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Understanding Sjogren's syndrome through the neurologist's eye

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Abstract

Sjögren’s syndrome (SS) is an autoimmune disease characterized by mononuclear cell infiltration and destruction of the lacrimal and salivary glands, which causes dryness of the eyes and mouth. It has a wide clinical spectrum. It can manifest as focal lesions, including focal or motor deficits, stroke, or cerebellar syndromes. Central nervous system involvement should be kept in mind in patients with SS, as it may have serious consequences. Herein, we report a 60-year-old female patient who was misdiagnosed with cerebrovascular disease in the emergency department.

Keywords: Sjögren’s syndrome, Autoimmune disorder, Stroke

Introduction

Sjögren’s syndrome (SS) is a chronic autoimmune disorder that involves exocrine glands, such as the lacrimal and salivary glands. Its prevalence is estimated to vary from 0.5% to 5.0%. In SS patients, central or peripheral neurological involvement may occur with a frequency ranging from 10% to 60%. Neurological presentations may develop in a large spectrum, including optic neuritis, multiple cranial neuropathies, transverse myelitis, aseptic meningitis, encephalomyelitis, epilepsy, stroke, polyneuropathy, and cognitive involvement. In SS, the central nervous system (CNS) may be affected at a rate of 1.5-20.0%, while the peripheral nervous system (PNS) is estimated to be affected at a rate of 10%. The disease may present with neurological findings in 39% of cases [1-3]. In SS, neurological involvement is more common among women (4- to 30-fold) [4]. In this case report, we discuss a patient who presented with weakness and numbness in the left arm and leg and left half of the face who had diffusion restriction on magnetic resonance imaging (MRI) and was diagnosed with SS based on a detailed history and test results.

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Case presentation

A previously healthy 60-year-old right-handed female was admitted to the hospital with complaints of weakness and numbness in the left arm and leg and in the right half of face. The patient's complaints of weakness and numbness started 6 hours before her hospital admission. Her blood pressure was 200/95 mmHg in the emergency department. The patient had no additional neurological complaints, such as speech disorder or loss of consciousness. The patient had normal results from a brain computerized tomography (CT). However, diffusion MRI revealed diffusion restriction in the corresponding Apparent Diffusion Coefficients (ADC) in the left thalamic region, periatrial region, and at the level of left basal ganglia (Figure 1). Based on these findings, the patient was considered to have ischemic cerebrovascular disease and oral clopidogrel (300 mg) and acetylsalicylic acid (100 mg) were administered. The patient was then consulted with our neurological department. She did not have any autonomic symptoms. Her initial neurological examination revealed normal mental status. However, she had right central facial paralysis, right hemi-hypoesthesia involving the right half of face, and her muscle strength was 4/5 in the right upper and lower extremities. Deep tendon reflexes as well as the Hoffman and Babinski signs were negative. Cerebral MR angiography (MRA) was within the normal range. The lesions located in the left periatrial region and at the basal ganglia level showed a hyperintense signal increase on the T2W and FLAIR images (Figure 2, 3). Unenhanced T1W image lesions had an iso-hypointense signal, while contrast-enhanced T1W image lesions showed no enhancement (Figure 4, 5). P100 latency was prolonged (128 ms and 118 ms in the left and right eyes, respectively), on visual evoked potential test. Nerve conduction studies were normal. The patient had normal hepatic and renal function tests, hepatic panel, anti-HIV test, complete blood count, chest radiography, electrocardiogram, and Doppler evaluation of the carotid-vertebral arteries. Protein C, protein S, anti-thrombin III, homocysteine, lupus anticoagulant, anti-cardiolipin antibody, and erythrocyte sedimentation rate were also normal. Factor V Leiden mutation was negative. The ANA test was positive (titer: >1/1000 - <1/3200; granular, spotted pattern), while her anti-Ro (SS-A) and anti-La (SS-B) antibodies were 2+. Rheumatoid factor was elevated (287 IU/ml), and C3 and C4 were decreased (0.38 and 0.08 g/L, respectively). Oligoclonal bands (OCB) assay in cerebrospinal fluid (CSF) was negative. IgG index was normal (0.46). Schirmer test was positive (bilateral < 5 mm). Vitamin B level was 176 pg/ml, and therefore, intramuscular cyanocobalamin was prescribed. A rheumatology consultation was requested with the preliminary diagnosis of SS. No other suggestions were made by the rheumatologists. Since the patient received steroid therapy and fulfilled the SS diagnostic criteria, a salivary gland biopsy was not performed. Thus, treatment with methylprednisolone (1000 mg/day, IV, for 7 days) and azathioprine (2.5 mg/kg/day) was started. Methylprednisolone was maintained at an oral dose of 1 mg/kg/day after day 7. On the 10th day after admission, the patient had nearly a complete recovery in right facial paralysis, muscle weakness at the right upper and lower extremities, and right hemi-hypoesthesia. The patient consented to participate in the study.

Figure 1: Diffusion-Weighted Imaging (DWI) showing lesions located in the left thalamic region, periatrial region, and at the level of left basal ganglia. These lesions revealed restriction in corresponding Apparent Diffusion Coefficients (ADC).

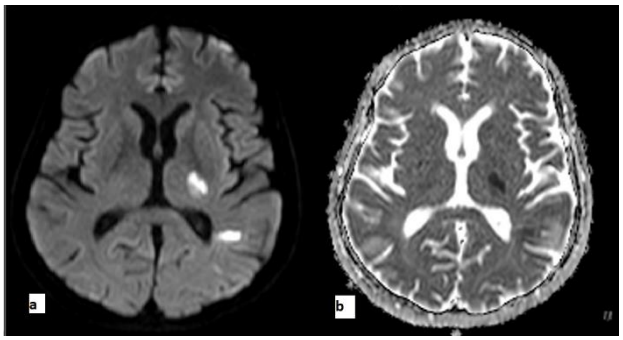


Figure 2, 3: The lesions located in the left periatrial region and at the basal ganglia level showed a hyperintense signal increase on the T2W and FLAIR images.

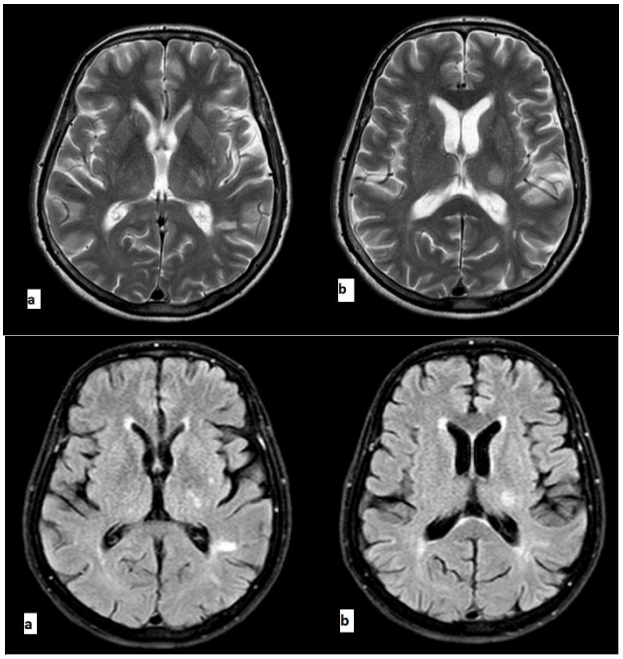
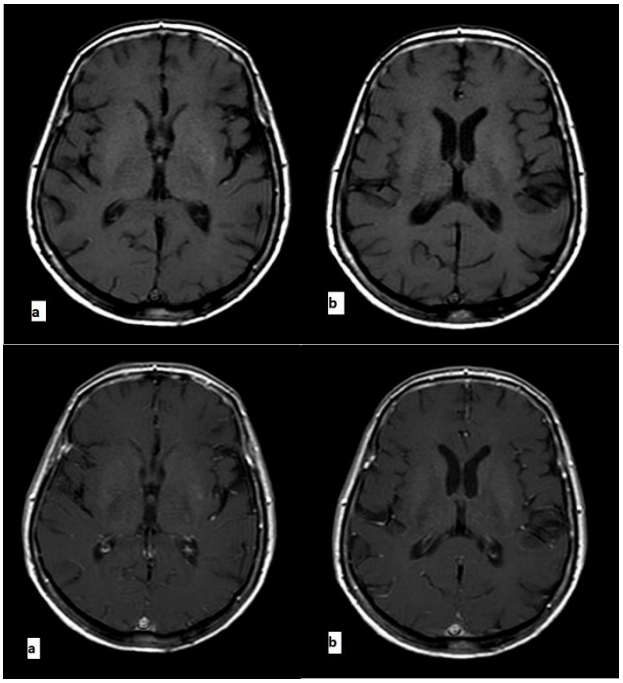


Figure 4, 5: Unenhanced T1 W image lesions show iso-hypointense signal, while contrast-enhanced T1W image lesions show no enhancement.



Discussion

SS is an autoimmune disorder with a gradual course [5]. Neurological signs comprise a wide spectrum. Herein, we report a 60-year-old female patient who had left hemiparesis and paresis in the right half of the face with hypoesthesia. The patient was misdiagnosed with cerebrovascular disease in the emergency department. Although projections about diagnostic criteria for SS vary, in recent years, a consensus was reached in using a revised version of European criteria, also known as American-European criteria [6]. These criteria include: 1) Xerophthalmia, 2) Xerostomia, 3) Positive Schirmer test or Rose Bengal test, 4) Presence of diagnostic histopathological findings in salivary gland biopsy, 5) Other specific salivary gland abnormalities (salivary gland scintigraphy, parotid scintigraphy), and 6) Presence of anti-Ro (SS-A) antibodies [7,8]. The presence of 4 of 6 of these criteria without any other related disease indicates primary SS. Based on the classification system, a diagnosis of SS should be made in cases with a weighted score ≥4. Salivary gland biopsy and anti-SS-A Ro, La appear as factors with the highest weighted values [9].

Our case met 4 of the diagnostic criteria, therefore, she was diagnosed with primary SS. Cranial nerves, PNS, and CNS can be involved in SS [10-12]. Although this patient had signs of CNS involvement, there were no signs indicating PNS involvement. In primary SS, type A (Ro) and type B (La) autoantibodies are elevated in the plasma. They are positive in 20-30% of cases in the early phase and in 62-80% of cases in the late phase. These auto-antibodies can be positive in other auto-immune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, primary systemic sclerosis, and primary biliary cirrhosis [13]. In the diagnosis of SS, the presence of periductal lymphocytic infiltration is a histopathological sign in patients with Sicca syndrome. It is important to note that standard serological tests are less sensitive than salivary gland biopsy.

Salivary gland biopsy should be performed prior to steroid use and the onset of advanced atrophic changes [14]. In the case presented herein, no salivary gland biopsy was performed since the patient previously received steroid therapy. Although CNS involvement rate was comparable in seropositive and seronegative patients in previous studies, it has been reported that more severe complications are associated with anti-Ro positivity, and that individuals with HLA-DR3 and DR4 are more vulnerable to more severe involvement of CNS in a genetic manner [15,16]. Such complications have considerable effects on both the treatment and prognosis of SS.

It remains controversial whether CNS involvement is associated with generalized vasculitis or an organ-specific antibody reaction. MRI is highly sensitive in showing cerebral dysfunction in SS patients. Periventricular or subcortical white matter lesions at T2-weighted images are the most observed findings (70-80%). In addition, hyper-intensity compatible with demyelination suggesting multiple sclerosis (MS), dilated sulci, ventricular dilatation and, in rare instances, corpus callosum lesions can also be seen. Such MRI findings are observed in 80% of primary SS patients with CNS involvement, including focal neurological signs [17,18]. In our case, lesions were detected at the left thalamic and periatrial regions and left basal ganglia in MRI. Although it was first thought that cerebral lesions may be compatible with lesions defined in SS, these lesions may also be related to risk factors, including age and hypertension. In addition, similar lesions can be found in vasculitic lesions and ischemic cerebrovascular diseases. In the patient described herein, vasculitis markers and factors other than anti-SS-A and anti-SS-B, which may predispose the patient to thrombosis, were normal. Since lesions with characteristics similar to those in the case presented herein can also be observed in vasculitic lesions and ischemic cerebrovascular diseases, the lesion in this patient was classified as an ischemic cerebrovascular occlusion secondary to SS hyper-intense signal increase at the left thalamic region on T2-FLAIR sequences. This classification was made even though the patient's vasculitis markers and factors other than anti-SS-A and anti-SS-B (enhancing predisposition to thrombosis) were normal. Moreover, the presence of lesions at the thalamus and basal ganglia excluded MS. The fact that the symptoms of SS were prominent suggested that these lesions were associated with SS.

There are few studies on the risk of ischemic stroke after a diagnosis of primary SS. Although patients with autoimmune disorders, such as inflammatory, systemic vasculitis, rheumatoid arthritis, and systemic lupus erythematosus tend to develop atherosclerosis, this is not the case in primary SS. Although SS does not increase the risk for ischemic stroke [19], anti-phospholipids and lupus anticoagulants are positive more frequently, which increase stroke risk [20]. When considered together, the case presented herein had normal carotid-vertebral CT angiography, normal echocardiography, and normal 24-hour Holter monitoring, and therefore, the patient was considered to have a stroke with neurological involvement of SS. There is no consensus regarding the best treatment of SS cases with CNS involvement. However, a conservative approach is recommended in cases with mild CNS involvement, while intravenous pulse corticosteroid and cyclophosphamide are used in patients with progressive neurological dysfunction and in those with active CNS disorder [21]. In our case, intravenous pulse steroid therapy was given over 7 days, and the patient had almost a complete clinical recovery. For maintenance, therapy continued with 1 mg/kg/day oral steroid and 2.5 mg/kg/day azathioprine. In the current case, clinical and cerebral MRI findings suggest MS in differential diagnosis. However, the patient may have an association of SS and MS. In SS, MS-like clinical and radiological manifestations can be seen, although it is rare. In the current case, CNS involvement of SS was considered based on a negative OCB test, the presence of xerostomia and xerophthalmia, positive ANA and anti-Ro antibodies, and a positive Schirmer test.

Conclusions

Based on the current case, we recommend careful assessment of patients presenting with clinical pictures suggesting ischemic cerebrovascular disease by MRI, blood tests, and additional imaging modalities. Early diagnosis in such cases is important to initiate treatment, direct SS prognosis, and prevent unnecessary treatments and costs.

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