. Simple or multiple regression analysis with IENF as the dependent variable was used to test for associations between IENF and normally distributed quantitative variables. Unpaired Student t- tests (2-tailed) or analysis of variance was applied when testing two or more groups of quantitative data. P- values less than 0.05 corrected for ties were considered significant. Analyses were performed using StatView.

Results

Seventeen patients (27%) had PN according to the neurologist's standards of conventional neurologic examination (Fig. 1).

For 19 patients (31%) NCS results were indicative of motor neuropathy. In 15 of these patients abnormally increased F-wave latency in ≥ 2 nerves was the only abnormal NCS

finding. NCS results indicated that 8 patients (13%) had sensory neuropathy, and 7 (11%) had sensorimotor neuropathy. Three patients (5%) had abnormal NCS findings following local injuries unrelated to PSS, and 7 (11%) had carpal tunnel syndrome, two of these cases were bilateral. The mean conduction velocities were significantly lower for patients with abnormally increased F-wave latencies versus normal F-wave latencies (Fig. 2A). Amplitudes of the motor responses tended to be lower in the group with normal F-wave latencies, but these differences did not reach statistical significance (Fig. 2B).

Eight patients (13%) were classified as having PN based on both clinical examination and the NCS. Of these eight, 3 (5%) had sensorimotor neuropathy, 3 (5%) had motor neuropathy, and 2 (3%) had sensory neuropathy.

The mean IENF density in patients with PSS was 9.2 ± 3.8 fibers/mm in the leg versus 9.6 ± 3.1 fibers/mm in the proximal thigh (P = 0.37, Fig. 3). The mean IENF densities in the leg were significantly lower in patients with PSS compared with normative values and with SLE patients also.[18,19] In 2 patients the densities were less than 3.4 fibers/mm, fitting the morphological definition of small-diameter nerve fiber neuropathy.[18] The NCS were normal in these two patients except for carpal tunnel syndrome in one of them. No associations were detected between abnormal clinical examination findings and IENF densities in the leg or thigh.

Comment

This is the first study to investigate the involvement of the peripheral nervous system in PSS using an unselected cohort of patients and applying the new international classification criteria for the disease.[15] This classification ensures that patients with “true” autoimmune PSS are optimally selected. The classification excludes patients with sicca syndromes due to other causes. Using this classification and applying fairly objective clinical, electrophysiological,

and morphometric criteria we identified a neuropathy in a considerable proportion of the PSS patients.

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 nerves accompanied by normal motor amplitudes. The nerve conduction velocity between knee and ankle was significantly lower in patients with prolonged versus normal F-wave latency. Notably, the increased F-wave latencies were bilateral in all 15 patients, strongly in favour of a generalized demyelinating process. However, for both groups of patients the conduction velocities were within the normal reference range. The more pronounced abnormalities in F-wave latency versus 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 neurophysiological parameter for detection of generalized motor nerve abnormalities,[20,21] and the long distance used for F-wave registrations improve the detection of slight changes. In addition, the F-wave latency reference range is narrower than the conduction velocity reference range. Although motor amplitudes were consistently lower in patients with increased F-wave latencies, these differences were nonsignificant, indicating that the prevailing neuropathic process is mainly demyelinating. Electromyographic studies would have strengthened the interpretation of the F-response abnormalities, but in a parallel study of a group of patients with systemic lupus erythematosus, F-wave latencies were increased in only 4 out of 60 patients (7%).[22] This suggests that the abnormal F-wave latencies observed in PSS patients were not accidental and that the pathogenesis for PN in the two diseases is different.

Small-diameter nerve fiber neuropathy was an infrequent finding. Further, there were no significant differences between the IENF densities in the leg and thigh. This pattern has

been reported in patients with sensory ganglionopathies,[23] but contrasts to findings in healthy subjects where significantly higher IENF densities were found in the proximal part of the thigh compared to the distal part of the leg.[24] However, in a small group of healthy subjects (N=15), we recently identified the same IENF pattern as in PSS, no proximal to distal gradient (unpublished). This discrepancy may be methodologically related and should be investigated in future studies.

There are likely several mechanisms underlying 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 biopsies in some studies,[4,7] but not in others.[8,14] On a more general basis neurons could be affected secondary to an inflammatory process involving the vasa nervorum.[12,25] In several other clinical conditions, like patients with anti-Hu or anti-sulfatide antibodies, an immunopathogenesis for PN is well documented.[26,27] Therefore, several antibodies with reactivity against the proximal regions of sensory and motor neurons are candidate actors in the PN of patients with PSS.

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Table 1

Number of patients with positive symptoms and signs according to the new international classification criteria for PSS.

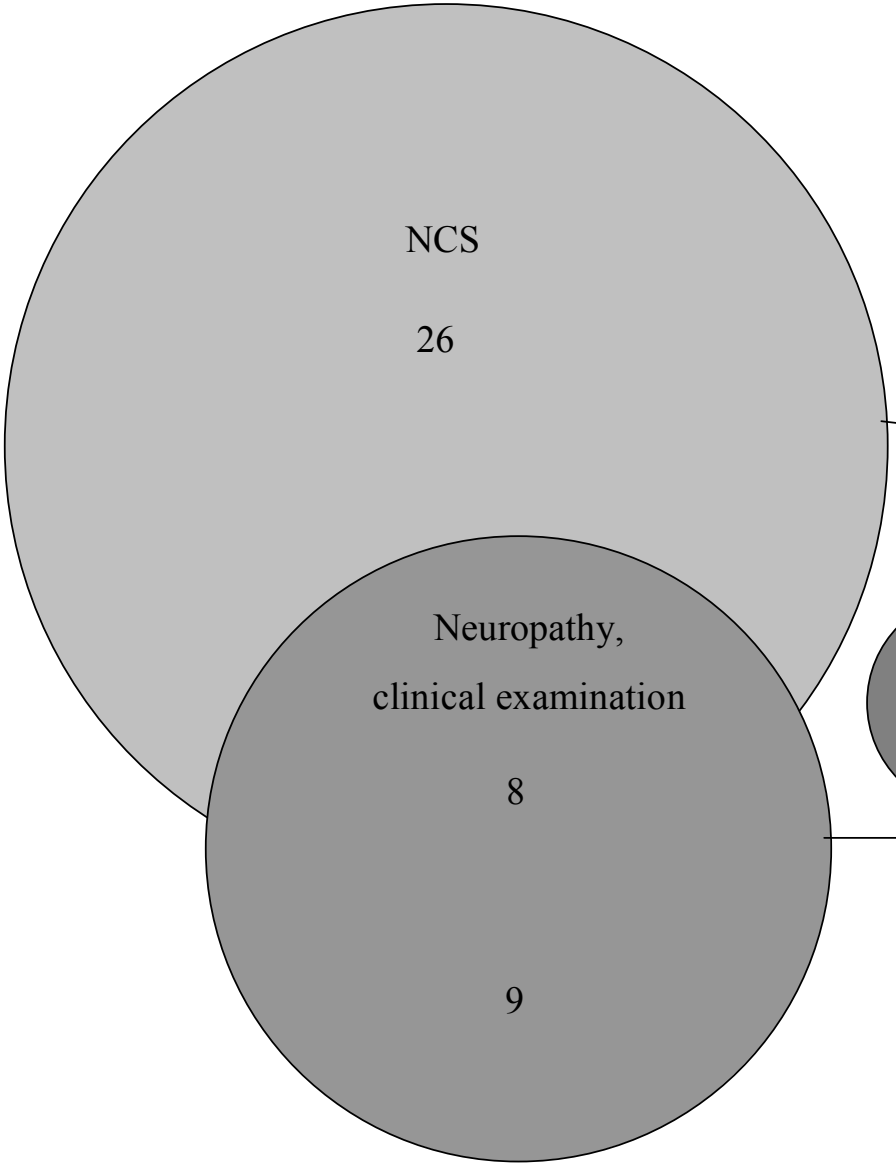
	Number (%) of patients with positive symptoms or tests
Ocular symptoms (N=62)	52 (84%)
Oral symptoms (N=62)	56 (90%)
Ocular signs (N=62)	46 (74%)
Salivary gland biopsy (N=56)	44 (71%)
Objective signs of salivary gland involvement (N=57)	46 (74%)
Autoantibodies (N=62) (anti-SSA or anti-SSB)	52 (84%)

Fig. 1 Venn diagram illustrating the number of patients with abnormal tests and the overlap of these tests in 62 patients with primary Sjögren's syndrome. NCS = Nerve Conduction Studies, IENF density = intraepidermal small-diameter nerve fibers per mm.

Fig. 2 (A) Nerve conduction velocities (mean $\pm$ 95% CI) in the peroneal and tibial nerves. *P* values are Bonferroni-corrected. * $P < 0.0001$, ** $P = 0.0036$, *** $P = 0.032$.

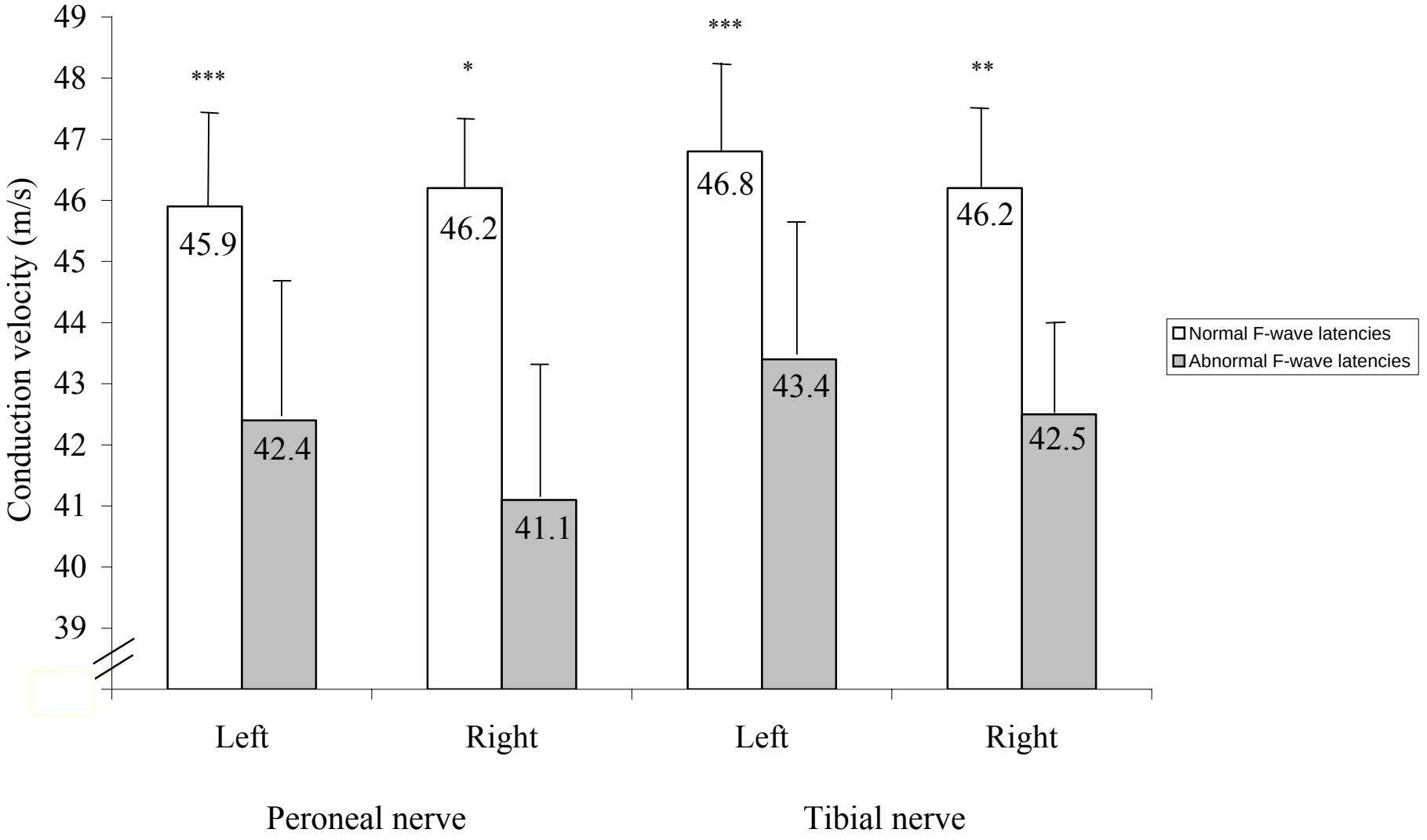
(B) Motor response amplitudes (mean $\pm$ 95% confidence interval) in the peroneal and tibial nerves.

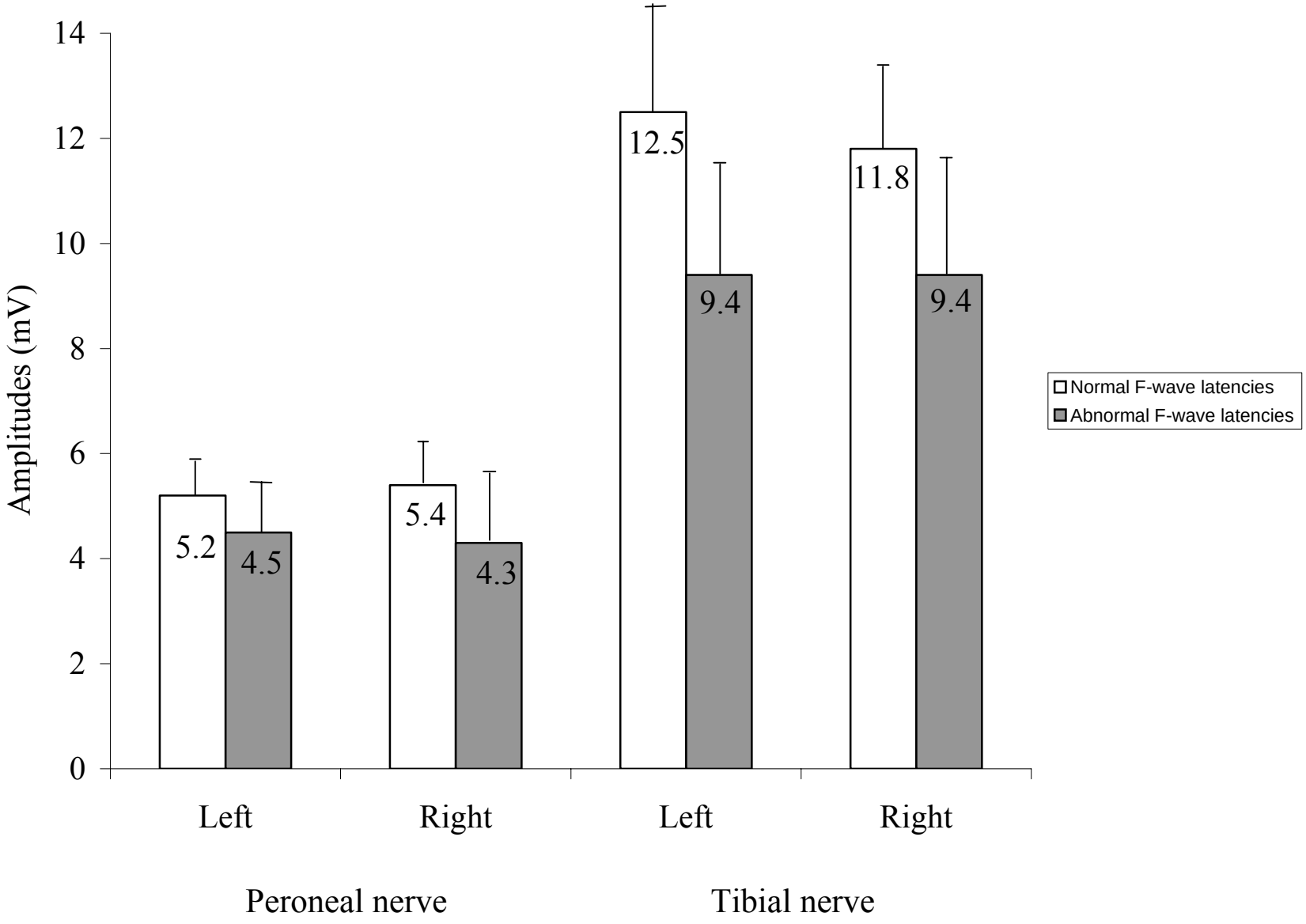
Fig. 3 Intraepidermal small-diameter nerve fiber (IENF) densities in the lower limb of patients with primary Sjögren´s Syndrome (N = 62). The lines represent the IENF densities in the thigh and corresponding leg of each patient.

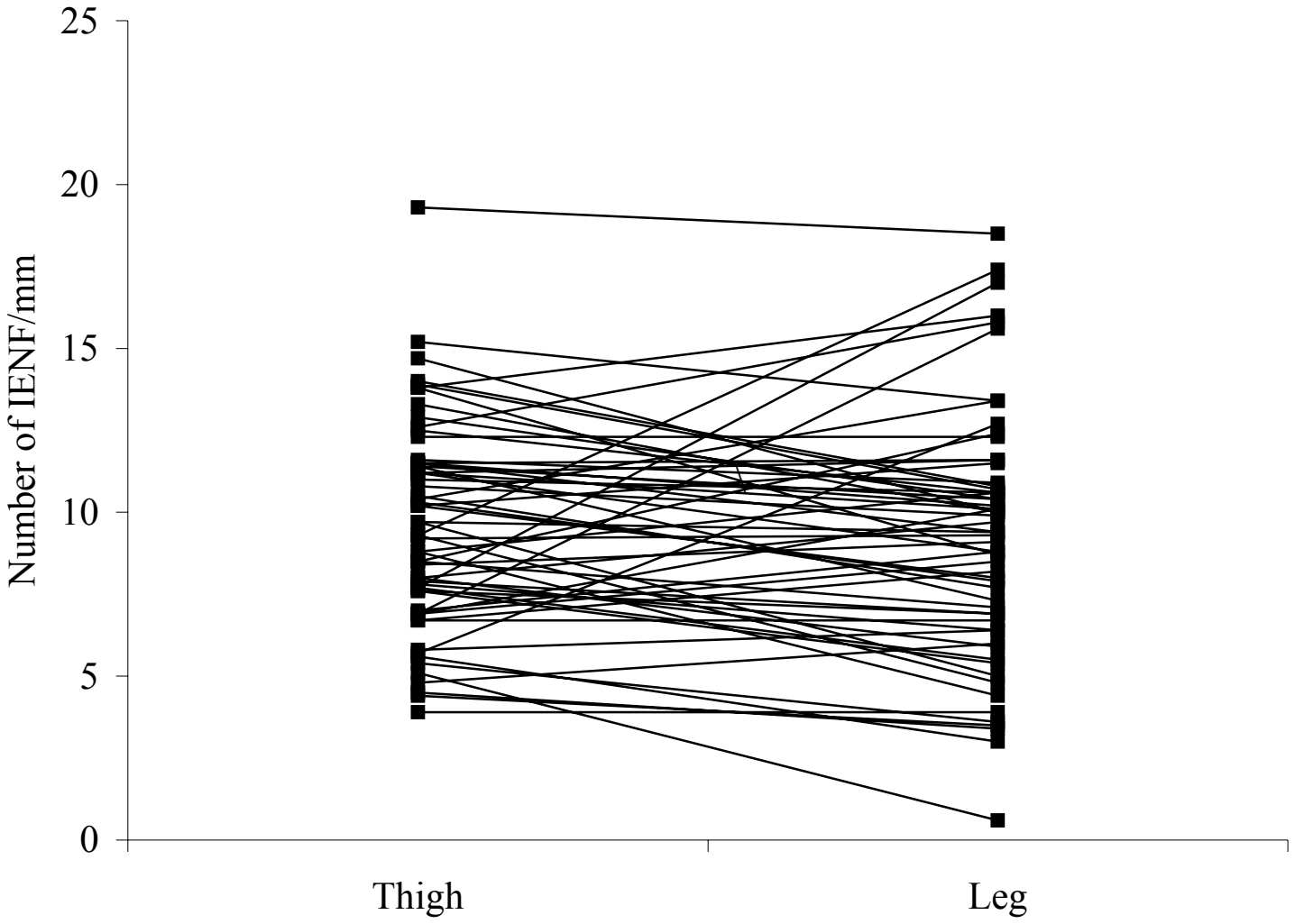


Number of patients with abnormal test.	
Test	No.
NCS	34
IENF density	2
Neuropathy on clinical examination	17

Total number of patients = 62


Conduction velocity (m/s)
49
48
47
46
45
44
43
42
41
40
39
***
*
***
**
45.9
42.4
46.2
41.1
46.8
43.4
46.2
42.5
Normal F-wave latencies
Abnormal F-wave latencies
Left
Right
Left
Right
Peroneal nerve
Tibial nerve


14
12
10
8
6
4
2
0
Amplitudes (mV)
5.2
4.5
5.4
4.3
12.5
9.4
11.8
9.4
Normal F-wave latencies
Abnormal F-wave latencies
Left
Right
Left
Right
Peroneal nerve
Tibial nerve


25
20
15
10
5
0
Number of IENF/mm
Thigh
Leg