Cross-sectional Study

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Neurological injury in primary Sjogren's syndrome

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Introduction: The incidence of neurological injury in primary Sjogren's syndrome varies between 2.5 and 60%. The authors aimed to evaluate its prevalence and characteristics in patients with primary Sjogren's syndrome in a sample of the Syrian population.

Patients and methods: Forty-eight patients with primary Sjogren's syndrome, attending outpatient clinics at Damascus Hospital between January 2020 and January 2022 in this cross-sectional study at the outpatient clinics, were interviewed and examined, and the necessary laboratory and radiological examinations were demanded. Information was collected on disease duration, onset time, and patterns of neurological symptoms.

Results: Forty-eight patients, including 42 females, aged 56.1 ± 10.3 years were enroled. Central nervous system involvement was found in 34 patients. 85% of patients had generalized nerve manifestations, while local nerve manifestations were found in 77,5% of patients. The common neurological manifestation was headaches, then cognitive disorders, and the most common pattern of headache was migraine. Beck Depression Index showed a significant increase in the apathy evaluation scale. The study of cognitive changes showed a significant increase in the Mini-Mental State Examination (MMSE) index. Carotid Doppler showed the presence of injury in 42.4% of patients. The magnetic resonance imaging showed positive findings in 21 patients and positive evoked potentials in 52% of patients.

Discussion: Studies showing the prevalence of Sjogren's neurological injury patterns are insufficient, but this was changed when the criteria for diagnosing Sjogren's syndrome was modified, and the definition of neurological traits in the context of the syndrome was expanded. The presence of a high rate of headaches, cognitive changes, and fatigue confirms that generalized nervous system injuries are more common than local injuries. Migraine was the most common pattern of headache found in patients with the syndrome compared with other patterns such as tension headaches and headaches due to medications, especially analgesics. This was associated with the presence of anti-SSA antibodies and Raynaud's phenomenon, which suggest that the headache mechanism may be due to vascular endothelial dysfunction or an immune-mediated inflammation injury of the neurovascular system. The changes that appeared on the MRI images suggested premotor cortex involvement rather than mesolimbic cortical impairment, and its presence was also associated with SSA antibody positivity, and it is caused by inflammation.

Conclusion: Primary Sjogren's syndrome should be considered as having any unspecified or specific neurological disorder.

Keywords: central nervous system involvement, neurological injury, primary Sjogren's syndrome, PSS

Introduction

Sjogren's syndrome is a rare auto-immune condition that affects exocrine glands and other body systems like the central nervous system (CNS)[1]. It is manifested by infiltration of lymphocytes, in particular lacrimal glands, the parotid gland, and the salivary glands, causing dryness of the mouth and eyes, but it may affect other areas like the bronchial tree, the pancreas, and the digestive system[2].

Sjogren syndrome affects 0.5–1.0% of the population[3]. Unfortunately, there is no study in Syria concerning its prevalence. The incidence of neurological injury is between 1 and 3%, according to many studies, but not in Syria that dealt with peripheral injury, and fewer studies that dealt with central injury[4].

HIGHLIGHTS

- Sjogren's syndrome is a rare auto-immune condition that affects exocrine glands and other body systems like the central nervous system.
- Central nervous system injuries are common such as headaches. The most common pattern of headache was migraine, associated with the presence of anti-SSA and anti-SSB antibodies.
- Primary Sjogren's syndrome should be considered as having any unspecified or specific neurological disorder, and these patients should be studied clinically, laboratory, and radiologically.
- The outcome would become better when adding corticosteroids to treatment.

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The new diagnostic criteria for Sjogren's syndrome in 2002[5] led to prescribe a higher prevalence of CNS injury, which ranged between 2.5 and 60%, and this may be due to the absence of a specific definition of neurological injury[6,7]. The central lesion may precede the syndrome for several years when it is diagnosed as another disease. CNS involvement is much less common, and connected with damage to cranial nerves and the autonomic nervous system. It may present as: headache, aseptic meningitis, seizures, cognitive disorders, and transverse myelitis. Myopathy, demyelinating lesions, and optic neuritis may also occur[8]. Peripheral injury manifests with polyneuropathy, mono, and multiple neuropathy, radicular polyneuropathy, sensory ataxic neuropathy, multiple cranial neuropathy, trigeminal neuropathy, and autonomic neuropathy. Acute onset is observed more in multiple mononeuropathy and multiple cranial neuropathies, whereas other forma are seen during the disease progression[8–12].

Therapy is focusing on improving the quality of life of patients with SS. General procedure such as air humidification, and smoking cessation play an important role. Various tear substitutes, and local anti-inflammatory treatment with cyclosporine are available to treat keratoconjunctivitis sicca[13]. Pilocarpine and cemiveline are effective in stimulating salivary flow[14]. Systemic treatment is often used according to the disease activity and the involved organs[15]. Hydroxychloroquine is used in mild to moderate disease, meanwhile, immunosupressants and biologics are used for severe disease, and important organs manifestations[13].

We aimed to study the prevalence and characteristics of neurological injury manifestations in a sample of Syrian patients with primary Sjogren's syndrome.

Patients and methods

A cross-sectional study was conducted at the outpatient clinics at Damascus Hospital between January 2020 and January 2022.

Our study is compatible with STROCSS 2019 guidelines[16]

Inclusion criteria: All patients with primary Sjögren syndrome diagnosed according to the American College of Rheumatology, and European League Against Rheumatism (ACR/EULAR) criteria[5].

Exclusion criteria: All patients with other rheumatic diseases and connective tissue conditions, patients with secondary Sjogren's syndrome, Hepatitis B and Hepatitis C[17], Hashimoto's thyroiditis, patients with suspected anti-cryoglobulinemia, and patients with any mental disorders.

Methods: Patients were interviewed and examined and the necessary laboratory and radiological examinations were demanded. Information was collected on disease duration, time of onset of neurological symptoms, and its pattern and characteristics (Table 1).

Study measurement

The international classification of headaches[18], presence of myofascial pain[19], Fatigue Severity Scale fatigue scale[20].
Depression score, Beck Depression Index (BDI), apathy evaluation scale apathy evaluation scale (AES)[21,22].
MMSE[23] for cognitive disturbance.
Visual analogue scale to assess pain[24],
(m RS) to assess the pyramidal symptoms[25].

Table 1

Measurements and scores used to evaluate the neurological involvement in primary Sjogren syndrome

Symptoms	Assessment
Headache	Headache classification
Depression	Depression score [20,21] AES/ BDI
Fatigue	FFS scale
Cognitive changes	MMSE
Pyramidal symptoms	(m RS)
Pain	Pain scale (VAS)

AES, apathy evaluation scale; BDI, Beck Depression Index; FSS, Fatigue Severity Scale; MMSE, Mini-Mental State Examination VAS, Visual analogue scale.

Blood tests include: Thyroid stimulating hormone, Alanine transaminase, Aspartate transaminase, Hepatitis C Virus core antigen, Erythrocyte sedimentation rate, C-Reactive Protein, Antinuclear antibodies, Anti-ds DNA, Perinuclear anti-neutrophil cytoplasmic antibodies, Cytoplasmic anti-neutrophil cytoplasmic antibodies, Anti Sjögren syndrome type A antigen, Anti Sjögren syndrome type B antigen, Anti-scl70, Anti RNP, and Cryoglobulin.

Carotid echo-Doppler was done, and a measurement of the inner epithelium of more than 1.4 mm taken from 1 cm to the branch-bifurcation was considered evidence of a sclerotic atheroma.

Magnetic resonance imaging was done on patients, meanwhile, electroencephalography and stimulating potentials were done for specific cases. There is no need for the control group as a cohort study.

Statistical study

Prevalence, frequency, and distribution of people's variables were determined using Student's test. The presence of statistical differences between clinical findings and laboratory evidence between the group was calculated using multivariate analysis of Variance, ANOVA. The P value was considered statistically significant if it was less than 0,05 with a 90% CI for SPSS 23 application.

Results

Forty-eight patients, forty-two females and six males, with primary Sjogren's syndrome were enroled in our study after signing the informed consent form, with a median age of 56.1 $\pm$10.3 years (males aged 55.3$\pm$16.9 years, females aged 57.6$\pm$15.8 years) and an average of the disease onset ranging from 5.7 to 10.3 years.

Dry eyes were found in 58.9% of the patients, dry mouth was found in 79.1%, thyroiditis was found in 26.8%, Raynaud's phenomenon was found in 29.3%, digestive manifestations were found 6.9%, cardiac events were found in 1.2%, pulmonary manifestations were found in 28.3%, and neurological injury was found in 70.7%. Neurological manifestations were found in 34 patients (70.7%), (2/6) males and 32/42 females, and the time for the onset of neurological symptoms was 3.1–4.9 years (Table 2).

Anti-SSA antibodies were positive in 41 patients (85.4%), while only 13 patients (27.8%) had positive anti-SSB antibodies, and 26 patients (54%) had positive antinuclear antibodies ($P = 0.000$, and $P = 0.001$, respectively). Biopsy was performed in

Table 2

Patients' demographical data

Patients numbers	34 (70,7%)
Female number	32
Male number	2
Disease duration (year)	5.7–10.3
Neurological onset duration (year)	3.1–4.9

only 7 (14.5%) patients with negative antibody results to confirm the diagnosis.

CNS involvement, which was found in 34 patients, was significantly higher than the peripheral nervous system prevalence, which was found in 27 patients ($P = 0.001$). 34 patients (85%) had generalized nerve manifestations, while local ones were found in 31 patients (77,5%) ($P = 0.005$). The common neurological manifestation was headaches in 18 patients (45%), then cognitive disorders in 16 patients (40%) (Table 3).

The most common pattern of headache was migraine, especially in patients with positive SSA antibodies ($P = 0.001$), and in patients with Raynaud's ($P = 0.001$), as shown in Table 4.

The statistical analysis ANOVA showed a positive correlation between positive Anti-SSA and Headache, cognitive disturbance, fatigue, myofascial pain, and neuralgia ($P = 0.02$, $P = 0.001$, $P = 0.02$, $P = 0.001$, $P = 0.001$, respectively).

BDI showed a significant increase in 43.8% of patients compared with only 34.7% of the AES with $P = 0.4$ and $P = 0.001$, respectively.

The study of cognitive changes showed a significant increase in the MMSE index ($P = 0.001$).

Carotid Doppler showed the presence of injury in 17 patients (42.4%), where thickening of the endothelial layer was found, and no serious obstruction was observed in any patient. There were moderate injuries of obstruction (30–70%) in 7 patients (17.5%), and the rate of mild obstructions was less than 30% in 12 patients (27.5%).

The magnetic resonance imaging showed the presence of infarcts in the basal nuclei, lenticular nuclei, and lesions similar to Multiple Sclerosis in 21 patients (52.5%), and their presence was not associated with the presence of atherosclerotic plaques on carotid Doppler ($P > 0.004$). The induction of evoked potentials was positive in 52% of patients.

Table 3

Patterns and frequency of neuro-injury in patients with primary Sjögren's syndrome

Neurological involvement	Percentage (%)
Headache	45
Cognitive disturbances	40
Neuralgia	38.7
Fatigue	34.7
Neuropathy	32.3
Sensory disturbances	21.3
Epileptic seizures	18.4
Pyramidal involvement	16.7
Muscular pain	14.9
Myofascial pain	13.9
Cerebellar symptoms	9.8
Encephalitis and meningitis	1.1

Table 4

Patterns of headache

Pattern of headache	Percent (%)
Migraine without aura	47.8
Migraine with aura	4.7
4.7% Cluster headache	2.2
Tension headache	11.4
Headache caused by Analgesics	6

Discussion

Forty-eight patients, forty-two females and six males were enroled in our study, with a median age of 56.1 ± 10.3 years, and an average of the disease onset ranging from 5.7 to 10.3 years. Dry eyes and dry mouth were the most frequent manifestations. Neurological manifestations were found in (70.7%) of patients, and the time for the onset of neurological symptoms was 3.1–4.9 years. Central involvement was significantly higher than the peripheral nervous system prevalence. The common neurological manifestation was headaches, then cognitive disorders. There was a positive correlation between positive Anti-SSA and Headache, cognitive disturbance, fatigue, myofascial pain, and neuralgia. BDI showed a significant increase in 43.8% of patients compared with only 34.7% of the AES. The study of cognitive changes showed a significant increase in the MMSE index.

Studies showing the prevalence of Sjogren's neurological injury patterns are insufficient[4,6–12], but this was changed when the criteria for diagnosing Sjogren's syndrome was modified, and the definition of neurological traits in the context of the syndrome was expanded[5,24].

The pathologic mechanism of CNS damage is unknown. T lymphocytes and dendritic cells may play a role by secretion of cytokines, which leads to vasculitis and damage to the dorsal root ganglia due to inflammatory infiltration, and antibodies against nervous tissue[8].

The study of Belin *et al.*[26] showed that the cause of neurological injury may be a defect in the subcortical region as supported by Lafitte *et al.*[27], where the study showed that the cause of cognitive disorders is a defect in that region, and the study of Escudero *et al.*[28] was not able to determine the normative characteristics which can be taken to classify headaches as primary Sjogren's syndrome despite its commonness.

The presence of a high rate of headaches, cognitive changes, and fatigue seen in this study confirms that generalized nervous system injuries are more common than local injuries[5,29]. Migraine was the most common pattern of headache found in patients with the syndrome compared with other patterns such as tension headaches and headaches due to medications, especially analgesics[5], and this is in concordance with our study.

This was associated with the presence of anti-SSA antibodies and Raynaud's phenomenon, which suggest that the headache mechanism may be due to vascular endothelial dysfunction or an immune-mediated inflammation injury of the neurovascular system. Mimic migraine headaches may be due to the direct effect of the disease[30], and it was found that the cause of cognitive disturbances is poor circulation in the frontal subcortical region.

As the relation between the MRI lesions and clinical manifestations is not well established. The changes that appeared on the MRI images suggested premotor cortex involvement. Knowing

that cognitive changes increase with age explains that it is caused by inflammation rather than microvascular damage[5,29]. Generalized nervous system injury is more common than local nervous system injury, and this is the reason for the clinical and histopathological differences with the defect caused by microscopic vasculitis, as shown by the simulated white matter injuries of multiple sclerosis[4,5].

The limitations of our study are the small sample size, and the one centre study. In addition to the study design which does not allow following up patients. We did not study the effects of treatment that may had CNS side effects or complications such as steroids or immunosuppressants[31,32].

The article which was written by Tobón *et al*.[33], which is not a study, talked about the epidemiology, prevalence, the pathophysiology, manifestations and types of CNS involvement,the diagnostic procedures, and finally, and the treatment of this involvement in primary Sjogren, Many CNS involvements, which were described in Tobón and colleagues' article, were not found in our results. In addition to that we use some of the diagnostic procedures he had mentioned.

Conclusion

CNS involvement in Primary Sjogren's syndrome should be carefully considered. Patients should be studied clinically, laboratory, and radiologically, especially MRI to detect these manifestations. Further, larger, and multicenter studies are recommended to evaluate the CNS manifestations in patients with primary Sjogren syndrome.

Ethical approval

Our trial has been performed in accordance with the declaration of Helsinki. Ethical approval was not necessary as there were no procedures or treatment used. Written informed consent was obtained from adult patients.

Consent

All patients have approved and signed consent.

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NA.

Authors contribution

T.D. wrote the abstract. N.K. wrote the introduction and discussion. M.F.B. and M.W. wrote the results. M.F.B. is the corresponding author. M.K. monitored the study. All authors reviewed the study before submitting.

Conflicts of interest disclosure

NA.

Research registration unique identifying number (UIN)

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Data availability statement

Not applicable.

Provenance and peer-review

N/A.

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