Neurological Involvement in Patients With Primary Sjögren’s Syndrome

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**Background/Objective:** The neurological involvement associated with primary Sjögren’s syndrome (pSS) can be life threatening. However, the specific characteristics of pSS-related neurological involvement remain obscure. This study aimed at determining the clinical characteristics of this neurological involvement in patients with pSS.

**Methods:** The clinical data of 205 patients with pSS who were admitted to our department between January 2015 and June 2017 were studied. Characteristics and laboratory findings of pSS patients with neurological abnormalities were compared with pSS patients without.

**Results:** Forty of the 205 patients with pSS exhibited neurological abnormalities (19.51%), of these, 13 patients exhibited central nervous system (CNS) involvement only; 20 patients exhibited peripheral nervous system (PNS) involvement only; and 7 patients exhibited both, yielding a total of 20 (9.76%) patients with CNS involvement and 27 (13.17%) patients with PNS involvement. The titers of anti-Sjögren’s syndrome type A (SSA) antibodies were significant higher while the presence of anti-Sjögren’s syndrome type B (SSB) antibodies was significant lower in patients with vs. without neurological involvement. Similar results were found in patients with CNS involvement. No significant differences between patients with and without neurological involvement were found for the other clinical parameters examined.

**Conclusions:** Neurological involvement in patients with pSS is common and needs to be carefully evaluated. Patients with pSS with a high titer of anti-SSA and low presence of anti-SSB antibodies might have a relatively high risk of developing neurological involvement. Future studies should focus on identifying biomarkers that may aid in the early diagnosis of neurological involvement in patients with pSS.

**Key Words:** central nervous system involvement, neurological involvement, primary Sjögren’s syndrome

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**P**rimary Sjögren’s syndrome (pSS) is a systemic autoimmune disease that mainly affects exocrine glands such as the lacrimal and salivary glands, eventually leading to xerophthalmia and xerostomia.1 Systemic involvement, which includes conditions such as pneumonitis, renal tubular acidosis, thyroiditis, and myositis, is also associated with pSS.2–4 Neurological involvement is a common systematic complication associated with pSS.3 It can be classified into two subsets, central nervous system (CNS) involvement and peripheral nervous system (PNS) involvement. Generally, the prevalence of neurological involvement in patients with pSS is about 20%; however, impressive variability in the prevalence, ranging anywhere from 0% to 67.5%, has been reported in previous studies.5–9 Neurological involvement can be a life-threatening complication of pSS, especially CNS involvement, the manifestations of which are heterogeneous.5–10 Given the heterogeneity in manifestations, the specific clinical characteristics of neurological involvement in pSS remain obscure.

The pathogenetic mechanisms responsible for the neurological involvement in pSS likewise remain unclear, and effective treatment strategies are relatively limited. Therefore, the early diagnosis and treatment of neurological involvement in patients with pSS are quite important. However, it is difficult to identify patients with pSS who are at high risk of developing neurological involvement, making such early diagnosis challenging. As such, studies describing the clinical characteristics of pSS-related neurological involvement are essential for improving our understanding of this disease and for providing us with clues that may aid in identifying those at risk of developing neurological development, which will ultimately promote early diagnosis and treatment. Hence, the aim of this study was to investigate the prevalence, clinical characteristics, and immunological features of the neurological involvement in Chinese patients with pSS.

**METHODS**

**Study Population**

This study included 205 patients with pSS (182 women, 23 men) who were referred to the inpatient department of the Rheumatology and Clinical Immunology sectors of The First Affiliated Hospital of Xiamen University between January 1, 2015 and June 30, 2017. The diagnosis of pSS was based on the 2002 American-European Consensus Group criteria for the classification of pSS.11

**Data Collection**

Clinical data, including detailed patient histories, clinical manifestations, laboratory findings, treatment strategy, and disease prognosis, were obtained from patients’ medical records from the first encounter.

**Patient History**

Data regarding clinical manifestations, including dry mouth and dry eye symptoms; presence/absence of articular involvement; recent temperature and weight conditions; the results of Schirmer’s test, salivary gland biopsy, and salivary gland scintigraphy; and other examination results including assessments of the lung, heart, and kidney, were extracted for each patient. In addition, all patients...
were assessed for disease activity using the European League Against Rheumatism Sjögren’s Syndrome Disease Activity Index (ESSDAI).

**Laboratory Data**

Data from routine blood examinations, routine urine assessments (dry chemistry tests), and conventional hepatorenal function examinations were collected. Laboratory parameters related to immune features were also collected in this study; this included the erythrocyte sedimentation rate (ESR; Westergren method), as well as the levels of C-reactive protein (CRP), complement 3 (C3), complement 4 (C4), immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM), which were detected with a BN II System, a highly automated protein quantitative analyzer manufactured by Siemens (Marburg, Germany). The primary principle of the BN II System is to detect the scattered light intensity of the immune complex formed by the protein and its specific antibody, whereby the intensity of the scattered light is proportional to the concentration in the specimen. Other immunological indicators, including the levels of anti-nuclear antibodies (ANA), anti-Sjögren’s syndrome type A (SSA) antibodies, and anti-Sjögren’s syndrome type B (SSB) antibodies, as well as the extractable nuclear antigen levels, were tested using line immunoassays according to the manufacturer’s instructions (EUROIMMUN, Germany). ANA positivity was defined as a titer ≥1/100.

**Classification of Neurological Involvement**

We evaluated the patients’ clinical manifestations, magnetic resonance images, nerve conduction studies, and electroencephalography examinations based on their medical records. Following assessment of their records, patients were divided based on whether they did or did not have neurological involvement, and the patients who had neurological involvement were separated into those with CNS involvement, PNS involvement, or both CNS and PNS involvement. Patients with CNS involvement were defined as those individuals with focal (motor and sensory loss with hemiparesis, movement disorders, and other cerebellar syndromes) or diffuse (encephalopathy, cognitive dysfunction, dementia, psychiatric abnormalities, and aseptic meningoencephalitis) neurological symptoms, or abnormal findings on magnetic resonance images, electroencephalography recordings, and/or in the cerebrospinal fluid according to the methods used by Gono et al. Patients with PNS involvement were identified through neurological examinations and/or nerve conduction studies, and included those individuals with axonal polyneuropathies, sensory gangliononeuropathy, mononeuritis, trigeminal and other cranial nerve neuropathies, autonomic neuropathies, and demyelinating polyradiculoneuropathy, according to the methods of a previous study. Neurological abnormalities caused by infections, small vessel disease related to hypertension, and adverse effects of medications were excluded from our analysis of the clinical characteristics of the neurological involvement in pSS.

**Statistical Analysis**

Data were analyzed using SPSS 19.0. For categorical variables, Chi-squared and Fisher’s exact tests were employed, while for continuous variables, Student’s t-tests and nonparametric Mann–Whitney U tests were performed. The level of statistical significance was set at p < 0.05. Continuous data are expressed as the mean ± the standard deviation, and categorical data are expressed as positive (+) or negative (−).

**RESULTS**

**Characteristics of Patients with pSS With vs. Without Neurological Involvement**

The data from a total of 205 patients who were diagnosed with pSS during the study period were evaluated. Of those 40 patients, 13 patients exhibited CNS involvement only, 20 patients exhibited PNS involvement only, and 7 patients exhibited both, yielding a total of 20 patients with CNS involvement and 27 patients with PNS involvement.

**TABLE 1. Characteristics of PSS-Related Nervous System Involvement**

| Case (%) | 40/205 (19.51) | 165/205 (80.49) | p value |
|----------|----------------|-----------------|----------|
| With CNS involvement only | 13 | / | / |
| Female ratio (%) | 37/40 (92.50) | 145/165 (87.88) | 0.581 |
| With PNS involvement only | 20 | / | / |
| With CNS and PNS involvement | 7 | / | / |
| Mean age at onset of pSS (years) | 46.43 ± 9.60 | 46.18 ± 15.02 | 0.899 |
| Symptoms of dry mouth (%) | 27/38 (71.05) | 108/155 (69.68) | 0.954 |
| Symptoms of dry eyes (%) | 21/38 (55.26) | 81/155 (52.26) | 0.915 |
| Articular involvement (%) | 9/40 (22.50) | 33/165 (20.00) | 0.725 |
| Fever (%) | 4/40 (10.00) | 20/165 (12.12) | 0.920 |
| Weight loss (%) | 5/40 (12.50) | 14/165 (8.48) | 0.630 |
| Schirmer’s test (%) | 17/17 (100.00) | 72/82 (87.80) | 0.252 |
| Positive salivary gland biopsy (%) | 26/35 (74.29) | 104/135 (77.04) | 0.652 |
| Positive salivary gland scintigraphy (%) | 22/25 (88.00) | 89/93 (95.70) | 0.256 |
| ILD (%) | 26/32 (81.25) | 92/131 (70.23) | 0.454 |
| Abnormal ECG (%) | 13/27 (48.15) | 36/88 (40.91) | 0.209 |
| Kidney calculus (%) | 2/28 (7.14) | 9/112 (8.04) | 0.955 |
| ESSDAI | 4.48 ± 3.50 | 4.04 ± 2.49 | 0.360 |

Data are presented as M (mean) ± SEM (standard error of the mean), n or %.

ILD indicates interstitial lung disease; ECG, electrocardiogram; ESSDAI, the EULAR-SS Disease Activity Index.
The clinical characteristics of the patients with and without neurological involvement are shown and compared in Table 1. Among the 40 patients with neurological involvement, 37 were women, accounting for the majority of patients with pSS with neurological involvement; the mean age of onset was 46.43 ± 9.60 years. However, no significant differences in the occurrence of these clinical characteristics were found between patients with and without neurological involvement. The ESSDAI, which reflects the disease activity of pSS, was numerically higher in patients with pSS with nervous system involvement than that in patients with pSS without nervous system involvement, yet not significant.

The laboratory findings of patients with and without neurological involvement are listed and compared in Table 2. As summarized in the table, the routine blood cell test results, including the white blood cell, neutrophil, lymphocyte, and monocyte counts, were similar between the patients with and without neurological involvement. The platelet count was higher in patients with vs. without neurological involvement, although the difference was not statistically significant. Additionally, neither the indicators of liver and kidney function, including the alanine aminotransferase, aspartate transaminase, total bilirubin, and creatinine levels, nor the urinary function indicators, including the presence of hematuria and pyuria situations, demonstrated statistically significant differences between patients with and without neurological involvement. None of the immunological variables, including the ESR, CRP, C3, C4, IgA, IgG, and IgM levels, were different between patients with and without neurological involvement. The levels of antibodies commonly found in patients with pSS, including ANA, anti-SSA, anti-Ro52, anti-SSB, and rheumatoid factor (RF), were also analyzed. Among these autoantibodies, no significant differences were found in ANA, anti-R052 and RF between pSS patients with and without neurological involvement. The titer of the anti-SSA antibody was significantly higher in patients with vs. without neurological involvement ($p = 0.017$). However, the frequency of anti-SSB positivity and the titer of the anti-SSB autoantibody were significantly lower in patients with vs. without neurological involvement ($p = 0.002$). None of the patients with pSS with neurological involvement had positive perinuclear anti-neutrophil cytoplasmic antibody findings and only four had positive cytoplasmic anti-neutrophil cytoplasmic antibody findings, which was similar to the findings in patients with pSS without neurological involvement.

### Table 2. Comparison of PSS-Related Nervous System Laboratory Findings

|                    | With Nervous System Involvement (n = 40) | Without Nervous System Involvement (n = 165) | $p$ value |
|--------------------|----------------------------------------|---------------------------------------------|-----------|
| White blood cell count (10^9/L) | 7.36 ± 5.54                          | 6.96 ± 3.37                                 | 0.559     |
| Neutrophil count (10^9/L)         | 5.69 ± 9.36                           | 5.09 ± 5.89                                 | 0.616     |
| Lymphocyte count (10^9/L)         | 1.87 ± 0.85                           | 1.75 ± 0.81                                 | 0.426     |
| Monocytes count (10^9/L)          | 0.66 ± 0.74                           | 0.58 ± 0.50                                 | 0.447     |
| Platelet count (10^9/L)           | 261.46 ± 112.05                       | 221.96 ± 113.16                             | 0.051     |
| Alanine aminotransferase (U/L)    | 29.16 ± 39.41                         | 27.55 ± 32.06                               | 0.790     |
| Aspartate aminotransferase (U/L)  | 30.58 ± 28.31                         | 26.31 ± 26.90                               | 0.385     |
| Total bilirubin (μmol/L)          | 8.92 ± 5.10                           | 10.42 ± 7.25                                | 0.234     |
| Creatinine (μmol/L)               | 55.46 ± 16.78                         | 55.61 ± 26.14                               | 0.975     |
| Hematuria (/μL)                   | 6.76 ± 8.51                           | 20.10 ± 103.88                              | 0.470     |
| Pyuria (/μL)                      | 29.95 ± 57.53                         | 32.58 ± 97.70                               | 0.884     |
| Erythrocyte sedimentation rate (mm/h) | 34.20 ± 25.58                     | 36.55 ± 27.64                               | 0.646     |
| C-reactive protein (mg/L)         | 10.28 ± 26.14                         | 10.78 ± 24.20                               | 0.910     |
| Complement 3 (g/L)                | 2.13 ± 7.08                           | 1.10 ± 1.51                                 | 0.386     |
| Complement 4 (g/L)                | 0.22 ± 0.19                           | 0.26 ± 0.41                                 | 0.651     |
| Immunoglobulin A (g/L)            | 3.61 ± 2.65                           | 3.03 ± 1.32                                 | 0.207     |
| Immunoglobulin G (g/L)            | 17.74 ± 6.85                          | 17.15 ± 6.34                                | 0.625     |
| Immunoglobulin M (g/L)            | 1.45 ± 0.89                           | 1.32 ± 0.93                                 | 0.464     |
| Nuclear particle pattern (%)      | 21/35 (60.00)                         | 86/146 (58.90)                               | 0.978     |
| Titer of ANA (%)                  | 1.69 ± 0.93                           | 1.83 ± 1.00                                 | 0.442     |
| Titer of anti-SSA (%)             | 2.47 ± 1.11*                          | 2.03 ± 1.26                                 | 0.046     |
| Titer of anti-Ro52 (%)            | 2.38 ± 1.13                           | 2.25 ± 1.21                                 | 0.573     |
| Titer of anti-SSB (%)             | 0.24 ± 0.61*                          | 0.87 ± 1.24                                 | 0.000     |
| Positive ANA (%)                  | 31/35 (88.57)                         | 129/146 (88.36)                              | 0.985     |
| Positive anti-SSA (%)             | 29/34 (85.29)                         | 113/146 (77.40)                              | 0.503     |
| Positive anti-Ro52 (%)            | 29/34 (85.29)                         | 113/142 (79.58)                              | 0.741     |
| Positive anti-SSB (%)             | 5/34 (14.71)*                         | 52/141 (36.88)                               | 0.047     |
| Rheumatoid factor (%)             | 10/24 (41.67)                         | 20/105 (19.05)                               | 0.061     |
| cANCA (%)                         | 0/30 (0.00)                           | 1/112 (0.89)                                | 0.531     |
| pANCA (%)                         | 4/30 (13.33)                          | 5/112 (4.46)                                | 0.129     |

Data are presented as M (mean) ± SEM (standard error of the mean), n or %. *$p < 0.05$ was considered to be significant.

ANA indicates antinuclear antibodies; Anti-SSA, anti-Sjögren’s syndrome type A antibodies (Ro 52/Ro 60); Anti-Ro52, anti-Ro52 antibodies; Anti-SSB, anti-Sjögren’s syndrome type B antibodies; cANCA, cytoplasmic pattern of antineutrophil cytoplasmic antibody; pANCA, perinuclear anti-neutrophil cytoplasmic antibody.
Characteristics of Patients with pSS With vs. Without CNS Involvement

As CNS involvement is a life-threatening complication of pSS, we further analyzed the clinical characteristics of patients with pSS with CNS involvement.

A total of 20 patients presented with CNS involvement, and 7 of these patients also presented with PNS involvement, yielding a prevalence of 3.41% for concomitant CNS and PNS involvement in our cohort of 205 patients with pSS. The clinical characteristics of patients with pSS with CNS involvement compared with pSS patients without CNS involvement (including those only with PNS involvement) are listed and compared in Table 3. For patients with CNS involvement, the mean age at onset was 48.1 ± 10.7 years and most of the patients were women. As shown in Table 3, none of those clinical manifestations were significantly different between pSS patients with and without CNS involvement. The mean ESSDAI in patients with CNS involvement was 4.05 ± 3.32, which showed no difference with that in patients with pSS without CNS involvement (4.13 ± 2.65).

Both biochemistry and immunological characteristics evaluated were not different in patients with and without CNS involvement except for anti-SSA and anti-SSB, as shown in Table 4. The titer level of the anti-SSA autoantibody was higher in the group with vs. without CNS involvement (p = 0.017), although the occurrence of anti-SSA positivity was not significantly different between the groups. As for the anti-SSB antibody, a lower titer level was identified in patients with vs. without CNS involvement (p = 0.002), although the occurrence anti-SSB positivity was not different between the groups. The RF level was assessed in 10 patients with CNS involvement, 5 of whom were RF positive; although the p value was 0.077 for the comparison between patients with and without CNS involvement, the level of statistical significance requires verification in a study with a larger sample size. Lastly, the frequency of perinuclear anti-neutrophil cytoplasmic antibody positivity and cytoplasmic anti-neutrophil cytoplasmic antibody positivity was 0% and 18.20% in patients with CNS involvement, respectively, and no statistically significant difference was found between patients with and without CNS involvement.

TABLE 3. Characteristics of PSS-Related CNS Involvement

| Characteristics                      | With CNS Involvement | Without CNS Involvement | p value |
|--------------------------------------|----------------------|-------------------------|---------|
| Case (%)                             | 20 (9.76)            | 185 (90.24)             |         |
| With CNS involvement only            | 13                   | /                       | /       |
| Female ratio (%)                     | 18/20 (90.00)        | 164/185 (88.65)         | 1.000   |
| With both CNS and PNS only involvement | 7                    | /                       | /       |
| Mean age at onset of pSS             | 48.05 ± 10.70        | 46.03 ± 14.44           | 0.447   |
| Symptom of dry mouth (%)             | 12/18 (66.67)        | 123/175 (70.29)         | 0.674   |
| Symptom of dry eyes (%)              | 8/18 (44.44)         | 94/175 (53.71)          | 0.540   |
| Articular involvement (%)            | 4/20 (20.00)         | 38/185 (20.54)          | 1.000   |
| Fever (%)                            | 2/20 (10.00)         | 22/185 (11.89)          | 1.000   |
| Weight loss (%)                      | 2/20 (10.00)         | 17/185 (9.19)           | 1.000   |
| Schirmer’s test (%)                  | 7/7 (100.00)         | 82/92 (89.13)           | 0.208   |
| Positive salivary gland biopsy (%)   | 13/18 (72.22)        | 117/152 (76.97)         | 0.583   |
| Positive salivary gland scintigraphy (%) | 12/13 (92.30)  | 99/105 (94.29)          | 0.746   |
| ILD (%)                              | 12/15 (80.00)        | 106/148 (71.62)         | 0.680   |
| Abnormal ECG (%)                     | 7/15 (46.67)         | 42/100 (42.0)           | 0.186   |
| Kidney calculus (%)                  | 0/15 (0.00)          | 11/125 (8.80)           | 0.365   |
| ESSDAI (%)                           | 4.05 ± 3.32          | 4.13 ± 2.65             | 0.901   |

Data are presented as M (mean) ± SEM (standard error of the mean), n or %.

ILD interest interstitial lung disease; ECG, electrocardiogram; ESSDAI, the EULAR-SS Disease Activity Index.

DISCUSSION

In this study, we reviewed the data from a large cohort of Chinese patients with pSS to investigate and describe the characteristics of the accompanying neurological involvement, especially CNS involvement. We found that the prevalence of neurological involvement in pSS patients was not low and needed to be carefully evaluated. The titer of anti-SSA antibodies were higher while the presence of anti-SSB antibodies was lower in patients with vs. without neurological involvement.

In our study, the prevalence of neurological involvement in patients with pSS was 19.51%, and the prevalence of CNS involvement in particular was 9.76%. However, as mentioned earlier, the prevalence of neurological involvement differs greatly among reports, ranging anywhere from 0% to 67.5%. Indeed, in a previous study by Morreale et al. who assessed 120 outpatients who were referred to the Neurology and Psychiatry departments, the presence of neurological involvement was revealed in 81/120 (67.5%) patients. The prevalence rate in that study is much higher than that identified herein. There may be several reasons for this difference. First, the department performing the research may be a factor; our inpatients were primarily admitted to the hospital from the Rheumatology department, while the patients in the study by Morreale et al. were from the Neurology department. Researchers from different departments have different levels of awareness of pSS and its neurological involvement.

Second, the ethnicity of the patients may affect the prevalence as the ethnicity was different between our study and others. Other reasons for the difference in the prevalence between our study and other studies may be due to the use of different study methods, the utilization of differing diagnostic criteria for pSS, and/or ambiguous classifications and definitions of neurologic involvement.

The pathological mechanisms underlying the neurological involvement in pSS are not yet clear. Regarding CNS involvement, differences in prevalence of neurological involvement between patients with and without CNS involvement.
TABLE 4. Comparison of CNS Laboratory Findings

|                                | With CNS Involvement (n = 20) | Without CNS Involvement (n = 185) | p value |
|--------------------------------|-------------------------------|-----------------------------------|---------|
| White blood cell count (10⁹/L) | 7.12 ± 6.05                   | 7.03 ± 5.38                       | 0.918   |
| Neutrophil count (10⁹/L)       | 6.31 ± 12.53                  | 5.09 ± 5.76                       | 0.678   |
| Lymphocyte count (10⁹/L)       | 1.88 ± 0.82                   | 1.76 ± 0.81                       | 0.542   |
| Monocytes count (10⁹/L)        | 0.80 ± 1.01                   | 0.57 ± 0.48                       | 0.341   |
| Platelet count (10⁹/L)         | 251.25 ± 109.41               | 227.15 ± 114.24                   | 0.369   |
| Alanine aminotransferase (U/L) | 26.21 ± 38.16                 | 28.02 ± 33.06                     | 0.823   |
| Aspartate aminotransferase (U/L)| 33.11 ± 32.13                 | 26.50 ± 26.60                     | 0.314   |
| Total bilirubin (μmol/L)       | 8.55 ± 3.87                   | 10.31 ± 7.14                      | 0.292   |
| Creatinine (μmol/L)            | 55.51 ± 20.41                 | 55.59 ± 25.06                     | 0.987   |
| Hematuria (μL)                 | 8.80 ± 11.15                  | 18.53 ± 98.50                     | 0.694   |
| Pyuria (μL)                    | 26.59 ± 45.16                 | 32.65 ± 95.01                     | 0.801   |
| Erythrocyte sedimentation rate (mm/h)| 35.44 ± 28.39 | 36.17 ± 27.18                     | 0.918   |
| C-reactive protein (mg/L)      | 10.70 ± 29.71                 | 10.68 ± 24.02                     | 0.998   |
| Complement 3 (g/L)             | 3.26 ± 9.87                   | 1.08 ± 1.43                       | 0.350   |
| Complement 4 (g/L)             | 0.39 ± 0.25                   | 0.25 ± 0.39                       | 0.866   |
| Immunoglobulin A (g/L)         | 3.47 ± 3.11                   | 3.11 ± 1.45                       | 0.628   |
| Immunoglobulin G (g/L)         | 17.86 ± 7.35                  | 17.20 ± 6.34                      | 0.682   |
| Immunoglobulin M (g/L)         | 1.20 ± 0.64                   | 1.37 ± 0.95                       | 0.477   |
| Nuclear particle pattern (%)   | 10/16 (62.50)                 | 97/165 (58.79)                    | 0.461   |
| Titer of ANA                   | 1.69 ± 0.79                   | 1.81 ± 1.00                       | 0.630   |
| Titer of anti-SSA              | 2.65 ± 0.86*                  | 2.06 ± 1.26                       | 0.017   |
| Titer of anti-Ro52             | 2.29 ± 1.21                   | 2.28 ± 1.20                       | 0.956   |
| Titer of anti-SSB              | 0.24 ± 0.56*                  | 0.80 ± 1.21                       | 0.002   |
| Positive ANA (%)               | 15/16 (93.75)                 | 145/165 (87.88)                   | 0.398   |
| Positive anti-SSA (%)          | 16/17 (94.12)                 | 126/163 (77.30)                   | 0.175   |
| Positive anti-Ro52 (%)         | 14/17 (82.35)                 | 128/159 (80.50)                   | 0.977   |
| Positive anti-SSB (%)          | 3/17 (17.65)                  | 54/158 (34.18)                    | 0.386   |
| Rheumatoid factor (%)          | 5/10 (50.00)                  | 25/119 (21.01)                    | 0.077   |
| cANCA (%)                      | 0/11 (0.00)                   | 1/131 (0.76)                      | 0.339   |
| pANCA (%)                      | 2/11 (18.18)                  | 7/131 (5.34)                      | 0.135   |

Data are presented as M (mean) ± SEM (standard error of the mean), n or %, *p < 0.05 was considered to be significant.

ANA indicates antinuclear antibodies; Anti-SSA, anti-Sjögren’s syndrome type A antibodies (Ro 52/Ro 60); Anti-Ro52, anti-Ro52 antibodies; Anti-SSB, anti-Sjögren’s syndrome type B antibodies; cANCA, cytoplasmic pattern of antineutrophil cytoplasmic antibody; pANCA, perinuclear anti-neutrophil cytoplasmic antibody.

Bakchine et al.17 pathologically confirmed the presence of vasculitis and direct infiltration of the CNS by mononuclear cells in a patient with primary Gougerot–Sjögren syndrome. Cerebral nerve involvement secondary to vasculitis has also been suggested as an important aspect in pathogenesis of CNS involvement.18 Autoantibodies have been speculated to play roles in neuropathic processes, and this might lead to both direct nerve injury and indirect injury by vascular damage.19 Several clinical studies have revealed differences in the presence of autoantibodies in patients with pSS with neurological involvement compared with pSS patients without neurological involvement, for example, in the levels of anti-SSA, anti-SSB, anti-alpha fodrin, anti-ganglioside GM1, and antineuronal antibodies. Both anti-GW182 (a protein located in cytoplasmic structures called GW bodies) and anti-SSA antibodies are thought to contribute to the neurological involvement in pSS, as anti-GW182 antibodies show an inhibitory effect on nerves,20 while anti-SSA antibodies are postulated to play roles mediating or potentiating vascular injury.20 In our study, we found that the titer of anti-SSA was significantly higher in patients with pSS with vs. without neurological involvement, and was even higher in patients with pSS with CNS involvement. However, the presence of anti-SSB antibodies and the titer of anti-SSB antibodies were lower in patients with pSS with vs. those without neurological involvement. Anti-SSA and anti-SSB antibodies are most characteristic autoantibodies of SS patients. They were originally described in 1961 as two precipitating antibodies reacting with different antigens contained in extracts from salivary and lacrimal glands of patients with SS.21 Although anti-SSA and anti-SSB antibodies have been used as useful diagnostic markers for SS, the pathological significance of them still remains to be clarified. Our findings support the notion that anti-SSA antibodies are involved in the pathogenesis of neurological involvement in pSS, and indicate that anti-SSA and anti-SSB antibodies may play different roles in the pathogenesis of pSS-related neurological involvement, though the specific mechanisms still need to be investigated.

Besides the involvement of autoantibodies, other clinical characteristics of the neurological involvement in pSS have also been revealed. In a study by Gono et al.,15 the frequency of fever was significantly higher (p = 0.006) in patients with pSS with vs. without neurological involvement. This finding is in contrast to that of the present study, as we did not identify a difference in fever frequency between patients with and without neurological involvement. This discrepancy between the previous and present study may stem from differences in patient ethnicities or inclusion criteria.
Several limitations of this study should be noted. First, the present study only included patients from the inpatient department, not the outpatient department, which may have led to selection bias. Second, due to the low prevalence of neurological involvement in pSS, the number of sample cases in this study is relatively small, and thus differences in various clinical factors may not have been uncovered. Studies with larger sample sizes are required to further confirm the clinical significance of our results.

In conclusion, the findings from our study support that neurological involvement in patients with pSS is an important issue that needs to be carefully evaluated. It can be difficult to distinguish patients with pSS who are likely to develop neurological abnormalities based on pSS-related clinical manifestations and routine blood tests, because they are often similar in patients with and without neurological involvement. Our results indicate that patients with pSS who have a high anti-SSA titer and low presence of anti-SSB antibodies might have a relatively high risk of developing neurological involvement, though this finding still needs to be confirmed in studies with larger cohorts. The identification of new biomarkers that may aid in the early diagnosis of pSS-related neurological involvement is essential.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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