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Abstract

Background—Involvement of the peripheral nervous system in patients with primary Sjögren's syndrome (SS) has been reported, but its prevalence in neurologically asymptomatic patients is not well known.

Objective—To assess clinical and neurophysiological features of the peripheral nervous system in patients with primary SS.

Patients and methods—39 (38 female) consecutive patients with primary SS, aged 20–81 years (mean 50), with a disease duration of 1–30 years (mean 8) were studied. The peripheral nervous system was evaluated by a questionnaire, physical examination, quantified sensory neurological examination, and neurophysiological measurements (nerve conduction studies). To assess autonomic cardiovascular function an orthostatic challenge test, a Valsalva manoeuvre, a forced respiration test, and pupillography were done.

Results—Abnormalities as indicated in the questionnaire were found in 8/39 (21%) patients, while an abnormal neurological examination was found in 7/39 (18%) patients. Abnormalities in quantified sensory neurological examination were found in 22/38 (58%) patients. In 9/39 (23%) patients, neurophysiological signs compatible with a sensory polyneuropathy were found. No differences were found in the autonomic test results, disease duration, serological parameters, or erythrocyte sedimentation rate between the patients with primary SS with and those without evidence of peripheral nervous involvement.

Conclusion—Subclinical abnormalities of the peripheral nervous system may occur in patients with primary SS selected from a department of rheumatology, but clinically relevant involvement of the peripheral nervous system in this patient group is rare.

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Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder, characterised by oral and ocular dryness due to lymphocytic infiltration of exocrine glandular tissue. In primary SS many extraglandular manifestations, such as involvement of lung, liver, kidney, blood vessels, and the nervous system, have been described.

Involvement of the central nervous system in primary SS is diverse[1][2] and includes focal deficits, such as hemiparesis, hemisensory deficits, seizure disorders, and movement disorders, and more diffuse disorders, such as headache, cognitive dysfunction, or psychiatric abnormalities.[2] Peripheral neurological disease is mainly manifested as mild sensory, mixed, trigeminal or latent motor neuropathy and mononeuritis multiplex.[3][4] The prevalence of peripheral neurological abnormalities in primary SS has been estimated as between 10% and 30%,[2][3][5] but has not been thoroughly investigated.[4] Recently, some studies and reports on the autonomic nervous system in primary SS have been described, in which subclinical disturbances of the parasympathetic nervous system were found in about 15% of the patients.[6–9] In our study for the first time quantified sensory testing of the peripheral nervous system was done in 39 patients with primary SS, as well as neurophysiological tests of the peripheral nervous system.

In both diabetes mellitus and chemotherapy induced neuropathy investigations of warmth and cold sensitivity and vibration sense have been shown to be more sensitive than global testing or neurophysiological investigation of the peripheral nervous system.[10–12]

The results of cardiovascular function tests for autonomic nervous system disturbances in this patient group have been extensively reported elsewhere, and these results were compared with those of the present study.[8]

Patients and methods

PATIENTS

After screening for exclusion criteria, 39 consecutive patients (38 female) with primary SS aged 20–81 years (mean 50) with a disease duration of 1–30 years (mean 8) were recruited from the Department of Rheumatology, Dr Daniel den Hoed Clinic, Rotterdam. All patients fulfilled the European criteria for primary SS.[13] Moreover, the patients without an abnormal salivary gland biopsy all showed peripheral sialectasias by sialography[14] and at least one out of four serological tests (antinuclear antibodies, rheumatoid factor, SS-A and SS-B antibodies) was positive (table 1).

The clinical disease spectrum of the included patients varied from arthralgia, myalgia, oral and ocular dryness to fatigue. None of the patients had spontaneous complaints of the nervous system. None of the patients had severe organ disease. None of the patients had concomitant diseases, such as neurological disease, amyloidosis, renal failure, or diabetes

Table 1 Clinical characteristics of 39 patients with primary Sjögren's syndrome. Values are presented as median and range unless indicated otherwise

Age (years)	49 (20–81)
Disease duration (years)	5 (1–30)
ESR (mm/1st h)	30 (11–97)
ANA (No (%) positive)	29 (74)
RF (No (%) positive)	19 (49)
SS-A (No (%) positive)	25 (64)
SS-B (No (%) positive)	14 (36)
Sialography (No (%) positive)	32 (83)
Salivary gland biopsy (No (%) positive)★	33 (85)

All patients had at least one serological test positive. In all patients at least sialography or salivary gland biopsy results were abnormal.

ESR = erythrocyte sedimentation rate; ANA = antinuclear antibodies; RF = rheumatoid factor; SS-A = Sjögren's syndrome A antibodies; SS-B = Sjögren's syndrome B antibodies.
★Lymhocytic infiltration in salivary gland biopsy specimen ($\geqslant 2$ foci or >50 lymphocytes/4 mm^2 gland tissue).

mellitus, known to affect the peripheral nervous system, and none used drugs that can give neuropathy. None of the patients fulfilled the established criteria of another connective tissue disease.

Written informed consent was obtained from all patients, and the study was approved by the medical ethics committee of the Dr Daniel den Hoed Clinic.

QUESTIONNAIRE

Before starting the tests a structural interview was carried out with all the patients. This questionnaire was derived from another questionnaire, used to assess neuropathic symptoms in patients with chemotherapy induced neuropathy.[15] This method covers symptoms of (sensory) neuropathy, like paraesthesias, pain in hands or feet, numbness, and loss of dexterity. The questionnaire included seven items and the results were assessed by the same neurologist (MvdB) and considered to be normal (0 items abnormal), minimal abnormal ($\leqslant 2$ items abnormal, slight paraesthesias), or abnormal (>2 items abnormal).

NEUROLOGICAL PHYSICAL EXAMINATION

All physical examinations, mainly concerning sensory functions, were performed by one of us (VvR). This method was also derived from a standardised neurological examination, used to assess neuropathic signs in patients with chemotherapy induced neuropathy.[15] The following items (18 in total) were tested: position sense (digitus I left foot), vibration sense (digitus I left foot), pin prick sense (digitus I left foot), tactile sense (digitus I left foot), position sense on the dorsum of the hand, vibration sense on the dorsum of the hand, pin prick sense on the dorsum of the hand, tactile sense on the dorsum of the hand, pin prick sense trigeminal area, tactile sense trigeminal area, walking on heels, walking on toes, Romberg's sign, two step test (testing the ability of stepping two steps for both legs separately), pupillary reactions, knee and ankle tendon joints reflexes.

The results were reviewed by the same neurologist (MvdB) and considered to be normal (0 items abnormal), minimal abnormal ($\leqslant 2$ items abnormal, or only abnormal tendon joint reflexes), or abnormal (>2 items abnormal).

QUANTIFIED SENSORY NEUROLOGICAL EXAMINATION

Quantitative evaluation of sensory deficits was done by vibration perception and by thermo-perception measurements.[12 16 17]

Vibration perception threshold (VPT)

The VPT was measured at the dorsum of the second metacarpal bone of the left hand. Patients were sitting in a quiet room with their left hand resting on a table. We used a Vibrameter type IV (Somedic AB, Stockholm, Sweden), a hand-held instrument that applied a vibration stimulus with a frequency of 100 Hz by means of a rod with a diameter of 13 mm. The rod was positioned at the middle of the second metacarpal bone. This device allows visual control of application, and the test results represent the actual displacement of the skin in micrometres on a calibrated digital display. Patients were first familiarised with the vibratory sensation of the Vibrameter. We used the method of limits as previously described[11]: increasing the stimulus strength from zero to the point were the vibratory sensation was first perceived, and then decreasing the stimulus strength from a slightly supramaximal level to the point where the sensation disappears; the average of these two values was taken as the actual VPT. We performed three measurements for each assessment, the mean of these measurements represented the final VPT.

The VPT has been shown to correlate well with neuropathic signs and symptoms.[11 18] Normal values were based on results of a healthy control population (tests performed by the same investigator and stored in our own database, normal values: mean control value ±2SD, control group: n=51, all female, mean age 43 years (range 20–70)).

Thermal discrimination thresholds (warmth sensitivity, cold sensitivity)

For determination of the warmth sensitivity (WS) and the cold sensitivity (CS) a thermal sensory analyser (TSA 2001, MEDOC, Israel) was used with a 3×5 cm Peltier element using the staircase method. In this method the patient was given temperature stimuli of varying magnitude. Measurement took place on the dorsum of the left hand; the baseline temperature of the element was 32°C. After each stimulus the patient had to tell whether he perceived the stimulus ("positive") or not ("negative") by pressing a yes/no button. To increase attention a beep was given before the stimulus, but at irregular intervals dummy stimuli were also administered. The possibility of dummy stimuli was mentioned to the patient. For the determination of the WS, thermal stimuli were given in three successive steps. Firstly, in rude steps the temperature of the stimuli was increased by increments of 2°C, until the first positive response was obtained. Then, the temperature of the stimuli was decreased by 0.5°C until a negative response was obtained.

Starting at that temperature, in the final part of the test the thermal stimulus was increased

or decreased in steps of 0.2°C, depending on the response to the preceding stimulus.

The test was stopped after four negative responses in the final phase; the mean of all thermal stimuli during this final phase was used as the definite value of WS. For CS, a similar procedure with stimuli below 32°C was carried out. Thermoperception has been shown to be a reliable technique to monitor chemotherapy induced neuropathy[18] and neuropathy in diabetes mellitus.[17] Normal values were based on the results of a healthy control population (tests performed by the same investigator and test results stored in our own database, normal values: mean control value ±2SD, control group: n=43, all female, mean age 40 years (range 20–70)).

NERVE CONDUCTION VELOCITY

Nerve conduction velocities (NCVs) were measured with a Nihon Kohden Neuropack Four Mini. Motor NCV of the ulnar and the peroneal nerves were assessed with surface electrodes of 1 cm diameter, on the musculus abductor digiti quinti and the musculus extensor digitorum brevis respectively. After identification of the start and of the compound motor action potential both the negative peak amplitude and the negative peak area of the compound motor action potential were automatically computed. For the determination of the NCV the distal latency and the latency after stimulation at the elbow/knee were obtained. Sensory NCVs were determined with antidromic stimulation. The median nerve and the ulnar nerve were assessed with coil electrodes, on the second finger and the fifth finger respectively.

The sural nerve NCV was determined with surface electrodes of 1 cm diameter. The distal latency was determined, and after measuring the distance between the stimulus and the recording site the velocity was calculated. The amplitude was measured from the negative to the positive peak. The minimal F wave latency of the peroneal nerve was determined after 10 supramaximal stimuli at the dorsum of the foot.

The H reflex of the gastrocnemius muscle was obtained with stimuli of 0.5 Hz of increasing strength of the tibial nerve, and was recorded with surface electrodes of 1 cm diameter. The H reflex latency, HM interval, and amplitude of the H reflex were measured. Finally, with the same position of the recording electrodes the Achilles tendon reflex was recorded with an electronic reflex hammer. The Achilles tendon reflex latency, amplitude, and negative peak area were determined. The length of the patient was recorded in centimetres.

For this study, normal values of NCV were obtained in a group of 42 healthy women, aged 23–80 years (mean age 50), who were relatives of patients or hospital employees.

CARDIOVASCULAR FUNCTION TESTS

The results of the cardiovascular autonomic function tests of this patient group have been extensively described.[8] Firstly, an orthostatic challenge test was done by continuous registration of blood pressure and heart rate during 15 minutes' horizontal rest and during 15 minutes of 60° head-up tilt. The difference in systolic blood pressure was taken as the measure of postural blood pressure change.

A drop in systolic blood pressure of >20 mm Hg was considered to indicate orthostatic hypotension—that is, sympathetic dysfunction. The Valsalva manoeuvre was performed by asking the patient to blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mm Hg for 15 seconds. The longest interbeat interval shortly after ending the manoeuvre to the shortest interbeat interval during the manoeuvre was expressed as the Valsalva ratio. A value of <1.20 indicates parasympathetic failure. Finally, the heart rate was measured during one minute of forced inspiration and expiration and the maximal-minimal heart rate during a 10 second breathing cycle was calculated. A value of <15 beats represent parasympathetic abnormality.

PUPILLOGRAPHY

The results of the pupillography tests of this patient group have also been previously described.[8] The pupillary system was stimulated with a pulse light stimulus to measure the constriction and dilatation latency times of the pupils. Average constriction latency time was determined as parameter of parasympathetic function.

The average dilatation latency time was determined as a parameter of ocular sympathetic function.

STATISTICAL ANALYSES

Values are presented as means (SD), unless indicated otherwise. The Wilcoxon test was used when appropriate. All correlations were analysed by Pearson's correlation coefficient. A p value <0.05 was considered to indicate significant differences.

Results

Table 1 gives clinical and demographic data of 39 patients with primary SS.

None of the patients spontaneously complained about neuropathic symptoms, but abnormalities in answering the questionnaire were obtained in 8/39 (21%) patients (abnormal two, minimal abnormal six). From these eight patients, six also showed abnormalities at physical examination. Five of these eight patients showed an abnormal VPT response (table 2), while three and two of these eight patients had abnormal CS and WS results (table 3), respectively. Only 4/8 patients also showed abnormal results of the nerve conduction studies.

At neurological examination abnormalities were found in 7/39 (18%) patients (abnormal four, minimal abnormal three). Three of these 7 patients showed also an abnormal VPT response, while three and two of these seven patients had abnormal CS and WS results, respectively. Five of these seven patients also showed abnormal nerve conduction results.

Table 2   Results of vibration perception thresholds in 38 patients with primary Sjögren's syndrome, according to age

Age (years)	No of patients	No (%) abnormal	Normal value
<31	4	3 (75)	<0.34
31–40	9	7 (78)	<0.43
41–50	8	4 (50)	<0.54
51–60	9	6 (67)	<0.68
61–70	5	1 (20)	<0.86
>70	3	1 (33)	<1.08
Total	38	22 (58)	

Normal values were based on mean results (stored in a database) of a control population and divided into age groups. Normal values: mean control value ±2SD.

Table 2 shows the results of the VPT; one patient did not understand the test procedure. In 22/38 patients (58%) abnormal results were found. In three of these 22 patients the results of the nerve conduction studies were also abnormal.

Table 3 shows the results of warmth and cold sensitivity in patients with primary SS. Only 35 patients were able to perform the test procedure. In 7/35 (20%) and 5/35 (14%) patients, respectively, WS and CS test results were abnormal.

Both WS and CS tests were abnormal in 2/35 (6%) patients. One of these two patients also showed abnormal results at neurophysiological examination, compatible with motor and sensory axonal neuropathy.

No correlation was found between the results of the VPT and warmth/cold sensitivity.

Neurophysiological abnormalities, like axonal neuropathy, mixed type neuropathy, sensory neuropathy, and motor neuropathy were found in 9/39 (23%) patients (table 4).

No relation was found between the results of the cardiovascular function test[8] and pupillography tests,[8] or with the results of the VPT or of WS/CS. No differences in the results of the cardiovascular function tests and in pupillography were found between the subgroups of patients with primary SS with or without neurophysiological abnormalities (patients with neurophysiological evidence for polyneuropathy as shown in table 4).

The mean age of the group with neurophysiological evidence for neuropathy was 60 and the mean age of the group without neurophysiological abnormalities was 46 ($p<0.05$).

No differences were found in disease duration, serological parameters, and erythrocyte sedimentation rate (ESR) between the subgroups of patients with primary SS with or without neurophysiological abnormalities.

Discussion

In this study of 39 consecutive patients with primary SS selected from a rheumatology outpatient clinic, no patient had spontaneous neuropathic complaints, but after specific questioning, symptoms compatible with peripheral nervous system abnormalities were admitted in 8/39 (21%) patients, mostly minor. In accordance with earlier studies we found in 7/39 (18%) patients abnormalities (in almost half of the patients only minor) by simple clinical neurological examination. By means of a quantified neurological examination, we found subclinical abnormalities in 22/38 (58%) patients with primary SS. Slight abnormalities in the nerve conduction studies were present in 9/39 (23%) patients.

Previous investigations of the peripheral nervous system in primary SS have been less extensive or retrospective, or both. No study was found in which warmth and cold sensitivity or vibration sense were measured. In most studies and case reports on the peripheral nervous system in primary SS the neurological symptoms are mild and mostly concern a symmetrical sensory neuropathy,[1] [19–25] which concurs with the results presented in our study. Although several reports of neuropathy in primary SS have been published, only a few systematic studies on a larger consecutive patient group have been performed. A retrospective study on 105 patients with primary and secondary SS showed mild neurological abnormalities (carpal tunnel syndrome, trigeminal neuralgia, symmetrical sensory neuropathy) in 17% of the patients.[26]

Andonopoulos *et al* prospectively evaluated 63 patients with primary SS for evidence of neurological manifestations by carrying out a physical examination and by determination of motor NCV.[3] In the study he described none of the patients volunteered neurological complaints. Sensory neuropathy was found in 17 (27%) of the patients and, furthermore, one of the patients showed a trigeminal neuropathy, one of the patients had pure motor neuropathy, and another eight had subclinical motor neuropathy. In another study on 46 patients with primary SS, clinical and electromyographical signs of polyneuropathy were found in 22% of the patients, but no differences were found in clinical or laboratory variables (such as ESR) between neuropathic and non-neuropathic patients,[5] compatible with the results of our study.

In an earlier study, central and peripheral manifestations of the nervous system were evaluated in 48 patients with primary SS. The

Table 3   Results of warmth and cold sensitivity in 35 patients with primary Sjögren's syndrome and 43 controls. Values are presented as means (SD) unless indicated otherwise

	Sjögren	Controls	Normal value	No (%) abn. Sjögren
WS	33.2 (0.93)★	32.7 (0.45)	≤33.6	7/35 (20)
CS	31.2 (1.20)	31.4 (0.34)	≥30.7	5/35 (14)

WS = warmth sensitivity in °C; CS = cold sensitivity in °C.
Normal values: mean control value ±2SD.
★p<0.005, Sjögren *v* controls.

Table 4   Results of quantified sensory neurological examination in nine patients with abnormal results of the neurophysiological measurements

Duration (years)	Age (years)	WS★	CS★	VPT★	Neurophysiological results
3	47	33.6	31.2	**0.63**	Mild sensory
10	81	32.7	**30.6**	**1.18**	Mixed type
7	63	**35.2**	30.5	0.5	Mot. and sens. axonal
5	32	33.1	31.4	0.41	Areflexia
1	70	33	31	**0.86**	Mostly axonal
2	74	33.2	**28.5**	0.69	Mild, mostly sensory
1	34	32.7	31.9	0.42	Mild axonal
5	69	32.8	31.3	**1.32**	Mild
30	72	33.6	31.9	0.53	Axonal sens. mot.

★VPT = vibration perception threshold; WS = warmth sensitivity in °C; CS = cold sensitivity in °C.
Abnormal values in bold.

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peripheral nervous system was evaluated by electrophysiological tests and, excluding entrapment neuropathy, 15% of the patients exhibited abnormalities of the peripheral nervous system. As in our study no correlation could be found between the patients with or without neurological abnormalities and other disease manifestations.[27]

Several other studies on the peripheral nervous system have shown some degree of peripheral nerve involvement in primary SS, varying from 25% to 87%, depending on the method of patient selection.[1 19 20] Most other reports on peripheral nervous system in primary SS are case reports or very small series.[21–23]

A major drawback of most previous studies on the prevalence and the spectrum of peripheral neuropathy in primary SS is represented by the lack of universally accepted criteria for the diagnosis of primary SS.[4 5] In this study a well defined group of patients with primary SS was examined: all the patients of the present study fulfilled the European criteria and, moreover, at least one of the more objective diagnostic tests (salivary gland biopsy, sialography) and at least one serological parameter were positive.

Furthermore, all patients tested were primarily seen at an outpatient clinic for rheumatology. Patients selected from a department of neurology will of course present with neurological abnormalities.[28]

The higher frequency of subclinical abnormalities of the peripheral nervous system in this study may be explained by our more extensive investigation, in which quantified sensory testing was also carried out.

Earlier studies on peripheral neuropathy in diabetes mellitus concur with these results as an abnormal vibration sensation was found in 80% of the patients, whereas in only 15% of these patients were abnormalities in nerve conduction velocity found.[10] Moreover, VPT and thermoperception have been shown to be reliable techniques to monitor chemotherapy induced neuropathy.[11 12]

The results of this study show that extensive clinical examination—that is, quantified sensory testing of the peripheral nerves, is more sensitive than neurophysiological testing. However, the clinical significance of those abnormal test results in patients with primary SS is limited as they were unrelated to clinical neurological symptoms.

Recently, we described subclinical parasympathetic disturbances in 15% of the patients now tested.[8] In this study no relation was found between the results of the autonomic cardiovascular function tests and signs of polyneuropathy, as revealed by nerve conduction studies. Moreover, no relation could be shown between the cardiovascular function tests and the results of the quantitative sensory measurements. Studies on the peripheral and autonomic nervous system in diabetes mellitus did show a relation between those two entities, but this may be explained by finding a higher prevalence of autonomic neuropathy and peripheral neuropathy[29] in diabetes mellitus.

Summarising, subclinical quantitative sensory and mild neurophysiological abnormalities of the peripheral neurological system were found in respectively 58% and 23% of the patients with primary SS. However, it may be concluded that in patients with primary SS selected from a department of rheumatology clinically relevant involvement of the peripheral nervous system is rare and, therefore, routine neurophysiological examination is not indicated.

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