Original Article

Neurological Involvement in Patients with Primary Sjögren's Syndrome: A Retrospective Cross-Sectional Study

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Abstract

Background: To determine the rate and types of neurological involvement in patients with primary Sjögren's syndrome (pSS) and to evaluate predictive clinical and immunologic features of neurological involvement. **Methods:** We retrospectively assessed 2127 patients with an ICD-10 code for Sjögren recorded in the hospital database. Among these patients, those meeting the pSS classification criteria and having neurological symptoms and an objective evaluation accordingly were enrolled. After comparing the patients with and without neurological involvement, peripheral and central involvement subtypes were also compared within themselves. **Results:** A total of 199 pSS patients were enrolled and neurological involvement was found in 31.6%. Peripheral nervous system (PNS) involvement was found in 23.5% of the patients, and central nervous system (CNS) involvement was found in 34.3%. Patients with neurological involvement had a higher frequency of Schirmer's test, anti-Ro/SS-A and anti-La/SS-B positivity and the presence of interstitial lung disease, articular involvement, lymphadenopathy, anemia and hypocomplementemia than patients without those. In multivariate regression analysis, only articular involvement had a higher risk for the development of neurologic involvement [OR 10.01 (4.18–23.97), *P* 0.0001]. Among the patients with PNS, the frequency of anti-Ro/SS-A positivity, low C3 and Schirmer's test positivity were statistically increased compared to those who were not in PNS ($P = 0.032$, $P = 0.044$, and $P = 0.029$, respectively). When compared in terms of CNS involvement, patients with CNS involvement were younger, had a shorter disease duration, and had a higher frequency of anti-Ro/SS-A positivity than patients without those ($P = 0.041$, $P = 0.027$, and $P = 0.046$, respectively). **Conclusions:** In our study, it was shown that one third of the symptomatic pSS patients had objective neurological involvement. The presence of neurological symptoms should be considered, especially in patients with articular involvement in pSS.

Keywords: Central nervous system, neurological involvement, peripheral nervous system, primary Sjögren's syndrome

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that primarily affects the exocrine glands and eventually leads to xerophthalmia and xerostomia.[1] Up to 75% of pSS patients may experience extraglandular involvement ranging from mild arthralgia to life-threatening vasculitis.[2,3] Neurological involvement, one of the most common extraglandular manifestations associated with pSS, is classified into two subgroups: peripheral nervous system (PNS) involvement and central nervous system (CNS) involvement.[4]

Symptomatology of neurological involvement is diverse depending on the site of involvement. pSS may initially manifest with neurological findings or neurological involvement may develop [years after the diagnosis of pSS.[5-7] Prevalence of neurological involvement due to pSS is approximately 20%, however, rates ranging from 0% to 67.5% have been reported depending on the methodology.[6,8-10] Some studies included asymptomatic cases, while others included cohorts of severe inpatients with extraglandular manifestations, resulting in a wide prevalence range.[11]

Pathogenetic mechanisms underlying neurological involvement with heterogeneous and variable symptomatology are yet to be clarified. Data on the immunological profiles of patients with pSS and the associated neurological involvement are scarce and contentious. Patients with pSS-related sensory neuropathy have a higher prevalence of both anti-Ro and anti-La antibodies, according to one study, whereas other studies have found neuropathies to be associated with a negative immunological profile.[10,12-15] Early diagnosis and treatment are crucial since treatment options for neurological involvement are limited. There is, however, no pathognomonic marker or associated serological or clinical features that may be used for early identification of the patients who are at risk of developing neurological involvement. Hence, studies that provide potential clues to identify pSS patients with an

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increased risk for the development of neurological involvement are needed. Accordingly, the aim of this study is to identify the types of PNS and CNS involvement in pSS patients, as well as to investigate any relationships between clinical and immunological features and neurological involvement. In addition, regarding the lack of information in the available literature, we contributed by providing our own data from a tertiary center in Turkey.

Methods

This study was carried out in accordance with the principles of the Declaration of Helsinki, with the approval of the Ankara City Hospital Ethics Committee (E1-21-2124). Patients with an International Classification of Diseases (ICD-10) code of pSS (M35.0) who applied to the Ankara City Hospital rheumatology outpatient clinic between May 1, 2019 and May 1, 2022 were evaluated retrospectively. Patient was accepted as a pSS patient in the case of meeting the 2016 American College of Rheumatology/European League Against Rheumatism criteria in the absence of another rheumatic condition [Supplementary Table].[16]

Patients with secondary Sjögren's syndrome, patients who have sicca symptoms but do not meet the pSS classification criteria, and patients with comorbidities potentially affecting the peripheral and central nervous systems (such as diabetes mellitus, chronic renal failure, thyroid disorders, amyloidosis, sarcoidosis, hepatitis C, Hepatitis B and HIV infections, alcohol abuse, vitamin B12 deficiency) were excluded. Demographic and clinical data, Schirmer's test (ST) results, salivary gland biopsy positivity, and medical treatments of patients were collected from hospital records, in addition to laboratory parameters including anti-nuclear antibody (ANA) immunofluorescence assay (IFA), anti-Sjögren syndrome type A (SSA) antibodies, anti-Sjögren syndrome type B (SSB) antibodies, anti-Ro52 antibodies, complement 3 (C3), complement 4 (C4), immunoglobulin G (IgG) and rheumatoid factor (RF) levels were collected. ANA positivity was defined as ≥1/100 titre. Sjögren's syndrome extranglandular involvemnets was evaluated according to the EULAR Sjögren's syndrome disease activity index (ESSDAI).[17]

Among patients with pSS, those who had a neurologic symptom and underwent an objective neurologic evaluation (electroneuromyography (ENMG)), magnetic resonance imaging (MRI) were enrolled in the study. Those who had a diagnosis of a peripheral or central nervous system disorder coherent with pSS (as defined in the PNS and CNS domains of ESSDAI) and could not be explained by another reason after these evaluations were considered to have neurological involvement. Demographics, clinical and laboratory data were compared between patients with and without neurological involvement.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22. Chi-square test was used for comparison of categorical variables, which were expressed as numbers and percentages. The continuous variables were investigated to determine whether they were normally distributed using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Descriptive analyses were demonstrated using tables of frequencies for the ordinal variables and using medians and interquartile ranges (IQR) for the non-normally distributed variables. The Mann–Whitney *U* test was used for the comparison of the data with a non-normal distribution. The normally distributed variables were expressed as mean ± standard deviation (SD), and the Student's *t* test was for comparison between groups. In all tests, *P* values lower than 0.05 were considered statistically significant.

A logistic regression analysis model was formed comprising variables that differ between patients with and without neurological involvement. These possible factors identified with univariate analyses ($P < 0.20$) were further entered into the multivariate analysis, with backward selection, to determine independent predictors of neurological involvement. Among correlated factors with similar effects on neurological involvement, only those with clinical significance were included. A 5% type-I error level was used to infer statistical significance.

Results

A total of 2,127 patients were detected to have an ICD-10 code of M35.0 recorded in the hospital database. Among those 199 patients meeting pSS classification criteria, had a neurological symptom and underwent an objective evaluation were included in the study. Of the 95% of patients were female, the mean ± SD age was 54 ± 11.54 years and the mean ± SD age at diagnosis was 48.6 ± 11.4 years.

Out of 199 patients, 31.6% had neurological involvement. Comparison of clinical and immunological features of pSS patients with and without neurologic involvement was shown in Table 1. Peripheral nervous system involvement was evaluated in 149 pSS patients and observed in 35 (23.5%), while CNS involvement was evaluated in 105 and observed in 36 (34.3%). The most common PNS involvement was axonal sensorimotor polyneuropathy (10.7%), and the most common CNS involvement was cerebral vasculitis (17.14%). Twenty-seven patients had only PNS, 28 had only CNS, 8 had both PNS and CNS manifestations [Table 2].

When patients with and without neurological involvement were compared, anti-Ro/SS-A and ST positivity were statistically higher in those who had neurological involvement ($P = 0.021$, $P = 0.020$, respectively) and interstitial lung disease (ILD) and joint involvement were more frequent ($P = 0.017$, $P < 0.001$, respectively). Patients with neurological involvement were more likely to be treated with azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CTX), rituximab (RTX), intravenous immunoglobulin (IVIg), and systemic corticosteroids (CS) [Table 1].

Table 1: Comparison of clinical and immunological features of pSS patients with and without neurologic involvement

	Without neurologic involvement, *n*=136	With neurologic involvement, *n*=63	*P*
Female, *n* (%)	131 (96.3)	58 (92.1)	0.201
Age, years, mean (SD)	53.8 (10.8)	54.4 (13.1)	0.755
Age of diagnosis, years, mean (SD)	48.6 (10.6)	48.8 (13.2)	0.911
Disease duration, months, median (IQR)	50 (71.5)	60 (60)	0.652
Xerostomia, *n* (%)	133 (97.8)	62 (98.4)	0.772
Xerophthalmia, *n* (%)	124 (91.2)	61 (96.8)	0.147
Parotid enlargement, *n* (%)	7 (5.1)	5 (7.9)	0.442
Positive Schirmer's test, *n* (%)	107 (78.7)	58 (92.1)	0.020
Positive salivary gland biopsy, *n* (%)*	117 (86.0)	55 (87.3)	0.667
Interstitial lung disease, *n* (%)	5 (3.7)	8 (12.7)	0.017
Renal involvement, *n* (%)	3 (2.2)	1 (1.6)	1
Articular involvement, *n* (%)	57 (41.9)	55 (87.3)	<0.001
Lymphadenopathy, *n* (%)	11 (8.1)	10 (15.9)	0.096
Lymphoma, *n* (%)	1 (0.7)	1 (1.6)	0.534
Medical treatments for Sjögren syndrome, *n* (%)			
Hydroxychloroquine	130 (95.6)	60 (95.2)	0.912
Methotrexate	15 (11)	7 (11.1)	0.986
Azathioprine	4 (2.9)	11 (17.5)	0.001
Mycophenolate mofetil	2 (1.5)	5 (7.9)	0.034
Cyclophosphamide	0	5 (7.9)	0.003
Rituximab	0	6 (9.5)	0.001
Intravenous immunoglobulin G	1 (0.7)	9 (14.3)	*P*<0.001
Corticosteroid	61 (44.9)	38 (60.3)	0.042
Positive ANA, *n* (%)	109 (80.1)	55 (87.3)	0.218
Positive anti-Ro/SS-A, *n* (%)	77 (56.6)	46 (73.0)	0.021
Positive anti-La/SS-B, *n* (%)	40 (29.4)	25 (39.7)	0.151
Rheumatoid factor, median (IQR)	9.5 (10)	10 (16)	0.345
Low C3, *n* (%)	11 (8.1)	10 (15.9)	0.096
Low C4, *n* (%)	3 (2.2)	2 (3.2)	0.685
Hypocomplementemia, *n* (%)	12 (8.8)	10 (15.9)	0.140
Anaemia, *n* (%)	13 (9.6)	15 (23.8)	0.007
Leukopenia, *n* (%)	13 (9.6)	8 (12.7)	0.503
Thrombocytopenia, *n* (%)	2 (1.5)	2 (3.2)	0.592
IgG, median (IQR)	13.4 (4.3)	13.3 (3.2)	0.858
Hypogammaglobulinemia, *n* (%)	1 (0.7)	1 (1.6)	0.575
Hypergammaglobulinemia, *n* (%)	22 (16.2)	10 (15.9)	0.957

ANA: Antinuclear antibodies, Anti-SSA: Anti-Sjögren's syndrome type A antibodies, AntiSSB: Anti-Sjögren's syndrome type B antibodies, IGG: Immunoglobulin G, *Salivary gland biopsy of 172 patients is known

Possible predictors related to neurological involvement in pSS were analyzed by regression analysis and shown in Table 3. The articular involvement and positive anti-Ro/SS-A had a significantly higher risk of neurological involvement in pSS [OR 10.01 (4.18–23.97), $P < 0.0001$]. The other variables evaluated (gender, xerophthalmia, positive ST, interstitial lung disease, lymphadenopathy, positive anti-La/SS-B, low C3, and anemia) were not found to be significantly associated with the development of neurological involvement.

When patients were compared according to PNS involvement, anti-Ro/SS-A positivity, low C3 and ST positivity were statistically higher in patients with PNS involvement than in patients without PNS involvement ($P = 0.032$, $P = 0.044$, $P = 0.029$, respectively). In addition, patients with PNS involvement had statistically higher rates of ILD and joint involvement than ($P < 0.001$ and $P < 0.001$, respectively) [Table 4]. In comparison between groups according to CNS involvement, patients with CNS involvement were younger and had shorter disease durations ($P = 0.041$, $P = 0.027$, respectively). Patients with CNS involvement more frequently had anti-Ro/SS-A positivity and joint involvement ($P = 0.046$, $P = 0.02$, respectively) [Table 4].

Discussion

Our results demonstrated that, out of 199 pSS patients who had a neurological symptom and were evaluated accordingly, 31.6% had a neurological involvement. The presence of joint manifestations increased the risk of neurological involvement tenfold. Anti-Ro/SS-A positivity was found to be more common in patients with both PNS and CNS involvement than in those

without. Furthermore, patients with PNS involvement had a lower C3 and a positive ST. Patients with CNS involvement were younger, had a shorter disease duration, and had a higher rate of joint symptoms.

Peripheral nervous system and CNS involvement have been found in pSS patients with varying prevalence. Central nervous system involvement has been reported in around 6%–48% of pSS patients, and PNS involvement in a wide range of up to 2%–60%.[6,18-20] In a previous study, the prevalence of neurological involvement in individuals with pSS was 19.5%, whereas the prevalence of CNS involvement was 9.8%.[21] In fact, the prevalence of neurological involvement varies widely between reports, ranging from 0% to 67.5%. In a previous study evaluating patients referred to the Neurology and Psychiatry departments, the presence of neurological involvement was demonstrated in 67.5% of the patients.[8] Clinicians' levels of awareness of pSS and neurologic involvement, the ethnicity of the patients, and diagnostic criteria used for the classification of pSS, the ambiguous characterization of CNS involvement may all have contributed to the variations in prevalence rates in studies. The frequency of neurological involvement in the patients in our study is similar to other studies. In our study, the rate of PNS involvement was 23.8%, and the rate of CNS involvement was 34.2% in patients with pSS who had neurologic symptoms and were evaluated. Due to our methodology, our results cannot clearly reflect the prevalence of pSS-related neurological involvement, yet, rates were similar to other studies.

Table 2: Frequency and types of peripheral and central nervous system involvements of pSS patients with neurological symptoms

	All patients, *n*=199 (%)
Peripheral nervous system involvement	35 (23.8)
Axonal sensorimotor polyneuropathy	16 (10.7)
Axonal sensory polyneuropathy	11 (7.4)
Multiple mononeuropathy	1 (0.7)
Radiculoneuropathy	4 (2.7)
Ganglionopathy	1 (0.7)
Chronic inflammatory demyelinating polyneuropathy	2 (1.3)
Central nervous system involvement**	36 (34.2)
Cerebral vasculitis	18 (17.1)
Transverse myelitis	5 (4.8)
Multiple sclerosis-like	5 (4.8)
Optic neuritis	4 (3.8)
Seizures	4 (3.8)

*Electroneuromyography of 149 patients is known. **Magnetic resonance images of 105 patients are known

In addition to glandular disease, joint symptoms may be seen in 20%–60% of pSS patients, and synovitis can be observed in one-third of these.[22] Articular involvement may precede the onset of pSS in 10%–20% of the cases, but it is concurrent with the onset of sicca symptoms in most patients.[23,24] Since joint involvement is an extraglandular manifestation of pSS, it has been reported to be associated with some other systemic features of the disease, such as renal involvement, cutaneous vasculitis, and peripheral neuropathy.[25,26] Similarly, articular involvement is associated with the presence of serological markers such as cryoglobulins, hyperglobulinemia, RF, and anti-Ro/SSA that characterize patients with extraglandular manifestations.[27,28] Rozis *et al*.[29] found that arthralgia occurs simultaneously with sicca symptoms and was associated with the presence of anti-Ro/SSA, anti-La/SSB antibodies in 50% of patients. In our study, we observed that the risk of neurological involvement was increased tenfold in patients with articular symptoms. Given that neurological involvement is more frequent in individuals with anti-Ro/SSA positivity, there may be a connection between anti-Ro/SSA positivity and an increased risk of neurological involvement in patients with joint involvement. Therefore, a detailed neurologic evaluation should not be neglected in patients presenting with articular manifestations.

The pathogenic mechanisms of pSS-related neurologic involvement are not yet well understood. There are different hypotheses, such as the infiltration of cytokines secreted by T lymphocytes and dendritic cells, vascular damage

Table 3: Effects of various variables on neurologic involvement with pSS patients in univariate and multivariate logistic regression analyses

Variables	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Female	4.26 (0.86–21.03)	0.075	4.31 (0.89–20.76)	0.068
Xerophthalmia	1.75 (0.30–10.01)	0.530	-	
Positive Schirmer's test	1.79 (0.58–5.53)	0.310	-	
Interstitial lung disease	1.31 (0.35–4.79)	0.683	-	
Articular involvement	9.63 (3.90–23.75)	<0.0001	10.01 (4.18–23.97)	<0.0001
Lymphadenopathy	0.81 (0.26–2.57)	0.725	-	
Positive anti-Ro/SS-A	2.14 (0.89–5.15)	0.087	2.06 (0.99–4.31)	0.053
Positive anti-La/SS-B	0.82 (0.35–1.97)	0.669	-	
Low C3	2.50 (0.79–7.89)	0.118	-	
Anaemia	2.00 (0.78–5.09)	0.145	2.15 (0.88-5.24)	0.091

OR: Odds ratio, CI: confidence interval

Table 4: Comparison of clinical and immunological features of pSS patients according to neurological involvement subgroups without peripheral and central neurological involvement

	Without PNS involvement, *n*:114	With PNS involvement, *n*:35	*P**	Without CNS involvement, *n*:69	With CNS involvement, *n*:36	*P***
Female, *n* (%)	110 (96.5)	33 (94.3)	0.562	66 (95.7)	32 (88.9)	0.187
Age, years, mean (SD)	53.3 (10.3)	57.2 (13.08)	0.067	55.1 (11.69)	49.8 (13.64)	0.041
Age of diagnosis, years, mean (SD)	48.3 (9.9)	51.6 (13.1)	0.118	48.9 (11.73)	44.5 (13.46)	0.092
Disease duration, months, median (IQR)	48 (72)	60 (66)	0.647	60 (80)	49 (54)	0.027
Xerostomia, *n* (%)	112 (98.2)	34 (97.1)	0.685	67 (97.1)	35 (97.2)	0.972
Xerophthalmia, *n* (%)	104 (91.2)	35 (100)	0.070	63 (91.3)	34 (94.4)	0.565
Parotid enlargement, *n* (%)	5 (4.4)	2 (5.7)	0.745	4 (5.8)	4 (11.1)	0.441
Positive Schirmer's test, *n* (%)	94 (82.5)	34 (97.1)	0.029	54 (78.3)	31 (86.1)	0.331
Positive salivary gland biopsy, *n* (%)***	104 (91.2)	33 (94.3)	0.561	59 (85.5)	30 (83.3)	0.730
Interstitial lung disease, *n* (%)	2 (1.8)	8 (22.9)	<0.001	4 (5.8)	4 (11.1)	0.441
Renal involvement, *n* (%)	1 (0.9)	1 (2.9)	0.416	2 (2.9)	0	0.545
Articular involvement, *n* (%)	53 (46.5)	31 (88.6)	<0.001	36 (52.2)	30 (83.3)	0.02
Lymphadenopathy, *n* (%)	10 (8.8)	7 (20.0)	0.068	8 (11.6)	5 (13.9)	0.735
Lymphoma, *n* (%)	1 (0.9)	1 (2.9)	0.416	1 (1.4)	0	1
Medical treatments for Sjögren syndrome, *n* (%)						
Hydroxychloroquine	111 (97.4)	33 (94.3)	0.335	66 (95.7)	34 (94.4)	1
Methotrexate	14 (12.3)	5 (14.3)	0.756	7 (10.1)	3 (8.3)	1
Azathioprine	6 (5.3)	8 (22.9)	0.002	4 (5.8)	7 (19.4)	0.30
Mycophenolate mofetil	1 (0.9)	5 (14.3)	0.003	2 (2.9)	0	0.545
Cyclophosphamide	1 (0.9)	4 (11.4)	0.011	0	5 (13.9)	0.04
Rituximab	0	5 (14.3)	0.001	2 (2.9)	2 (5.6)	0.608
Intravenous immunoglobulin G	3 (2.6)	6 (17.1)	0.006	2 (2.9)	7 (19.4)	0.07
Corticosteroid	50 (43.9)	24 (68.6)	0.011	31 (44.9)	21 (58.3)	0.192
Positive ANA, *n* (%)	89 (78.1)	31 (88.6)	0.170	57 (82.6)	31 (86.1)	0.644
Positive anti-Ro/SS-A, *n* (%)	65 (57)	27 (77.1)	0.032	39 (56.5)	27 (75.0)	0.046
Positive anti-La/SS-B, *n* (%)	35 (30.7)	15 (42.9)	0.183	18 (26.1)	12 (33.3)	0.435
Rheumatoid factor, median (IQR)	9.7 (13)	10 (15)	0.688	9 (8)	10 (16)	0.228
Low C3, *n* (%)	7 (6.1)	6 (17.1)	0.044	9 (13)	7 (19.4)	0.386
Low C4, *n* (%)	3 (2.6)	2 (5.7)	0.335	0	1 (2.8)	0.343
Hypocomplementemia, *n* (%)	8 (7.0)	6 (17.1)	0.073	12 (17.4)	7 (19.4)	0.795
Anaemia, *n* (%)	10 (8.8)	11 (31.4)	0.001	10 (14.5)	4 (11.1)	0.628
Leukopenia, *n* (%)	13 (11.4)	4 (11.4)	1.0	3 (4.3)	6 (16.7)	0.060
Thrombocytopenia, *n* (%)	2 (1.8)	2 (5.7)	0.235	1 (1.4)	0	1
IgG, median (IQR)	12.6 (3)	12.8 (5)	0.734	12.3 (4)	12.6 (4)	0.519
Hypogammaglobulinemia, *n* (%)	1 (0.9)	1 (2.9)	0.416	1 (1.4)	0	1
Hypergammaglobulinemia, *n* (%)	17 (14.9)	7 (20.0)	0.474	12 (17.4)	5 (13.9)	0.783

PNS: Peripheral neurological involvement, CNS: central neurological involvement, ANA: Antinuclear antibody, IgG: Immunoglobulin G, C3: complement 3, C4: complement 4. *Comparison of patients with and without peripheral nervous system. **Comparison of patients with and without central nervous system. *** Salivary gland biopsy of 172 patients is known

mediated by autoantibodies, and ischemia due to small vessel vasculitis.[30] In particular, autoantibodies are predicted to play a role in neuropathic processes, both directly to the nerve and indirectly via vascular injury.[31] Several clinical studies have found differences in autoantibody (such as anti-SSA and anti-SSB) between pSS patients with and without neurological involvement. Anti-SSA antibodies, in particular, are thought to have a role in mediating and accelerating vascular damage.[32] It has been reported that anti-Ro/SSA positivity increases the risk of axonal neuropathy.[15] In the study of Fan *et al*.,[21] the presence and titre of anti-La/SSB antibodies were found to be lower in patients with neurological involvement compared to those without, while CNS and neurological involvement were associated with high titres of anti-Ro/SSA. In our study, the anti-Ro/SSA positivity rate was statistically higher in patients with both PNS and CNS involvement compared to those without neurologic involvement. There was no association seen between anti-La/SSB positivity and neurological involvement. Our findings support the hypothesis that anti-SSA antibodies play a role in the pathophysiology of neurological involvement in pSS and suggest that anti-SSA positive patients should be carefully monitored for the development of neurological manifestations.

The complement system is a crucial component of innate immunity, and the C3 complement is the system's core

molecule.[33] Few studies have shown that low serum C3 levels correlate with extraglandular manifestations such as vasculitis, interstitial lung disease, and disease activity.[34-37] Ye *et al*.[38] demonstrated that low blood C3 levels are an independent risk factor for neurological involvement in both pSS and sSS patients under the age of 50 and that it can be a good immunological predictor of neurological complications. In our study, low serum C3 levels, which indicate overactivation and consumption of the complement system, were found to be especially associated with patients with PNS involvement. These findings support the immunological role of the complement system in neuronal damage and suggest that the C3 level maybe useful to predict PNS involvement.

A significant subset of pSS patients may present with neurological signs without sicca symptoms. It is important to identify these patients and prevent delays in diagnosis. Therefore, the evaluation of sicca symptoms together with functional tests such as the objective, noninvasive ST is extremely important for the diagnosis of pSS. In studies, ST positivity was found in 56-89% of patients with pSS-related neuropathies.[39] In our study, ST was positive in 97.1% of patients with PNS, which was statistically greater than in patients without. These findings highlight the importance of completing the ST in suspicious patients, even if they do not have any dry eye symptoms, and suggest that there may bea relationship between xerophthalmia and PNS involvement.

Neurologic manifestations may precede or follow the diagnosis of pSS. Accordingly, it has been reported that the neurological symptoms may appear 4 years before the diagnosis of pSS in 25%–60% of patients and 6–8 years after the diagnosis of pSS in the remaining individuals.[5] The study indicated that when sicca symptoms were present during neurological involvement, the time between the beginning of neurological symptoms and the diagnosis of pSS was considerably shorter.[10] In our study, patients with CNS involvement were younger and had a shorter disease duration. At the same time, although these patients had a shorter disease duration, they had an increased rate of joint involvement.

In case of severe neurological manifestations, prompt diagnosis and adequate treatment are crucial. Yet, there is no clear guideline for the treatment of pSS-related neurological involvement. In emergent conditions, high-dose pulse CS therapy is considered to be the primary line of treatment. AZA and MMF treatments are used in maintenance therapy in patients with both PNS and CNS involvement.[40] Cyclophosphamide and RTX use should be considered in severe PNS involvements such as mononeuritis multiplex and progressive CNS involvement.[41,42] In addition, PNS involvements like axonal sensory/sensorimotor neuropathy and sensory ataxic neuropathy may benefit from IVIg therapy.[43] In our study, it was found that patients with neurological involvement needed more CS, AZA, MMF, CTX, RTX, and IVIG therapies than patients without neurological involvement.

Our study had some limitations. Firstly, the retrospective and cross-sectional design of our study and the small sample size limited accurate assumptions that may have been provided by long-term prospective follow-up. Second, because the patients with symptoms are investigated in terms of neurological involvement and imaging modalities are used, individuals with no or few symptoms were probably overlooked. In addition, another limitation of our study is that we did not evaluate pSS patients with evoked potential tests. Likewise, it is possible that small fiber neuropathy was also often overlooked since asymptomatic individuals were not evaluated with skin biopsies. Therefore, determining the true prevalence of neurological involvement in patients with pSS with our study was improbable.

In conclusion, neurological involvement in patients with pSS is an important issue that should be carefully evaluated. Our results demonstrated that in patients with neurological involvement, anti-SSA positivity, a low C3 level and ST positivity were more frequent. The presence of articular manifestations increased the risk of neurologic involvement tenfold. This conclusion, however, should be validated in larger cohort studies and looked into for biomarkers of neurological involvement.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table: ACR/EULAR Classification Criteria for Primary Sjögren Syndrome

Item	Weight/Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1foci/4 mm^2	3
Anti-SS-A/Ro positive	3
Ocular Staining Score ≥5 (or Van Bijsterveld score ≥4) in at least one eye	1
Schirmer's test ≤5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 ml/min	1

After controlling the inclusion criteria (dry eyes and/or mouth for at least 3 months without other explanation) and exclusion criteria, the classification criteria can be used. The diagnosis of SjS is confirmed when ≥4 points of the classification criteria are reached