Mod Rheumatol (2003) 13:160–167 

ORIGINAL ARTICLE

**Yusuke Miwa · Shigeko Inokuma · Yoshimi Yokoe**
**Yuko Okazaki · Takeo Sato · Reika Maezawa**

# Peripheral nervous system involvement complicated due to vasculitis in cases of primary Sjögren's syndrome: case studies in a single hospital and a literature review

Received: May 11, 2002 / Accepted: October 2, 2002

**Abstract** To determine the background features of peripheral nervous system (PNS) involvement in cases of primary Sjögren's syndrome (SS), we studied the nervous system involvement, mainly that of PNS, in patients with primary SS who were admitted to our hospital during a period of 19 years. Nine of 82 admitted patients with primary SS had PNS involvement and 12 had central nervous system (CNS) involvement. Among 182 secondary SS patients, 25 had CNS involvement, and none had PNS involvement. The nine patients with PNS involvement were older and their disease duration was shorter than those with CNS involvement and either primary or secondary SS. Four patients exhibiting active progression of PNS involvement had concomitant vasculopathy clinically that was confirmed by nerve or skin biopsy examination, with an increase in the serum C-reactive protein level. According to the literature, among 17 reported SS patients with PNS involvement, 13 had primary SS, and 13 had vasculitis as confirmed by biopsy examination. Nervous system involvement in cases of SS is not rare. PNS involvement was observed mostly in elderly patients with primary SS, and its active progression was concomitant with vasculopathy.

**Key words** Peripheral nervous system (PNS) involvement · Primary Sjögren's syndrome (SS) · Vasculopathy

Y. Miwa[1] (✉) · S. Inokuma · Y. Yokoe · Y. Okazaki · T. Sato · R. Maezawa
Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

*Present address:*
[1]The First Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
Tel. +81-3-3784-8532; Fax +81-3-3784-8742
e-mail: y-miwa@mbf.ocn.ne.jp

## Introduction

Primary Sjögren's syndrome (primary SS) is a chronic systemic disease that primarily and principally affects exocrine glands. It can also involve other organ systems, including the central and peripheral nervous systems (CNS and PNS, respectively), as an extraglandular manifestation.[1] Recent studies have revealed a much higher incidence, 10% to 50%,[2] of nervous system, involvement than previously supposed. Among these patients, concomitant manifestations of vasculitis were frequently observed.[3–5] However, the spectrum of clinical features including the type of disturbance and presence of inflammatory vascular diseases (IVDs) has remained controversial. Thus far, few studies have focused on these issues affecting a large group of patients.

IVDs are also increasingly recognized as a complication of primary SS, occurring in approximately 33% of patients with primary SS.[3] The most common clinically observable IVD in cases of primary SS is cutaneous vasculitis, presenting most frequently as purpuric or urticarial skin lesions.

We have recently treated four primary SS patients exhibiting active PNS involvement during their hospitalization; they had vasculitis as confirmed by biopsy examination. Thus, we studied all the admitted patients with primary and secondary SS in our hospital during a period of 19 years, regarding PNS involvement and IVDs as a complication, as well as other clinical and laboratory features. The incidence of CNS involvement was also studied. We also reviewed the literature, focusing on the relationship of vasculopathy with PNS involvement.

## Patients and methods

Eighty-two patients with primary SS and 182 patients with secondary SS, among a total of 2174 inpatients of Tokyo Metropolitan Komagome Hospital from 1981 to 1999 with rheumatic and allergic diseases, were retrospectively

studied regarding PNS and CNS involvement. The diagnosis of primary SS was based on the criteria established by the Japanese Ministry of Health and Welfare (1977).[6] Secondary SS has the same definition as that of primary SS except that the former is complicated with other rheumatic diseases.

CNS involvement included signs and symptoms that have been known to complicate SS.[4,7–9] Cerebrospinal fluid analysis, electroencephalography, single-photon emission computed tomography, computed tomography, and magnetic resonance imaging of the brain performed in most patients were used in the diagnosis.

PNS involvement was diagnosed in patients presenting neural pain and/or paresthesia, palsy, and muscle weakness without features of myogenic diseases or other obvious causes, based on physical neurological examination. Electromyography (EMG) or the nerve conduction velocity test was conducted, and if the disease was suspected to be active, sural nerve biopsy was performed, if possible. When an active cutaneous manifestation was observed, skin biopsy was performed.

The laboratory findings obtained are listed in Table 1.

Statistical analyses were conducted using Welch's *t* test, Student's *t* test, and Fisher's exact probability test.

Among the nine patients with primary SS complicated with peripheral neuropathy, four had severe symptoms that developed acutely before their admission; their clinical courses are described next.

The literature from 1969 to 2000 was searched through Medline, using SS, PNS involvement, and mononeuritis multiplex as key words. Because the most commonly reported PNS involvement in patients with SS in the literature was mononeuritis multiplex, relevant data on these cases are listed in Table 2.

## Case reports

### Patient 1

A 70-year-old woman had been thought to have polymyalgia rheumatica because of severe myalgia 1 year previously when SS was diagnosed. She had a fever of 38°C, and paresthesia in her fingers bilaterally and toes of the right foot. Physical examination revealed edema and livedo reticularis in her lower legs, mottled cyanosis on the soles and heels, paresthesia in the fingers bilaterally and toes of the right foot, and right peroneal nerve palsy. Laboratory findings are listed in Table 1, together with those of patients 2 to 4. Antineutrophil cytoplasmic antibody (ANCA) was not measured. EMG revealed a high amplitude neuromuscular unit (NMU) voltage in the deltoid nerve, and the motor nerve conduction velocity test revealed low amplitude in the left median nerve. Her right sural nerve biopsy revealed demyelination and fiber loss in the medullated nerve, perivascular infiltration of lymphocytes and mononuclear cells in small epineural arterioles and capillaries, and destruction of the vessel wall and occlusion of the lumen (Fig. 1). Mononeuritis multiplex was the diagnosis. Oral administration of prednisolone (0.8 mg/kg body weight/day) treated her paresthesia, edema, and livedo reticularis but partial palsy in the right foot remained. Subsequent laboratory tests revealed normal findings.

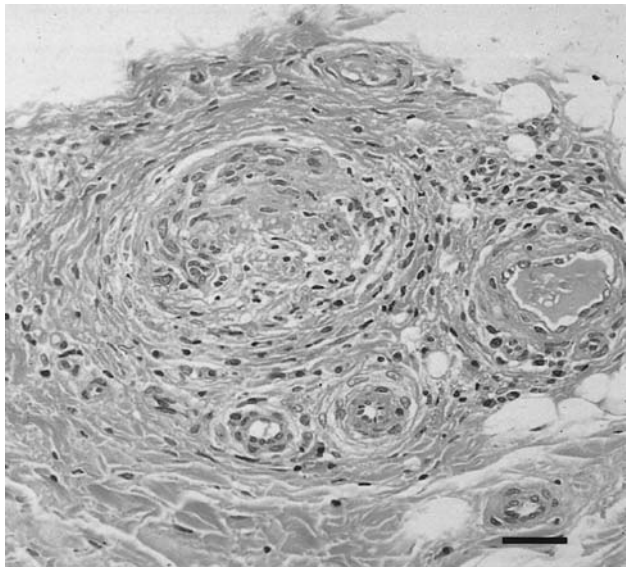

**Fig. 1.** Micrograph of biopsied sural nerve (patient 1): Demyelination, perivascular infiltration of lymphocytes and mononuclear cells in small epineural arterioles and capillaries, and destruction of vessel wall and occlusion of vessel lumen. H&E stain, ×25. *Bar* 400 μm

### Patient 2

A 56-year-old woman had a history of severe abdominal pain, but emergency laparotomy found no gross abnormality. Severe scattered exanthema with petechiae and pigmentation recurrently appeared on her lower legs. Fever, paresthesia in the legs, pain of the left arm, and severe myalgia in the lower limbs developed. She then experienced intermittent transient migratory palsy in her arms and legs. ANCA was not measured; the creatinine phosphokinase level was not elevated, but hepatitis C infection and cryoglobulin were detected. In EMG of the left tibialis muscle, a low-amplitude NMU voltage of short duration was prominent; the nerve conduction velocity test was not performed. The skin biopsy revealed vasculitis with perivascular and extravascular infiltration of neutrophil, eosinophil, and mononuclear cells in the wall of small arterioles with leukocytoclasis (Fig. 2). Mononeuritis multiplex and SS were the diagnoses after her admission. These clinical features improved soon after the treatment with repeated plasma exchange and oral administration of cyclophosphamide. However, paresthesia in the feet remained.

### Patient 3

A 75-year-old woman had a 3-year history of recurrent polyarthritis, finger edema, and exanthema and livedo reticularis in both legs. She had a fever of 38°C and severe

**Table 1.** Clinical features and laboratory findings of the nine patients with peripheral nervous system involvement associated with primary Sjögren's syndrome

| Patient | Age/ sex | Disease duration of PNS (months)[a] | Biopsy/ vasculitis | Neurological diagnosis | Skin manifestation | WBC ($10^9$/l) | ESR (mm/h) | CRP (mg/dl) | $\beta_2$-Mg (mg/l) | IgG (mg/dl) | Anti-SS-A/Ro (titer) | Anti-SS-B/La (titer) | ANCA (EU) | Cryoglobulin | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 70/F | 0 | Nerve/+ | MNM | Livedo, purpura, pigmentation, edema | 11.90 | 73 | 3.5 | 7.9 | 2717 | Negative | Negative | NA | NA | PSL | PR |
| 2 | 56/F | −2 | Skin/+ | MNM | Purpura, pigmentation | 3.10 | 134 | 11.1 | 4.7 | 2697 | 1 : 512 | 1 : 64 | NA | Positive | PP, CY | PR |
| 3 | 75/F | 0 | Nerve/+[b] | MNM | Livedo, purpura, exanthema | 14.40 | 143 | 20.9 | 5.1 | 2900 | Negative | Negative | 117 | Negative | p-MPSL, PSL | PR |
| 4 | 70/F | −1 | Nerve/+ | MNM | Livedo, pigmentation | 15.70 | 131 | 24.2 | 8.2 | 2870 | Negative | Negative | 225 | Negative | p-Betamethasone | PR |
| 5 | 36/F | 36 | Nerve/−[c] | Nervous system involvement with glove and stocking distribution | Raynaud's phenomenon | 8.80 | 7 | 0.2 | NA | 1718 | 1 : 16 | Negative | NA | NA | PSL | NC |
| 6 | 65/F | 11 | NA | Polyneuropathy | Pigmentation | 4.60 | 15 | 0.2 | 1.6 | 1806 | Negative | Negative | NA | NA | PSL | NC |
| 7 | 60/F | 21 | Nerve/+ | MNM | NA | 3.60 | 18 | 0.1 | 0.3 | 1224 | Negative | Negative | NA | NA | NSAID | NC |
| 8 | 31/F | −1 | NA | Small fiber neuropathy | Palmar erythema | 9.40 | 13 | 0.4 | 1.9 | 1700 | 1 : 32 | Negative | NA | NA | p-MPSL, PSL | NC |
| 9 | 42/F | −1 | NA | Adie's syndrome | Livedo | 4.00 | 76 | 4.4 | 2.7 | 4480 | 1 : 128 | Negative | NA | NA | PSL, AZP | NC |

PNS, peripheral nervous system involvement; MNM, mononeuritis multiplex; NA, not available; WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; ANCA, antineutrophil cytoplasmic autoantibodies; $\beta_2$-Mg, $\beta_2$-microglobulin (normal ranges are 4.0–8.0 × 109/l for WBC, 3–15 mm/h for ESR, 0–0.3 mg/dl for CRP, 0.8–1.7 mg/dl for $\beta_2$-Mg, 871–2007 mg/dl for IgG); PSL, prednisolone; PP, plasmapheresis, CY, cyclophosphamide; p-, pulsed; MPSL, methylprednisolone; AZP, azathioprine; PR, partial remission; NC, no change

[a] After appearance of subjective sicca

[b] Ischemic change suggestive of vasculitis

[c] Only defluvium of advanced medullated nerve was observed

**Table 2.** Mononeuritis multiplex associated with Sjögren's syndrome reported in the literature

| Patient | Reference | Year | Age/sex | Sjögren's syndrome | Biopsy/ vasculitis | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Kaltreider and Talal[10] | 1969 | 41/F | Primary | Muscle/+ | NA | NA |
| 2 | | | 52/F | Primary | Muscle/+ | PSL | NA |
| 3 | Massey[11] | 1980 | 54/F | NA | NA | NA | NA |
| 4 | Drosos et al.[12] | 1989 | NA/F | Primary | NA | NA | NA |
| 5 | Tanaka et al.[13] | 1989 | 32/F | NA | Nerve/+ | p-MPSL, CY | PR |
| 6 | Andonopoulas et al.[14] | 1989 | NA/F | Primary | Skin/+ | PSL, CY | PR |
| 7 | Andonopoulas et al.[15] | 1990 | NA/F | Primary | Skin/+ | NA | NA |
| 8 | Kumazawa et al.[16] | 1993 | 63/F | Primary | Skin/+ | NA | NA |
| 9 | | | 67/F | NA | Skin/+ | NA | NA |
| 10 | | | 67/F | NA | Nerve/+ | NA | NA |
| 11 | | | 57/F | Primary | Nerve/+ | NA | NA |
| 12 | | | 77/F | Primary | Nerve/+ | NA | NA |
| 13 | Yamanishi et al.[17] | 1994 | 36/F | Primary | Nerve/+ | PSL, p-MPSL, PP | PR |
| 14 | Hebbar[2] | 1995 | 41/F | Primary | NA | PSL | PR |
| 15 | | | 52/F | Primary | Skin/+ | PSL, p-MPSL, PP | PR |
| 16 | | | 45/F | Primary | Skin/+ | PSL, p-MPSL, IVIG, PP | PR |
| 17 | Tajima et al.[18] | 1997 | 51/F | Primary | Nerve/− | PSL | PR |
| 18 | Miwa et al. (this study) | | 70/F | Primary | Nerve/+ | PSL | PR |
| 19 | | | 56/F | Primary | Skin/+ | PP, CY | PR |
| 20 | | | 75/F | Primary | Nerve/+ | p-MPSL, PSL | PR |
| 21 | | | 70/F | Primary | Nerve/+ | p-Betamethasone | PR |
| 22 | | | 60/F | Primary | Nerve/+ | NSAID | NC |

NA, not available; PSL, prednisolone; p-MPSL, pulsed methylprednisolone; IVIG, intravenous injection immunoglobulin; PP, plasmapheresis; CY, cyclophosphamide; PR, partial remission; NC, no change

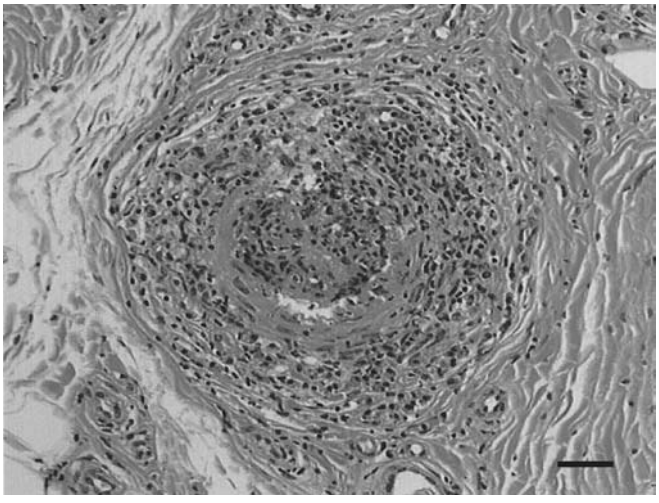

**Fig. 2.** Micrograph of biopsied skin of lower leg (patient 2): leukocytoclastic vasculitis with perivascular and extravascular infiltration of neutrophil, eosinophil, and mononuclear cells in the wall of small arterioles with leukocytoclasis. H&E stain, ×25. *Bar* 400 μm

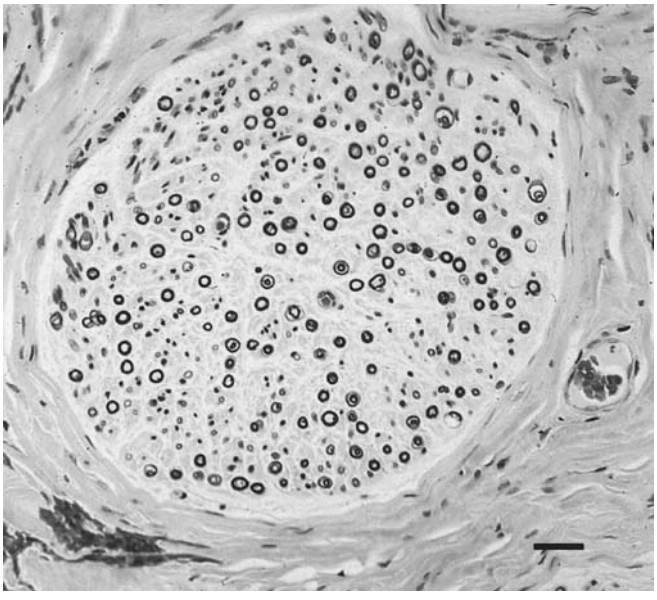

**Fig. 3.** Micrograph of biopsied sural nerve (patient 3): demyelination, Wallerian degeneration, and multifocal fiber loss in fasciculus, suggestive of ischemic neuropathy caused by vasculitis, although vessels were not included in the specimen. Klüver–Barrera stain, ×100. *Bar* 100 μm

myalgia in her thighs 1 month before admission. One week later, paresthesia in her right hand developed, and she became unable to walk due to a left drop foot. The serum myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) level was 117 enzyme-linked immunosorbent assay units (EU; normal range, 0–10 EU). Her lip biopsy revealed much lymphocyte invasion. EMG revealed polyphonic NMU voltage in the left tibial nerve, and the nerve conduction velocity test revealed low amplitude in the left median nerve, left tibial nerve, and left peroneal nerve. The left sural nerve biopsy revealed demyelination, Wallerian degeneration, and multifocal fiber loss in the fasciculus, suggestive of ischemic neuropathy caused by vasculitis, although vessels were not included in the specimen (Fig. 3). Mononeuritis multiplex, involving the left peroneal nerve and left ulnar and left median nerves, was the diagnosis. Three courses of methylprednisolone pulse therapy (one course of 1000 mg/day for 3 days) and oral administration of prednisolone (1.2 mg/kg body weight/day) were ad-

ministered. Palsy and paresthesia initially remained in her left leg, but ceased to progress further and then improved. Subsequent laboratory tests revealed improved findings.

### Patient 4

A 70-year-old woman had a history of interstitial pneumonia and pure red cell aplasia. She experienced hypesthesia initially in the left foot. Hypesthesia, hyperalgesia, and livedo reticularis in both lower legs were observed. The serum MPO-ANCA level was 225 EU. Her lip biopsy revealed much lymphocyte invasion. EMG was not conducted, but the nerve conduction velocity test revealed a decrease in velocity and low amplitude in the left tibial nerve and peroneal nerve. The left sural nerve biopsy revealed demyelination and elimination of axons, necrotizing vasculitis with perivascular inflammation of lymphocytes and plasma cells in small epineural arterioles and capillaries, and destruction of the vessel wall and occlusion of the vessel lumen (Fig. 4). Mononeuritis multiplex was the diagnosis. One course of betamethasone pulse therapy (100 mg/day for 3 days) was followed by oral administration of betamethasone (0.34 mg/kg body weight/day). Her condition and laboratory data improved, but partial palsy in the left foot remained.

### Prevalence of PNS and CNS involvement in SS, and background features of SS patients with such involvement, in our hospital

Among 82 patients with primary SS, 74 were women and 8 were men; 9 had PNS involvement and 12 had CNS involvement (Table 3); the prevalences of PNS and CNS involvement did not differ significantly. Manifestations of CNS involvement observed in 12 patients with primary SS included aseptic meningitis in 2 patients, pachymeningitis in 1, organic brain syndrome in 4, and headache in 1.

Among 182 patients with secondary SS, 168 were women and 14 were men; 25 had CNS involvement and none had PNS involvement. Furthermore, among 25 patients with secondary SS and CNS involvement, 18 had systemic lupus erythematosus.

The prevalence of PNS involvement was significantly higher among patients with primary SS, but that prevalence of CNS involvement did not differ between patients with primary SS and those with secondary SS. The nine patients with primary SS complicated with PNS involvement were significantly older than those with secondary SS complicated with CNS involvement ($P = 0.042$), and also older, although not significantly, than those with primary SS complicated with CNS involvement ($P = 0.107$). Their ages did not differ from those of patients with primary SS without either nervous system involvement ($P = 0.619$). They had shorter disease duration than other patient groups, although not significantly ($P = 0.230$ versus those with primary SS complicated with CNS involvement; $P = 0.310$ versus those with secondary SS complicated with CNS involvement). The mean age and disease duration did not differ between both patient groups with CNS involvement ($P = 0.865$ and $P = 0.961$, respectively).

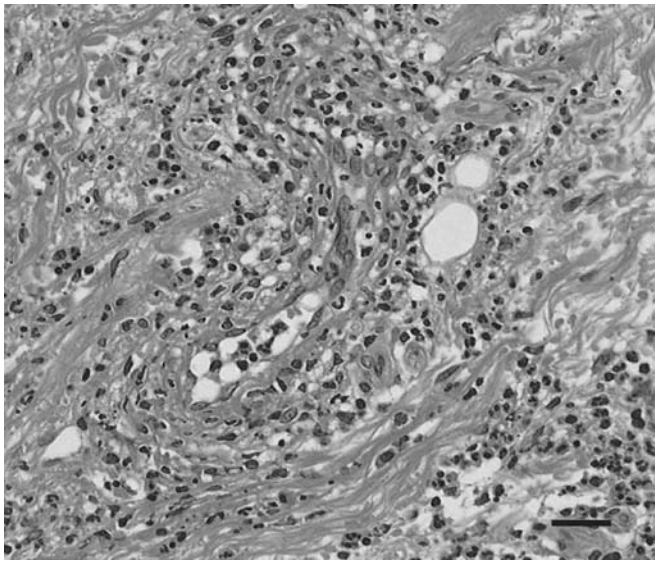

**Fig. 4.** Micrograph of biopsied sural nerve (patient 4): necrotizing vasculitis with perivascular inflammation of lymphocytes and plasma cells in small epineural arterioles and capillaries, and destruction of vessel wall and occlusion of vessel lumen. H&E stain, ×50. *Bar* 200 μm

**Table 3.** Background features of patients with peripheral and central nervous system involvement associated with primary and secondary Sjögren's syndrome (SS)

| | Primary SS ($n = 82$) | | Secondary SS ($n = 182$) |
|---|---|---|---|
| | With PNS | With CNS | With CNS |
| *n* | 9* | 12 | 25 |
| Sex (male/female) | 0/9 | 1/11 | 0/25 |
| Age (mean ± SD, years) | 56.2 ± 16.1** (with MNM: 66.2 ± 7.9, $n = 5$) | 44.4 ± 15.3 | 44.1 ± 14.1 |
| Disease duration (mean ± SD, months) | 7.1 ± 13.3 | 15.7 ± 23.8 | 18.1 ± 36.1 |
| Extraglandular manifestation (*n*) | 8*** | 2 | / |
| Vasculitis (confirmed by biopsy) | 5**** | 0 | / |

PNS, peripheral nervous system involvement; CNS, central nervous system involvement; MNM, mononeuritis multiplex
* $P = 0.001$ versus secondary SS; ** $P = 0.042$ versus secondary SS with CNS; *** $P = 0.002$ versus primary SS with CNS; **** $P = 0.006$ versus primary SS with CNS

### Features of primary SS patients with PNS involvement

Among five of nine primary SS patients with PNS involvement other than the four already described, patient 5 had a mild PNS involvement of the glove and stocking distribution, patient 6 had polyneuropathy, patient 7 had mononeuritis multiplex, patient 8 experienced neuropathy caused by small fiber neuropathy, and patient 9 had Adie's syndrome (see Table 1). The neuropathies in these five patients had developed before their admission and were thought to have been inactive. All the nine patients with primary SS complicated with PNS involvement had had at least one of the following generalized manifestations or extraglandular involvement: fever (patients 2, 3, and 4), arthritis (patients 6 and 8), Raynaud's phenomenon (patient 5), edema (patients 2, 3, and 6), alopecia (patient 3), purpura (patients 1, 2, and 3), ecchymosis (patient 6), and livedo reticularis (patients 1, 3, and 6). All the four SS patients with active PNS involvement had clinically concomitant vasculopathy in the skin, and pathologically in three nerve biopsy specimens and in one skin specimen. Inflammatory reactants and immunoglobulin G levels increased only in patients in the active phase of PNS involvement, except that patient 9 had elevated levels with the development of pulmonary disturbance (see Table 1). The serum $\beta_2$-microglobulin levels increased in all four patients exhibiting active PNS involvement, without a concomitant increase in the serum creatinine level. The mean age of the five patients with mononeuritis multiplex was $66.2 \pm 7.9$ years.

## Discussion

### Difference in PNS between primary and secondary SS

Primary SS principally affects the exocrine organ system but may involve the PNS. Patients with PNS involvement often have palsy, adversely affecting their daily activities and quality of life. The aim of this study was to determine the prevalence and clinical features of primary SS patients complicated with PNS involvement, and whether any common characteristic features underlie it.

This study showed a high prevalence of nervous system involvement in patients with primary or secondary SS in a single hospital. CNS involvement was observed at almost the same prevalence of about 14% in patients with primary or secondary SS. In contrast, PNS involvement developed only in patients with primary SS at a prevalence of 11%; it was not observed in 182 patients with secondary SS. The most common form of PNS involvement was mononeuritis multiplex. All four patients who exhibited active progression of mononeuritis multiplex clinically showed concomitant vasculitic lesions that were confirmed by biopsy examination.

In the literature, some retrospective studies estimated the prevalence of PNS involvement in primary SS to be 10%–50%. A previous report stated that mononeuritis multiplex was not frequent.[19] Mellgren et al. reported that 33 (30%) of the total 110 SS patients (primary, 33; secondary, 77) had PNS involvement, and 28 of these 33 had primary SS[20]; none of them had mononeuritis multiplex; 2 nerve biopsy specimens of those taken from 11 patients showed vessel wall inflammation and necrosis, diagnostic characteristics of necrotizing vasculitis. On the other hand, Kaltreider and Talal reported that 2 of 10 patients with PNS involvement, of 109 patients with either primary or secondary SS, were diagnosed as having mononeuritis multiplex.[10] The nerve and/or muscle biopsy of these 2 patients revealed necrotizing vasculitis, perivasculitis, and demyelination. Hebbar reported that 6 of 115 patients (5.2%) with primary SS had PNS involvement[2]; 3 of these 6 patients had mononeuritis multiplex (see Table 2). Cutaneous biopsy for purpura and/or livedo in primary SS patients with PNS involvement revealed leukocytoclastic or lymphocytic vasculitis.[4] The prevalence of peripheral vasculitis was up to 75%.[4,5] In all these studies, PNS involvement is a complication of primary SS rather than secondary SS; vasculopathy is the principal cause of PNS involvement; mononeuritis multiplex is the most prevalent.

### The characteristics of histology

Molina et al.[3] classified 50 primary SS patients with peripheral vasculitis confirmed by biopsy examination (in the skin in 46, in the muscle in 4, and in the nerve in 4 patients) into two histopathological prototypes, neutrophilic inflammatory vascular disease and mononuclear cell inflammatory vascular disease. They documented a high prevalence (80%) of concomitant nervous system complication, in both CNS and PNS, with both types of IVD. The concomitance of IVD and active nervous system disease suggests that vascular inflammation in the nervous system similar to peripheral vasculitis might play a role in the pathogenesis of neurological diseases in both primary and secondary SS.

In the case of a connective tissue disorder, particularly rheumatoid arthritis[21] and SS,[4,5] selective invasion of vessels, ranging from predominant mononuclear cell infiltration into arteriolar wall to destructive necrotizing vasculitis of small arteries and veins, has been associated with PNS involvement. Andonopoulos reported that among 17 of 63 patients with primary SS exhibiting peripheral neuropathy, 2 had mononeuritis multiplex with vasculitis.[15] In their series, lip biopsy of 1 patient aged 63 years revealed findings indicative of SS, despite the absence of subjective sicca symptoms and negativity for the rose bengal stain test.

### Clinical and laboratory features

In our four patients with SS, active cutaneous symptoms appeared concurrently with or antedated the development of MNM. Eight of the nine presented patients (record was not available in one patient) also had skin lesions that were interpreted to be vascular involvement. Biopsy specimens of the sural nerve from patients 1 and 4 showed infiltration of mononuclear cells in the vessel wall with wall necrosis. Axonal demyelination characteristic of the neuropathy

caused by vascular impairment was also observed in specimens from patients 1, 3, and 4, although the biopsy specimen from patient 3 did not include vessels. Biopsy specimens of the skin from patient 2 showed mononuclear and polymorphonuclear cell infiltration and necrosis of the wall of small arterioles with leukocytoclasis, suggestive of necrotizing vasculitis, indicating that underlying vasculitis induced both skin and nerve lesions.

Positive MPO-ANCA in patients 3 and 4 also suggests microscopic polyangitis. However, MPO-ANCA often becomes positive in SS. Positive cryoglobulinemia with hepatitis C infection was seen in patient 2. The percentage of MPO-ANCA or hepatitis C infection without PNS is unknown. When PNS involvement including vasculitis progressed, the serum CRP and immunoglobulin G levels were elevated, and the serum $\beta_2$-microglobulin level increased acutely, suggesting acute inflammation with activation of underlying immunomodulation.

The literature review for PNS involvement and primary SS revealed mononeuritis multiplex (total of 17 cases; see Table 2), Adie's syndrome (total of 9 cases), polyneuropathy (total of 9 cases), trigeminal sensory neuropathy (total of 7 cases), and carpal tunnel syndrome (total of 2 cases).[2,3,9,10,20,22,23] Seventeen cases with the most common diagnosis of mononeuritis multiplex are listed in Table 2. All patients were female and most were middle aged or older. All had primary SS except for 4 cases who had no available description. All but one of the nerve or skin biopsy specimens from 14 patients revealed vasculitis. Seven patients who had available description improved partially with prednisolone, pulsed methylprednisolone, immunoglobulin, cyclophosphamide, or plasmapheresis therapy.

It was notable that all four patients had no subjective sicca symptoms either in the mouth or eyes when they experienced neurological abnormalities; SS was only suspected at the time of their first examination for neuropathy. Paresthesia would rather be an important early symptom, as it was observed first, mainly in the feet. Neuropathy has been reported to be generally symmetrical, although in some it could also be asymmetrical, and the cranial (particularly trigeminal) nerve was involved in about 55% of cases.[19] In all the four patients with active PNS involvement, neuropathy developed asymmetrically but bilaterally.

### Response to therapy

Immunosuppressive or antiinflammatory therapy cured the patients of both cutaneous and PNS abnormalities simultaneously. These observations obtained from our study and the literature suggest that inflammatory vascular infiltrates, similar to those found in the skin, would appear in PNS and be involved in the pathogenesis of nervous system disorder in patients with primary SS.

In the case when cutaneous symptoms appeared concurrently with or antedated the development of paresthesia or myalgia, PNS involvement is strongly indicated. Increases in serum C-reactive protein (CRP), $\beta_2$-microglobulin, and immunoglobulin G levels would be supporting evidence.

In summary, this study showed that nervous system involvement in patients with either primary or secondary SS is not rare. Peripheral nervous system involvement includes mononeuritis multiplex, and develops mainly in cases of primary SS. As cutaneous findings suggestive of vasculopathy are frequent in cases of PNS involvement, vasculopathy would be the common cause. Older age, shorter disease duration of subjective sicca, acute onset of sensory disturbance with increases in serum CRP, $\beta_2$-microglobulin, and immunoglobulin G levels are also indications of PNS involvement including vasculitis.

## References


1. Frost-Larsen K, Isager H, Mathorpe R. Sjögren's syndrome treated with bromhexine: a randomized clinical study. Br Med J 1978;115:79–81.
2. Hebbar M. Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjögren's syndrome. Ann Intern Med 1995;146:235–8.
3. Molina R, Provost TT, Alexander EL. Peripheral inflammatory vascular disease in Sjögren's syndrome. Arthritis Rheum 1985;28:1341–7.
4. Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjögren's syndrome. Medicine (Baltim) 1982;61:247–57.
5. Alexander EL, Provost TT. Sjögren's syndrome. Association of cutaneous vasculitis with nervous system disease. Arch Dermatol 1987;123:801–10.
6. Tadashi O. Annual Report of the Ministry of Health and Welfare Sjögren's Disease Research Committee (in Japanese). Ministry of Health and Welfare, Tokyo, 1977.
7. Escudero D, Latorre P. Central nervous system disease in Sjögren's syndrome. Ann Intern Med 1995;146:239–42.
8. Attwood W, Poser CM. Neurologic complications at Sjögren's syndrome. Neurology 1961;11:1034–41.
9. Kenett RP, Harding AE. Peripheral neuropathy associated with the sicca syndrome. J Neurol Neurosurg Psychiatry 1986;49:90–2.
10. Kaltreider HB, Talal N. The neuropathy of Sjögren's syndrome. Trigeminal nerve involvement. Ann Intern Med 1969;70:751–62.
11. Massey EW. Sjögren's syndrome and mononeuritis multiplex. Ann Intern Med 1980;92:130.
12. Drosos AA, Andonopoulos AP, Lagos G, Angelopoulos NV, Moutsopoulous HM. Neuropsychiatric abnormalities in primary Sjögren's syndrome. Clin Exp Rheumatol 1989;7:207–9.
13. Tanaka Y, Tsukada N, Koh CS, Yanagisawa N. A case of Sjögren's syndrome with mononeuritis associated with high levels of circulating immune complexes (in Japanese). Rinsho Shinkeigaku 1989;29:339–42.
14. Andonopoulas AP, Lagos G, Drosos AA, Moutsopoulos HM. Neurologic involvement in primary Sjögren's syndrome: a preliminary report. J Autoimmun 1989;2:485–8.
15. Andonopoulas AP. The spectrum of neurological involvement in Sjögren's syndrome. Br J Rheum 1990;29:21–3.
16. Kumazawa K, Sobue G, Yamamoto K, Shimada N, Mitsuma T. Autonomic dysfunction in sensory ataxic neuropathy with Sjögren's syndrome (in Japanese). Rinsho Shinkeigaku 1993;33:1059–65.
17. Yamanishi Y, Taoka Y, Mukuzono H, Aoi K, Ishibe Y, Yamana S. Cyclophosphamide-responsive subclinical Sjögren's syndrome in a patient with initial peripheral and central nervous system involvement (in Japanese). Ryumachi 1994;34:633–8.
18. Tajima Y, Mito Y, Owada Y, Tsukishima E, Moriwaki F, Tashiro K. Neurological manifestations of primary Sjögren's syndrome in Japanese patients. Int Med 1997;36:690–3.

19. Pittsley RA, Talal N. Neuromuscular complication of Sjögren's syndrome. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology. Vol 39. Amsterdam: North Holland; 1980. p. 419–33.
20. Mellgren SI, Conn DL, Stevens JC. Peripheral neuropathy in primary Sjögren's syndrome. Neurology 1989;39:390–4.
21. Conn DL, Dyck PJ. Angiopathic neuropathy in connective tissue disease. In: Dyck PJ, Thomas PK, Lambertt EH, Bunge R, editors. Peripheral neuropathy. 2nd ed. Philadelphia, London: Sanders; 1984. p. 2027–43.
22. Font J, Valls J, Cervera R, Pous A, Ingelmo M, Graus F. Pure sensory neuropathy in patients with primary Sjögren's syndrome. Ann Rheum Dis 1990;49:775–8.
23. Jean-Marie P, Louise C, Francois B, Francois C. Vasculitic neuropathy in rheumatic disease and Sjögren's syndrome. Neurology 1982;32:839–45.