

Pure Sensory Neuropathy in Primary Sjögren's Syndrome. Longterm Prospective Followup and Review of the Literature

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ABSTRACT. Objective. To study the clinical course, response to therapy, and longterm outcome of pure sensory neuropathy (PSN) in a series of patients with primary Sjögren's syndrome (SS) followed prospectively in our referral centers.

Methods. We studied 15 patients (13 women, 2 men) with primary SS and PSN. All patients fulfilled 4 or more of the European diagnostic criteria.

Results. At diagnosis of PSN, clinical manifestations included numbness and paresthesias (11 patients), trigeminal neuropathy (6 patients), and Adie's pupil syndrome (4 patients). In 7 patients, PSN was diagnosed prior to SS, in 5 the diagnoses were made simultaneously, and in the remaining 3 patients PSN was diagnosed after the appearance of SS symptomatology. The mean duration of the prospective PSN followup was 10 years (range 1–20). The progression of PSN was acute in 1 patient (producing severe dysfunction in less than 1 month), subacute in 3 patients, and in the remaining 11, the symptoms progressed slowly over the ensuing years to other extremities. Patients were treated with corticosteroids ($n = 13$), cyclophosphamide ($n = 4$), and intravenous immunoglobulins ($n = 1$), and 2 patients received no treatment. In spite of treatment, most patients showed an indolent and insidious longterm PSN course.

Conclusion. We found 3 differentiated clinical courses of the PSN in patients with primary SS: subacute progression in less than 1 month (7%), late acceleration of PSN 2–4 years after an initial indolent onset (20%), and a very longterm insidious, chronic evolution (73%). Prospective analysis of the longterm course of PSN shows a chronic and insidious evolution in most patients with PSN and SS, with a poor response to treatment, although stabilization of symptomatology for long periods is often observed. (J Rheumatol 2003;30:1552–7)

Key Indexing Terms:

PURE SENSORY NEUROPATHY

PRIMARY SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and that usually presents as a persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands¹. In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary

SS. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the disease spectrum extends from an organ-specific autoimmune disease (autoimmune exocrinopathy)² to a systemic process (musculoskeletal, pulmonary, gastric, hematological, vascular, dermatological, renal, nervous system involvement, and lymphoproliferation)^{3–7}.

Neurological features are well documented in primary SS, and peripheral nervous system disease (including polyneuropathies, mononeuropathies or trigeminal neuropathy) is reported in 10–32% of patients^{8–10}. Pure sensory neuropathy (PSN) is recognized as a characteristic neurological complication of primary SS caused by damage of the sensory neurons of the dorsal root and gasserian ganglia^{11–13}. Clinically, PSN is characterized by asymmetrical sensory involvement, usually starting in the upper limbs and predominantly affecting kinesthetic and vibratory sensations. Some patients also have associated Adie's pupil or trigeminal sensory involvement. The diagnosis of PSN is important because, although it may precede that of primary SS, it is not associated with systemic vasculitis, and treat-

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ment with corticosteroids may be ineffective. The differential diagnosis of PSN includes paraneoplastic syndrome, tabes dorsalis, vitamin B12 or E deficiency, paraproteinemias, and acute idiopathic cases^{14,15}. There is very little information available on prospective longterm evolution of PSN in patients with primary SS. We analyzed the clinical course and longterm outcome of PSN in 15 patients with primary SS followed prospectively, and also exhaustively reviewed the literature focusing on the evolution of this specific neurologic manifestation of primary SS.

MATERIALS AND METHODS

We prospectively investigated the clinical course of PSN in 15 SS patients followed in our units. All patients fulfilled 4 or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993¹⁶. All patients underwent a complete history and examination, as well as diagnostic tests for SS applied according to the recommendations of the EC Study Group¹⁶. No patient presented clinical or immunologic evidence of other systemic autoimmune diseases, or clinical or analytical evidence of a prothrombotic state or associated infectious processes.

The study was coordinated by FG, who prospectively collected the cases from the different centers between 1980 and 1995. The patients entered the prospective protocol study when PSN was diagnosed. A prospective clinical evaluation was carried out at 6-month intervals. Grading of disease severity was evaluated by a modified Rankin scale¹⁵. All patients were diagnosed with PSN according to previous studies^{11,13}. Nerve conduction tests were performed at PSN diagnosis. 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 by the electrical stimulation of the supraorbital nerve. Other neurological disorders (such as central nervous system, medullary, or muscular processes) were ruled out by differential diagnosis and, when necessary, by EMG, nerve or muscle biopsy, cerebrospinal fluid analysis, measurement of somatosensory evoked potentials and neurological imaging technics.

Immunologic tests included antinuclear antibodies (ANA; indirect immunofluorescence using mouse liver as substrate), antibodies to double-stranded DNA(ds-DNA; determined by Farr technique), precipitating antibodies to the extractable nuclear antigens Ro/SSA and La/SSB (counterimmunoelectrophoresis), and rheumatoid factor (RF; by latex fixation and Waaler-Rose tests). Complement factors (C3 and C4) were estimated by nephelometry (Behring BNA nephelometer). Serum cryoglobulins were measured after centrifugation. Blood samples were obtained and kept at 37°C for 30 min before separation. Serum was prepared by centrifuging at 37°C for 10 min at 2500 rpm. Fresh centrifuged serum was incubated at 4°C for 7 days after collection, and examined for cryoprecipitation. The cryocrit was obtained by centrifuging at 2000 rpm (750 g) for 30 min at 4°C. The cryoprecipitate was diluted in warm saline for 1 h. Finally, cryoprecipitate was characterized by agarose gel electrophoresis and immunofixation.

RESULTS

Characteristics of SS patients. Of the 15 patients with PSN, 13 were women and 2 men. SS onset occurred between age

24 and 82 years (mean 52 yrs) and, at the time of study, the mean age of patients was 61 years (range 38–84). All patients presented xerostomia and 13 xerophthalmia. Positive ocular diagnostic tests (Schirmer's test and/or Rose Bengal staining) were positive in 13 patients, parotid scintigraphy was positive in 9, and labial minor salivary gland biopsy showed lymphocytic infiltrates (grade 3 or 4) in 11 patients. The most common extraglandular manifestations were thyroiditis in 5 patients, articular involvement in 3, Raynaud's phenomenon in 2, pulmonary involvement in 2, and cutaneous vasculitis in 1 patient. The most frequent immunologic features were positive ANA in 13 patients, anti-Ro/SSA in 10, RF in 4, and anti-La/SSB in 2. No patient had a positive test for anti-dsDNA or anti-Sm antibodies.

Neurological description at PSN diagnosis. Neurological manifestations at PSN diagnosis are summarized in Table 1. Neurological abnormalities in all patients were characterized by loss of proprioceptive and kinesthetic sensibility. The onset of neurological symptoms was asymmetrical and insidious. Clinical manifestations included numbness and paresthesias (11 patients), trigeminal neuropathy (6 patients), and Adie's pupil (4 patients). Severe involvement of the upper extremities was associated with pseudoathetosis and loss of spatial discrimination. We also analyzed the temporal relationship between SS and PSN onset. PSN was diagnosed prior to SS in 7 patients, and neuropathic symptoms preceded sicca symptoms by a median interval of 3.5 years (range 1–8 yrs). In 5 patients, both diagnoses were made simultaneously. In the remaining 3 patients, PSN was diagnosed posterior to SS symptomatology, and sicca symptoms preceded neuropathic symptoms by a median interval of 5.2 years (range 1–10 yrs).

The results of the EMG examination were homogeneous. 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 reflexes and T waves were absent in all patients. Most of the neurographic tests of sensory nerves showed abnormal results, often with absent responses. 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 all patients.

Longterm prospective followup. The mean duration of prospective PSN followup was 10 years, with a minimum of 1 year and a maximum of 20. We identified 3 differentiated clinical courses according to the rate of PSN progression.

Subacute progression of PSN in less than 1 month was observed in one patient (7%). Patient 7, a 75-year-old man, was diagnosed with primary SS one year previously. He developed moderate involvement of the lower and upper extremities, with paresthesia and impairment of joint position and vibratory senses. In spite of high doses of corticosteroids,

Table 1. Neurological manifestations and followup of pure sensory neuropathy (PSN) in 15 patients with primary SS.

Patient	Sex	Age of PSN Diagnosis, yrs	Age of SS Diagnosis, yrs	PSN Onset	PSN Features at Diagnosis	Treatment	Prospective followup, yrs	PSN Course
1	F	34	24	Indolent	AP, SALE	Oral Pred (< 0.5 mg/kg/day) Oral CYC	15 years	Insidious and chronic
2	F	32	40	Indolent	AP, SAUE	Oral Pred (< 0.5 mg/kg/day)	20 years	Insidious and chronic
3	F	28	33	Indolent	AP, SAUE, SALE	—	18 years	Insidious and chronic
4	F	65	65	Indolent	TN	Oral Pred (1 mg/kg/day) Pulsed CYC	11 years	Initial insidious course Late progression at 4th year (SAUE) Very slow progression after therapy
5	F	63	58	Indolent	SAUE	Oral Pred (< 0.5 mg/kg/day) Oral CYC	5 years	Insidious and chronic
6	F	75	76	Indolent	TN, SAUE	Oral Pred (< 0.5 mg/kg/day)	2 years (miss)	Insidious and chronic
7	M	75	74	Subacute	SAUE, SALE	Oral Pred (1 mg/kg/day) Pulsed CYC	1 year (death)	Continued progression
8	F	58	59	Indolent	TN	Oral Pred (< 0.5 mg/kg/day)	5 years	Insidious and chronic
9	M	56	60	Indolent	SALE	Oral Pred (1 mg/kg/day) Immunoglobulins IV	5 years	Initial insidious course Late progression at 4th year (SAUE) Improvement after therapy
10	F	40	44	Indolent	AP, TN, SALE	Oral Pred (1 mg/kg/day) IVmethylprednisolone	11 years	Initial insidious course Late progression at 2nd year (SAUE) Very slow progression after therapy
11	F	57	57	Indolent	SAUE, SALE	Oral Pred (1 mg/kg/day)	5 years	Insidious and chronic
12	F	82	82	Indolent	SALE	—	2 years (death)	Insidious and chronic
13	F	31	33	Indolent	SAUE	Oral Pred (< 0.5 mg/kg/day)	7 years	Insidious and chronic
14	F	36	36	Indolent	TN	Oral Pred (< 0.5 mg/kg/day)	6 years	Insidious and chronic
15	F	58	58	Indolent	TN	Oral Pred (< 0.5 mg/kg/day)	8 years	Insidious and chronic

SS: Sjögren's syndrome, PSN: pure sensory neuropathy, AP: Adie's pupil, SALE: sensory alteration in lower extremities, SAUE: sensory alteration in upper extremities, TN: trigeminal neuropathy, Pred: prednisone, CYC: cyclophosphamide.

teroids and intravenous pulses of cyclophosphamide, neuropathic symptoms progressed rapidly, producing severe dysfunction in less than 1 month. He died 1 year later due to acute myocardial infarction.

In 3 (20%) patients, we observed an initial quiescent phase lasting 2 to 4 years, followed by progressively more severe symptomatology (late acceleration of PSN progression). In Patient 4, there was progressive involvement of the upper extremities 4 years after an initial onset consistent with trigeminal neuropathy. Treatment with corticosteroids and intravenous pulses of cyclophosphamide stabilized her symptomatology, and both neurological manifestations progressed more slowly during the remainder of the followup. Patient 9 initially developed mild paresthesiae and numbness in the feet. Four years later, these symptoms began to worsen, ascending to the thighs, and with the development of a progressive loss of dexterity in both hands, leaving the patient unable to walk without a cane. Treatment with intravenous immunoglobulin and high doses of corticosteroids was started, which resulted in a clinical improvement maintained to the present day. Finally, Patient 10 developed moderate involvement of her upper extremities 2 years after an initial onset consistent with Adie's pupil,

trigeminal neuropathy, and paresthesiae in the feet. In spite of high doses of oral and intravenous corticosteroids, she suffered a very slow progression of PSN during the remainder of the prospective followup.

In the remaining 11 patients (73%), PSN showed a chronic and insidious longterm evolution. In these patients, the main impairment was usually the proprioceptive defect present in the extremities affected at the onset of the neuropathy. Nine patients were treated with oral corticosteroids (0.5–1 mg/kg/day), and oral cyclophosphamide was added in 2 cases. Neurological symptoms remained stable during the entire followup, with mild or moderate involvement. In 3 patients, the prospective followup was very longterm (more than 15 years), with an indolent and insidious evolution.

DISCUSSION

The natural course of PSN in patients with primary SS is not well known, due to the absence of prospective and longterm analyses. This series describes the prospective longterm evolution of PSN in 15 patients with well defined primary SS (an initial description of some patients was published^{11,13,17}). At onset of the neuropathy the sensory

involvement may be unilateral and mimic lesions in the spinal cord or thalamus. In this setting, magnetic resonance studies and the EMG evaluation will identify the peripheral cause of the sensory deficit. This sensory neuropathy is very similar to that observed from other causes such as high dose vitamin B6 or paraneoplasia, or idiopathic¹⁸. However, the absence of anti-Hu antibodies, a marker of paraneoplastic sensory neuropathy¹⁹, and the presence of Adie's pupil syndrome or trigeminal sensory neuropathy should raise the possibility of underlying SS. In addition, other causes of autonomic neuropathy with sicca symptoms, mainly diabetes, should be considered in the differential diagnosis.

Three important points have emerged from this study: the specific clinical and immunologic SS characteristics, the differentiated patterns of PSN evolution, and a common poor response to treatment. In this study, PSN was diagnosed before primary SS in 7 of the 15 patients, as reported by various authors^{12,20-23}. Table 2 summarizes the main SS-related clinical features in patients with PSN reported by other authors^{8,10,20-34}. Of these patients, 54 (92%) were women, with a mean age of 56 years (range 21–76). Xerostomia was observed in 84% of patients and xerophthalmia in 78%. Ocular tests were positive in 85% of patients and salivary gland biopsy was positive in 83%. Positive immunological markers were frequently found; ANA were positive in almost 80% of patients and anti-Ro/SSA antibodies in 50% of patients. We have confirmed these figures, finding positive immunological markers in 13 of 15 patients with PSN, with a predominance of positive ANA and anti-Ro/SSA antibodies. In the study by Griffin, *et al*²⁴, patients also showed a high frequency of autoantibodies (ANA in 12 cases and antibodies to Ro/SSA in 4). Although the role of Ro/SSA and La/SSB antibodies in the pathogenesis of the sensory neuropathy is unknown, the high incidence of positive ANA and anti-Ro/SSA antibodies

suggests that they may be helpful in the diagnosis of patients with sensory neuropathy of unclear origin. It seems that PSN may be an infrequent neurological manifestation of primary SS. No studies have analyzed the prevalence of PSN in primary SS. However, of the 400 SS patients followed in our department³⁵, 29 (7%) presented peripheral neuropathy, of whom only 8 (2%) presented PSN. Thus, it seems that PSN may occur in less than 5% of patients with primary SS.

Second, we have described 3 differentiated clinical courses: subacute progression in less than 1 month (7%), late acceleration of PSN 2–4 years after an initial indolent onset (20%), and a very longterm, insidious, chronic evolution (73%), including some patients with very longterm indolent evolution of more than 15 years of prospective followup in spite of treatment. Previous studies have also described the predominance of this chronic course, although most were retrospective and with a short period of followup (Table 3). In one series²⁴ the initial progression was indolent in 8 patients, subacute in 2, and acute in 3, with a mean duration of PSN followup of 3.5 years (ranging from 5 months to 15 years). Other authors³⁶ describe a chronic, indolent evolution in 5 patients with PSN, with a mean duration of PSN followup of 2.5 years (ranging from 3 months to 6 years). Nevertheless, the small number of SS patients with PSN reported does not allow the definition of a well differentiated clinical and immunologic pattern of disease expression, but only the different rate of PSN progression.

Finally, the third interesting point is the role of therapy in PSN. In our prospective followup, 1 patient (7%) showed a continued progression, 2 (13%) showed a very slow progression after treatment, 11 (73%) an insidious and chronic PSN course in spite of treatment, and only 1 patient (7%) showed a clinical improvement of PSN after therapy. Table 3 summarizes the clinical course and response to treat-

Table 2. Epidemiological, clinical, and immunological features of primary SS in patients with PSN: previous studies.

Author	Patients	Sex Female	Mean age, yrs	Xerophthalmia	Xerostomia	Ocular Tests	Lip Biopsy	ANA	Ro/SSA	La/SSB	RF
Griffin ²⁴	13	11	54	9	10	13	12	12	4	0	4
Satake ²⁵	1	1	59	1	1	1	1	1	1	1	1
Moll ²⁶	1	1	73	ND	ND	ND	ND	1	0	0	ND
Alexander ⁸	5	5	49	5	5	5	5	ND	ND	ND	ND
Kaplan ²⁷	2	2	38	2	2	1	2	1	1	1	2
Oobayashi ²⁸	1	1	49	1	1	ND	1	1	1	ND	1
Kennett ²⁰	3	3	55	2	2	3	3	2	1	1	2
Peyronnard ¹⁰	1	1	66	1	1	1	1	ND	ND	ND	1
Gemignani ²⁹	5	5	58	3	3	ND	ND	3	2	ND	3
Kachi ³⁰	3	3	67	3	3	ND	ND	ND	ND	ND	ND
Hankey ²¹	1	1	64	1	1	ND	ND	1	ND	ND	ND
McCombe ³¹	1	—	38	1	1	1	—	0	0	0	0
Kumazawa ³²	2	2	67	1	2	—	2	ND	2	0	ND
Pascual ³³	1	1	66	1	1	1	ND	1	1	1	ND
Asahina ³⁴	2	2	48	1	1	2	2	1	2	0	1
Present series	15	13	61	13	15	13	11	13	10	2	4
Total (%)	59	54 (92)	56	45/58 (78)	49/58 (84)	41/48 (85)	40/48 (83)	37/48 (77)	25/49 (51)	6/43 (14)	19/46 (41)

Table 3. Neurological manifestations and followup of the pure sensory neuropathy in patients with primary SS and PSN previously published.

Author	Patient	Sex	PSN Onset	Treatment	Followup	PSN Course
Griffin ²⁴	1	F	Subacute	Oral pred	15 yrs	Progression for 4 yrs and stabilization
	2	F	Acute	AZA	5 mo	Stabilization after 4 mo
	3	F	Indolent	Oral pred, AZA	4 yrs	Continued progression
	4	F	Indolent	Pred, pulsed CYC	3.5 yrs	Continued progression at a slowed rate
	5	F	Indolent	Pred, CYC	6 yrs	Continued progression
	6	F	Indolent	Pred, plasma exchange	1.5 yrs	Stabilization
	7	F	Indolent	None	1 yr	Continued progression
	8	F	Indolent	Oral pred	2.5 yrs	Stabilization
	9	F	Indolent	Pred, Leukeran	4 yrs	Continued progression
	10	M	Indolent	Cytosan, pred	2 yrs	Progression
	11	F	Acute	None	7 mo	Spontaneous stabilization
	12	F	Subacute	Oral pred IVmethylprednisolone, AZA	2 yrs	Improvement after therapy
	13	M	Acute	None	1 yr	Limited progression
Gemignani ²⁹	1	F	—	Pred	1 yr	Slight improvement
	2	F	—	Deflazacort, hydroxychloroquine	3 mo	Stabilization
	3	F	—	None	6 yrs	Spontaneous stabilization
	8	F	—	Pred, AZA	2.5 yrs	Stabilization
	9	F	—	Pred, pulsed CYC	3 yrs	Slight improvement

ment in 18 patients from previous studies with well documented followup. In spite of treatment (mainly corticosteroids), only 1 (6%) showed clinical improvement, while 2 patients (11%) showed slight improvement after treatment, 7 (39%) showed a stabilization of their symptomatology, 2 (11%) showed a limited progression with later stabilization, and the remaining 6 (33%) showed a continued progression. Various treatment regimes were tried at different stages of the disease in a series of 13 SS patients with PSN²⁴. A clear and prompt response could be identified in only 1 patient, while in another patient, cessation of progression and functional improvement occurred in the absence of any drug therapy. However, some authors have obtained a good treatment response in patients with SS and PSN using plasmapheresis³⁷, D-penicillamine³⁴, or intravenous immunoglobulins^{31,33}.

In conclusion, pure sensory neuropathy typically may affect some patients with primary SS, with a high prevalence of positive immunological markers (ANA and anti-Ro/SSA) and frequently as the first manifestation of a latent primary SS. We have described 3 differentiated clinical courses: subacute progression of PSN in less than 1 month (7%), late acceleration of PSN some years after an initial indolent onset (20%), and a very longterm insidious, chronic evolution (73%). The longterm course of PSN is chronic and insidious in most patients, with a poor response to treatment with corticosteroids or immunosuppressive agents, although stabilization of symptomatology (spontaneously or after treatment) during very long periods is often observed.

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