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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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Primary 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 systemic 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.[5–8] Neurological involvement can be a life-threatening complication of pSS, especially CNS involvement, the manifestations of which are heterogeneous.[8–10] 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

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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,[12–14] or abnormal findings on magnetic resonance images, electroencephalography recordings, and/or in the cerebrospinal fluid according to the methods used by Gono et al.[15] Patients with PNS involvement were identified through neurological examinations and/or nerve conduction studies, and included those individuals with axonal polyneuropathies, sensory ganglioneuronopathy, mononeuritis, trigeminal and other cranial nerve neuropathies, autonomic neuropathies, and demyelinating polyradiculoneuropathy, according to the methods of a previous study.[16] 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

	With Nervous System Involvement	Without Nervous System Involvement	*p* value
Case (%)	40/205 (19.51)	165/205 (80.49)	/
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.

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 titers 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%.[5–8] Indeed, in a previous study by Morreale et al.[5] that 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.[5] 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,

TABLE 3. Characteristics of PSS-Related CNS Involvement

	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 (80.0)	106/148 (71.62)	0.680
Abnormal ECG (%)	7/15 (46.67)	42/100 (0.42)	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.

TABLE 4. Comparison of CNS Laboratory Findings

	With CNS Involvement (n = 20)	Without CNS Involvement (n = 185)	*p* value
White blood cell count (10^9/L)	7.12 ± 6.05	7.03 ± 3.58	0.918
Neutrophil count (10^9/L)	6.31 ± 12.53	5.09 ± 5.76	0.678
Lymphocyte count (10^9/L)	1.88 ± 0.82	1.76 ± 0.81	0.542
Monocytes count (10^9/L)	0.80 ± 1.01	0.57 ± 0.48	0.341
Platelet count (10^9/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,[20–26] while anti-SSA antibodies are postulated to play roles mediating or potentiating vascular injury.[26] 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.[27] 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 needs 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 abnormities 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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