Primary Sjögren's syndrome with central nervous system involvement

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ABSTRACT

الأهداف: وصف المظاهر السريرية، والمخبرية، والتشخيصية الإشعاعية لمتلازمة مرض جوغرن الأولي (PSS) المؤثر على الجهاز العصبي المركزي (CNS).

الطريقة: أجريت دراسة رجعية ل12 حاله من الإناث تم تشخيصيهن بمتلازمة جوغرن الأولي –مستشفى الملك فيصل التخصصي ومركز الأبحاث – مدينه الرياض خلال الفترة من 1991م حتى 2009م. تم استناد تشخيص متلازمة جوغرن وفقاً لمعايير التشخيص الأوروبي الأمريكي. قمنا بتحليل المظاهر السريرة والإشعاعية وخصائص المناعة.

النتائج: كان متوسط العمر 40 عام (المدى 58–16)، كان المرضى من الإناث و أصبن بأعراض عصبيه نشطه والتي سبقت الأعراض التقليدية للمرض من إصابة الغدد اللعابية والدمعية 33% من المرضى. عانى 8 (66%) من التهاب في الحبل الشوكي. عانى 9 من المرضى(75%) من التهاب الأعصاب البصرية، وعانى البقية من أعراض وعلامات عصبيه متباينة. كانت نسبة الاختبارات المناعية (anti–SSA and anti–SSB) مرتفعه في 7 من المرضى (58%). أظهرت نتائج خزعه الغدد اللعابية الثانوية التهابات في 11 مريضه (92%). وأظهر التصوير بالرنين المغناطيسي للمخ بؤر متناثرة في المادة البيضاء بالدماغ في 7 من المرضى (58%). وأظهر التصوير بالرنين المغناطيسي للعمود الفقري العديد من بؤر فرط الكثافه hyperintensity في صورة T2 في 6 من المرضى(50%)، وكذلك آثار فرط الكثافه في أجزاء طويل من الحبل الشوكي العنقي لدى مريضتين (16%).

خاتمه: تدل النتائج التي توصلنا إليها بان تأثر الجهاز العصبي(CNS) المركزي في متلازمة جوغرن الأولي(PSS) مختلف ومتباين بشكل كبير في أعراضه الإكلينيكية السريريه. كذلك يمكن لهذا التأثر أن يسبق الأعراض التقليدية لمرض جوغرن من التهاب الغدد اللعابية والدمعية بسنوات. يمكن لمتلازمة جوغرن الأولية محاكاة مرض التصلب الويحي المتعدد (RRMS)، ولذلك ينبغي النظر في الحالات المشتبه بها وإجراء اختبارات الكشف المبكر. أما الخطط العلاجية فهي في انتظار دراسات مستقبليه بأعداد اكبر.

Objectives: To describe the clinical, laboratory, and radiological features of Primary Sjögren's syndrome (PSS) with central nervous system (CNS) involvement.

Methods: A retrospective case series of 12 female patients with PSS and CNS involvement at King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia from 1991-2009. The diagnosis of PSS is defined by the American-European Diagnostic Criteria. We analyzed the clinical, radiological, and immunological features.

Results: The mean age was 40 years (range 16-58 years); all patient were females and presented with active neurological symptoms. The neurological involvement preceded the classic sicca symptoms (33%). Eight patients (66%) presented with myelopathy, 9 patients (75%) had optic neuritis, and the rest had variable neurological signs. Immunological tests (anti-Sjögren's syndrome A and anti-Sjögren's syndrome B) were high in 7 patients (58%). Minor salivary gland biopsy revealed inflammatory cell infiltrate in 11 patients (92%). Brain MRI showed scattered white matter changes in 7 patients (58%). Spine MRI showed multiple foci of hyperintensity in T2-weighted image in 6 patients (50%), and long segment of hyperintensity at the cervical spinal cord in 2 patients (16%).

Conclusion: Our findings demonstrate that CNS involvements in PSS have great clinical variability and could precede the classic sicca symptoms by years. Primary Sjögren's syndrome can mimic multiple sclerosis (primary progressive multiple sclerosis or relapsing remitting multiple sclerosis), therefore a screening test for PSS should be considered in suspected cases. A well-defined management protocol awaits studies with larger case numbers.

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Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by inflammatory mononuclear cells infiltrate of the exocrine glands, like the lacrimal and salivary glands leading to keratoconjunctivitis sicca syndrome. Other exocrine glands such as pancreas, bronchial tree, and gastrointestinal tract can be affected. Sjögren's syndrome can occur in a Primary Sjögren's syndrome (PSS) form or in the secondary form, which complicates other rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. The extraglandular SS can involve many organs including musculoskeletal, renal, and vascular and nervous systems.[1] The prevalence of neurologic involvement in PSS is varyingly reported.[2,3] Some researchers suggest nervous system involvement is up to 25% of SS.[4,5] When it affects the peripheral nervous system, it may cause sensory polyneuropathy or mononeuritis multiplex.[6,7] However, central nervous system (CNS) disease involvement has a wide clinical manifestation and variable patterns, which make the diagnosis of PSS difficult or delayed.[3-5,8-13] This article presents our findings in 12 female patients with PSS and various neurological manifestations. The aim of the study was to describe the clinical spectrum of CNS disease among patients with PSS. We also analyzed the radiologic and diagnostic laboratory tests of these patients.

Methods. This was a retrospective chart review. Our center, King Faisal Specialist Hospital and Research Centre, is a major tertiary care center in Saudi Arabia and all cases are ICD9 classified. The medical records department was requested to provide a list of all cases with a diagnosis of possible, probable, or definite SS over the period from 1991-2009, before which date no MRI was available in this center. Forty-nine charts were reviewed and 37 were excluded due to the following reasons: patients with medication induced xerostomia and xerophthalmia, and patients with secondary SS. Other patients excluded are patients with lymphoma, hepatitis C infection, and sarcoidosis, graft versus host disease, and acquired immunodeficiency syndrome. In addition, all patients with definite primary progressive multiple sclerosis (PPMS) or relapsing remitting multiple sclerosis (RRMS) that did not fulfill the diagnostic criteria of SS were excluded.

Twelve patients, all female, of ages 16-58 years (mean 40) fulfilled the study inclusion criteria, with PSS and CNS involvement seen between January 1991 and January 2009. All patients with active neurologic signs at time of presentation or over the period of follow up and that fulfilled the American-European diagnostic criteria of SS[14,15] were included. The American-European diagnostic criteria required a minimum of 4 out of 6 of the following: history of xerostomia, history of xerophthalmia, signs of dry eyes, radiological signs of salivary gland involvement, positive immunologic blood markers, and positive histopathology of salivary glands (**Table 1**).

The clinical characteristic of PSS includes glandular sicca symptoms, excessive tooth decay, and/or recurrent salivary gland enlargement. Schirmer's test was considered abnormal if <5 mm wetting of the paper strip occurred after 5 minutes. Salivary gland scintigraph and sialograph, as well as rose Bengal stain[14] of the cornea were not performed. The histopathological feature considered consistent with SS is a focal score of equal or greater than one in minor salivary gland biopsy. The focus is defined as accumulation of at least 50 mononuclear cells, and the focus score[14] is the number of foci per 4 mm^2 of glandular tissue.

The laboratory blood analysis for SS includes screening for antibodies to Ro/SSA and La/SSB. The standard methodology used in our hospital laboratories was enzyme linked immunosorbent assay (ELISA). In addition, blood screening for other autoimmune disorders was performed, which included antinuclear antibodies pattern screen and quantitative study, rheumatoid factor, anti-ribonucleoprotein (RNP), antineutrophil cytoplasmic antibody (ANCA), anti lupus, anticardiolipin antibodies, and measurement of Complement factors (C3 and C4). Normal cerebrospinal fluid (CSF), analysis was demonstrated in all patients. The MRI examination of the brain and spinal cord was performed on 1.0 or 1.5 Tesla superconductive magnet imaging sequences included multiplanar T1- and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) sequence. Four patients had Gadolinium-enhanced T1-weighted brain studies. Magnetic resonance angiogram was not performed. Both brain and spinal cord MRI studies were analyzed by a certified neuroradiologist in the radiology department of the hospital (**Table 2**).

Statistical analyses were used to compare the subgroup of patients with PSS using non-parametric tests. The qualitative variables were expressed as percentage and the quantitative variables were expressed as range and mean.

Results. All the 12 patients were females with a mean age of 40 years, range 16-58 years (**Table 2**). The mean age at onset of symptoms is 34 years (range 16-46 years). Xerostomia was reported in 10 patients (83%), and xeropthalmia in 11 patients (92%). The sicca symptoms preceded the neurologic symptoms in 8 patients (66%). Four patients (33%) presented with neurologic findings prior to the sicca symptoms. The mean delay between the onset of both symptoms is 4.5

years. Objective xerophthalmia testing using Schirmer's test was conducted in 11 patients and was positive in 9 patients (75%). Minor salivary gland biopsies were performed in 11 patients (92%) and showed foci of lymphocytic cell infiltrate consistent with SS in all of them. In addition, fibrosis and atrophy of minor salivary gland acini was also demonstrated in a few biopsies.

Laboratory and immunologic tests. Laboratory and autoimmune serology finding includes antinuclear antibody (ANA) screen with high titer level was found in 8 patients (66%). The ANA pattern seen frequently is the speckled pattern (80%) however, homogenous and mixed speckled and nuclear pattern were seen infrequently. Both anti-Ro/SSA and anti-La/SSB were detected in 7 patients (58%). One patient had only anti-La/SSB. None of the patients were positive for double stranded DNA, anti-RNP or Sm antibodies.

Neurologic clinical findings. 1) Brain and brainstem involvement: Focal and multifocal lesions were found in 2 (16%) patients. Involvement of brainstem and cerebellum was found in an additional 2 patients (16%). All patients had recurrence of neurologic deficit that resulted in the disease being mistaken as RRMS. Seizure of generalized type was reported in one patient. Cognitive impairment was seen in 3 patients (25%); in one patient it occurred in rapid course suggesting acute encephalopathy and/or encephalitis and 2 had chronic course like progressive sub cortical dementia.

2) Spinal cord involvement: A clinical syndrome suggestive of acute or sub-acute myelopathy was found in 8 patients (66%). The most common site of involvement in the spinal cord is the cervical (6 [50%]) followed by thoracic (3 [25%]). In 3 patients, a relapsing-remitting course of cervical transverse myelitis was seen that mimics multiple sclerosis or neuromyelitis optica (**Tables 1**).

3) Optic neuritis: Optic neuritis was seen in 9 patients (75%). Bilateral optic neuritis at onset was seen in 6 patients (50%).

4) Peripheral neuropathy: Sensory neuropathy was seen in 2 patients (16%). The nerve conduction study suggests an axonal type of sensory neuropathy in both patients.

Table 1 - Summary of clinical and diagnostic data for patients with Primary Sjögren's syndrome.

No.	Age	Clinical presentation	Xerostomia	Xerophthalmia	Schirmer's test	Salivary gland biopsy	Anti-SSA/SSB antibodies.
1	58	Right facial palsy, numbness right body, ataxia, dementia, sensory neuropathy	Positive	Positive	Normal	Positive	Positive
2	56	Seizure, sensory neuropathy	Positive	Positive	Positive	Not done	Positive
3	53	Optic neuritis, acute encephalopathy, spastic paraparesis, memory difficulties	Positive	Positive	Positive	Positive	Normal
4	50	Thoracic/cervical myelopathy, left hemiparesis	Normal	Positive	Positive	Positive	Positive
5	45	Cervical myelopathy, optic neuritis	Positive	Positive	Positive	Positive	Normal
6	39	Dementia, bilateral optic neuritis	Positive	Positive	Positive	Positive	Normal
7	37	Recurrent cervical myelopathy, bilateral optic neuritis	Positive	Positive	Normal	Positive	Positive
8	35	Bilateral optic neuritis, ataxia, internuclear ophthalmoplegia, thoracic myelopathy	Positive	Positive	Not done	Positive	Positive
9	34	Bilateral optic neuritis, right hemiparesis	Positive	Positive	Positive	Positive	Normal
10	34	Bilateral optic neuritis, cervical myelopathy	Normal	Positive	Positive	Positive	Positive
11	26	Recurrent cervical myelopathy, optic neuritis	Positive	Positive	Positive	Positive	Normal
12	16	Recurrent cervical myelopathy, bilateral optic neuritis	Positive	Normal	Positive	Positive	Positive

MRI findings. 1) MRI of the brain: All patients had MRI of the brain. Two types of finding were reported, the first is the scattered and disseminated subcortical T2 white matter lesions in the brain (**Figure 1a &1d**) and brainstem that mimicked foci of demylination (**Figure 1b**). This has been seen in 58% of the patients. In addition, black holes that resemble lacunar infarcts were seen in this type (**Figure 1c**). Involvement of basal ganglia and corpus callosum were found in 16% of patients.

Table 2 - Demographic and clinical characteristics of patients with Primary Sjögren syndrome.

Clinical data	n	(%)
Women/men (% women)	12	(100)
Mean age at onset (years)	40	
Xerostomia	10	(83)
Xerophthalmia	11	(92)
Sicca symptoms at neurologic involvement	8	(66)
Schirmer's test	9*	(75)
Positive salivary gland biopsy	11	(92)
Anti SSA/SSB antibodies	7	(58)

*only 11 patients were tested

The second type is the confluent periventricular white matter disease (**Figure 2a-2d**) which was found in 25% of the patients. Diffuse cerebral atrophy was found in 16% of patients and normal MRI brain was found in 2 patients.

2. MRI of spine. Ten patients had MRI of the spine and 3 patients had normal study. In 2 patients, a long segment of cervical cord myelitis and myelomalacia was seen (**Figures 3a-3e**). The average length was 5 levels at the cervical cord region. Other findings include multifocal disseminated T2 high intensity lesions over all spinal cord segments but more prominent over the cervical and thoracic regions of the spinal cord. This was found in 41% of patients. Chronic spinal cord generalized atrophy was seen in one patient (**Figure 3f**).

Discussion. Primary Sjögren's syndrome is a known autoimmune disorder that could affect the nervous system along with the classic glandular involvement and sicca symptoms. Several data in the literature listed the peripheral nervous system complication,[6-8,16-18] however, few reports described and analyzed the involvement of the CNS.[2-5,9-13] Although the exact prevalence of CNS complication in PSS is variable[2] in different reports it may reach up to 25%.[4,5] Our study indicates that the CNS involvement is not uncommon and could have higher prevalence than peripheral nervous system

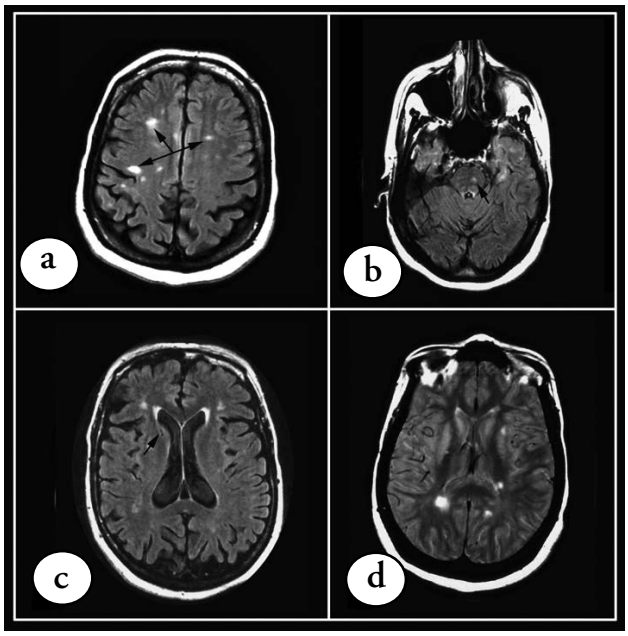

Figure 1 - Brain MRI **a**) fluid-attenuated inversion recovery (FLAIR) showing multiple foci of white matter hyperintensity (arrows) **b**) FLAIR sequence showing brain stem hyperintense lesions (arrow). **c**) FLAIR sequence showing low signal intensity-black holes (arrow) and diffuse brain atrophy. **d**) The white matter foci in Proton density sequence.

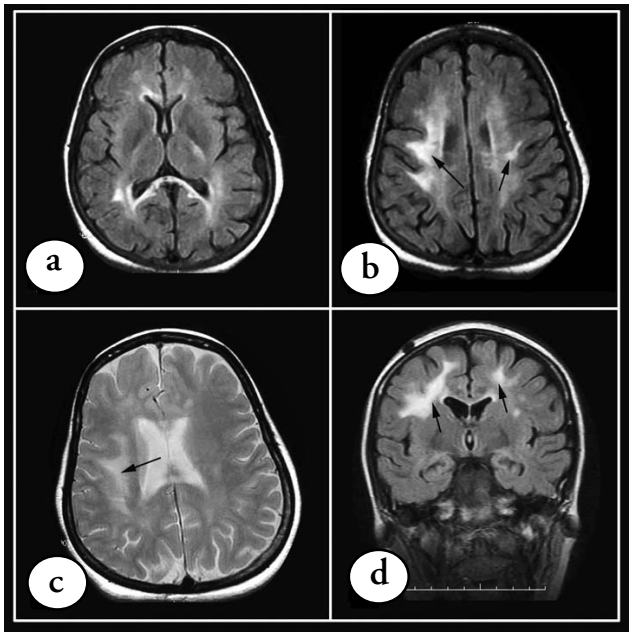

Figure 2 - Brain MRI fluid-attenuated inversion recovery (FLAIR) sequence (A, B, D) and proton density (C) showing the confluent periventricular white matter lesion (arrows).

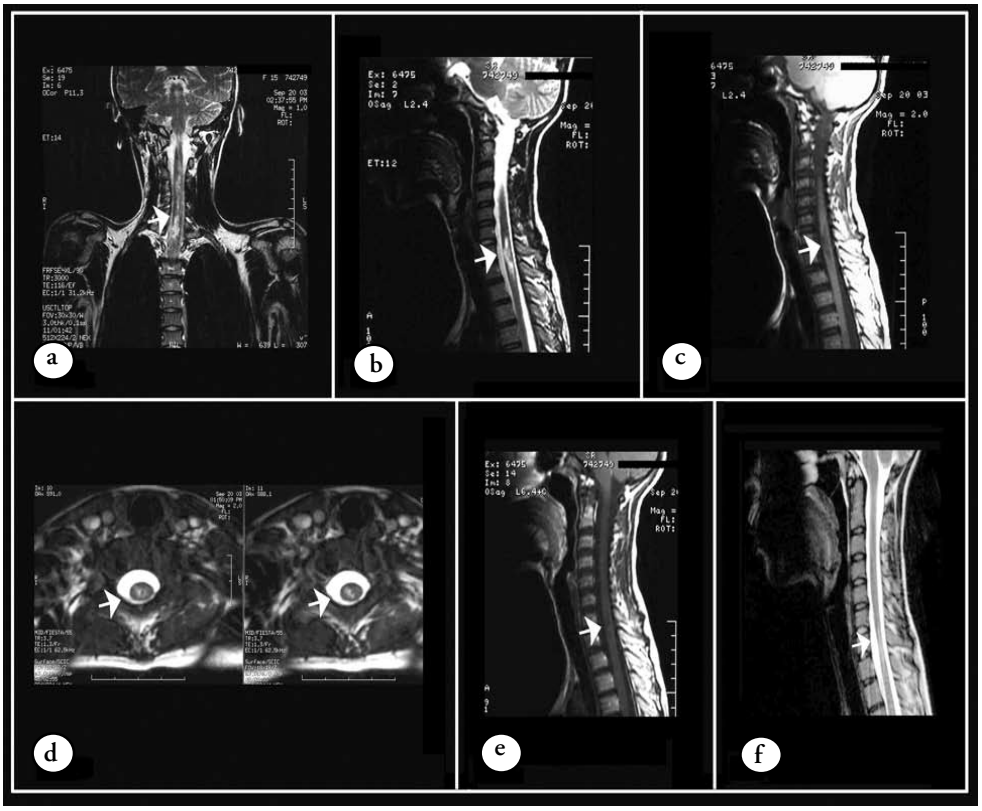

Figure 3 - Spinal cord MRI **a, b, d**) sagital and axial T2 weighted images showing the extended T2 hyperintensity segment in acute cervical myelitis (arrows). **c**) T1 weighted image showing the myelomalacia (arrow). **e**) Gadolinium-enhanced T1 weighted image showing faint enhancement (arrow) **f**) T2 weighted image, 2 years follow up study showing segmental T2 cervical cord hyperintensity and spinal atrophy (arrow).

complication.[9,10,16] Similar to the other reported studies,[1,6,13] a female gender predominance was found in our study. This can be explained by the fact that the female gender has a higher incidence of autoimmune disorders.[13]

In agreement with the available literature,[2-5,9-13] our study highlighted the wide variability in the CNS involvement of PSS. We found that the spinal cord disease followed by optic neuritis are the 2 most common sites of involvement followed by focal and multifocal brain lesions.[19-21] Since the neurologic manifestation can precede the classic glandular sicca syndrome,[10] the diagnosis of PSS can be difficult. The most confusing mimickers are neuromyelitis optica,[22,23] RRMS, and PPMS.[24-27] Atypical clinical presentation may help distinguishing both diseases. For example, recurrent long segments of myelitis especially at the cervical region or bilateral optic atrophy at onset is an atypical presentation for multiple sclerosis and thus make PSS probability high on the list. Another helpful factor in differentiation is the age of onset; our data showed a trend for age of onset to be later than that for multiple sclerosis. Therefore, high index of suspicions and screening for SS is essential for early diagnosis.

The brain MRI findings of the disease are non-specific and the findings can be seen in a wide variety of conditions, such as multiple sclerosis, acute disseminated encephalomyelitis, vasculitis, and other autoimmune diseases, such as systemic lupus erythematosus.[28,29] Interestingly, the MRI of the spine showed a peculiar predilection to the cervical region of the spinal cord and an extensive long segment of involvement, seen as T2 high signal intensity, suggesting acute myelitis intermixed with areas of myelomalacia as seen in most of the patients. We demonstrated the importance and the usefulness of performing the appropriate immunologic tests in the diagnosis of PSS. We also tried to apply the recommended American-European diagnostic criteria[1,15] in our small cohort, and to prove their efficiency and accuracy in confirming the diagnosis.

There are fewer reports in the literature of severe disability with CNS involvement than with peripheral involvement.[13] In this study, the longest follow up was 5 years, and major disability was seen in patients with spinal cord involvement. Relapse occurs with the use of one immune suppressive agent like steroid. Adjuvant

immune suppressive agents used include: azathioprine, chlorambucil, and cyclophosphamide. Remission has been achieved in our study with the use of multiple immune suppressive medical therapies. Having said that, the prognosis and the success of management protocols were not appropriately assessed in this study, as the study is of a retrospective nature and the number of encountered patients was small, as well as the fact that many patients were lost to follow up. Future studies to address the optimal response to immunotherapy in a larger cohort are needed.

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