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Sjögren's Syndrome Presenting with Temporary Hemiplegia Mimicking Transient Ischemic Attack

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Sjögren's syndrome manifests with a wide variety of neurologic symptoms. This case report presents a 53-year-old woman with Sjögren's syndrome associated with temporal hemiplegia, which was suspected to be a transient ischemic attack. After induction of immunosuppressive therapies [high-dose prednisolone (1 mg/kg/day) and intravenous cyclophosphamide (total 5 g)], the hemiplegia did not reappear and the blood flow abnormalities remarkably improved as depicted on electroencephalography and single photon emission computed tomography. This case suggests that temporal hemiplegia presenting with transient ischemia-like attack symptoms may be a neurologic manifestation of Sjögren's syndrome and responsive to immunosuppressive therapy.

Keywords: extraglandular manifestation; immunosuppressive therapy; neurological symptom; Sjögren's syndrome; transient ischemic attack
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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by destruction of the lacrimal and salivary glands, as a result of lymphocytic infiltration; thus, the primary symptoms of SS are dry eyes and dry mouth. However, SS may also manifest with various extraglandular symptoms, including peripheral and central nervous system (CNS) involvement (Brito-Zeron et al. 2016).

CNS is involved in 2-5% of cases of primary SS (pSS), while peripheral neuropathy in 5-15% of cases of pSS (Alunno et al. 2019). The CNS complications of pSS are rare and manifested by a wide range of simple symptoms, such as meningitis, seizure, cerebral vasculitis, and transverse myelitis (Delalande et al. 2004; Margaretten 2017; Mekinian et al. 2020). Cerebral vasculitis causes arterial stroke, accompanied by abnormalities on MRI (Ferreiro et al. 1987). In contrast, some pSS patients have subjective cognitive difficulties referred to as "brain-fog," which often precede the diagnosis of pSS (Manzo et al. 2019). These diverse clinical manifestations may lead to delayed diagnosis of SS (Soliotis et al. 2004). The pathophysiology of CNS involvement in pSS is yet to be elucidated, and immunosuppression may have a therapeutic effect on neurologic symptoms of SS (Kampylafka et al. 2016). This case report presents a patient with pSS that manifested with repeated episodes of temporal hemiplegia, which was initially suspected to be a transient ischemic attack (TIA). Furthermore, the remarkable therapeutic effect of immunosuppressive therapies on this neurologic symptom is also described.

Case Presentation

A 53-year-old woman, diagnosed with Raynaud's phenomenon and sicca symptoms 4 years before, initially evaluated for a 4-month history of several episodes of severe weakness and numbness of the left upper and lower extremities. Each episode lasted approximately 30 minutes, and the episodes occurred twice or thrice each month. Moreover, during this 4-month period, the patient experienced symptoms of cognitive impairment, such as forgetting how to use her mobile phone and an inability in per-

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forming simple calculations.

The patient was admitted to a community hospital for similar TIA-like symptoms and underwent magnetic resonance imaging (MRI), magnetic resonance angiography of the brain, and angiocardiography to check for thrombi, which revealed no abnormalities. She had no history of diabetic mellitus, hyperlipidemia, or hypertension. Thus, a collagen disease was suspected due to Raynaud's phenomenon and sicca, despite the absence of any musculoskeletal, skin, and constitutional symptoms. Anti-nuclear antibody testing was performed, for which the titer was strongly positive (1:2,560, speckled) (reference value < 80). The patient was then referred to our institution for further evaluation and diagnostic testing.

The patient's laboratory test results were significant of the following: C-reactive protein was 1.2 mg/dL; serum immunoglobulin G (IgG) was slightly elevated at 2,191 mg/dL (reference value 870-1,700); complement levels (C3, C4, CH50) were normal; anti-SSA (Ro) (140 IU/mL) (reference value < 10), anti-SSB (La) (286 IU/mL) (reference value < 10), and rheumatoid factor (19 IU/mL) (reference value < 10) were positive; prothrombin time was 105.5% (reference value 70-130) and activated partial thromboplastin time was 31.9 s (reference value 24.3-36.0), protein C activity was 97% (reference value 70-150), protein S activity was 69% (reference value 56-162); and anti-RNP, Smith, double-stranded DNA, cardiolipin, beta2-glycoprotein antibodies, lupus anticoagulant, myeloperoxidase antineutrophil cytoplasmic antibody (ANCA), and proteinase 3-ANCA were negative. Schirmer test showed decreased tear secretion (right eye 2 mm, left eye 5 mm). Gum test showed reduced salivary flow rates (6 mL/10 min), and a lip biopsy revealed focal lymphocytic sialadenitis (Fig. 1). Urinalysis revealed no proteinuria and occult blood. Based on the 2016 American College of Rheumatology and European League Against Rheumatism criteria (Shiboski et al. 2017), the patient was diagnosed with pSS, and further

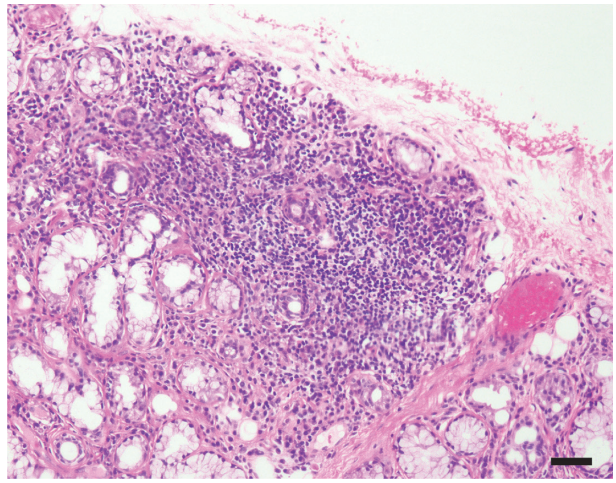

Fig. 1. Histopathology of minor salivary gland.
Lymphocytic sialadenitis with periductular aggregates of > 50 lymphocytes, compatible with Sjögren's syndrome (hematoxylin-eosin staining, × 40). Scale bar shows 100 μm.

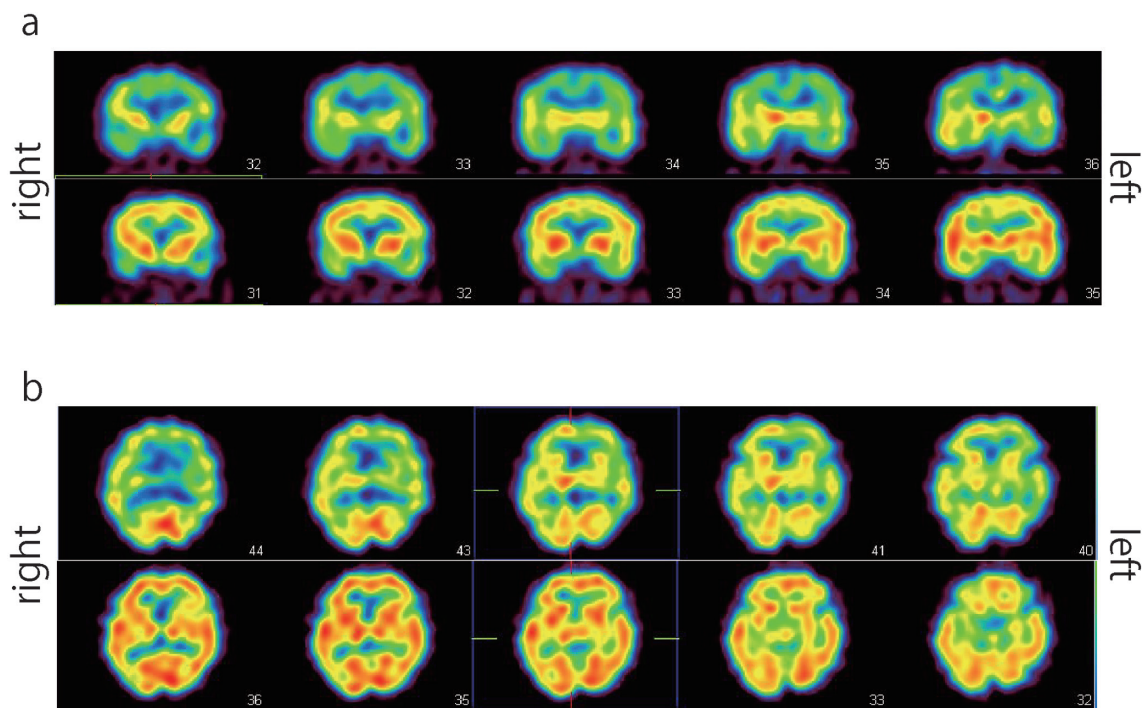

Fig. 2. Single photon emission computed tomography.
Brain blood flow was evaluated before (upper panels) and 7 months after immunosuppressive therapies (lower panels) in each coronal (a) and transverse (b) section. Blood flow was remarkably improved after the treatments.
SPECT, Single photon emission computed tomography.

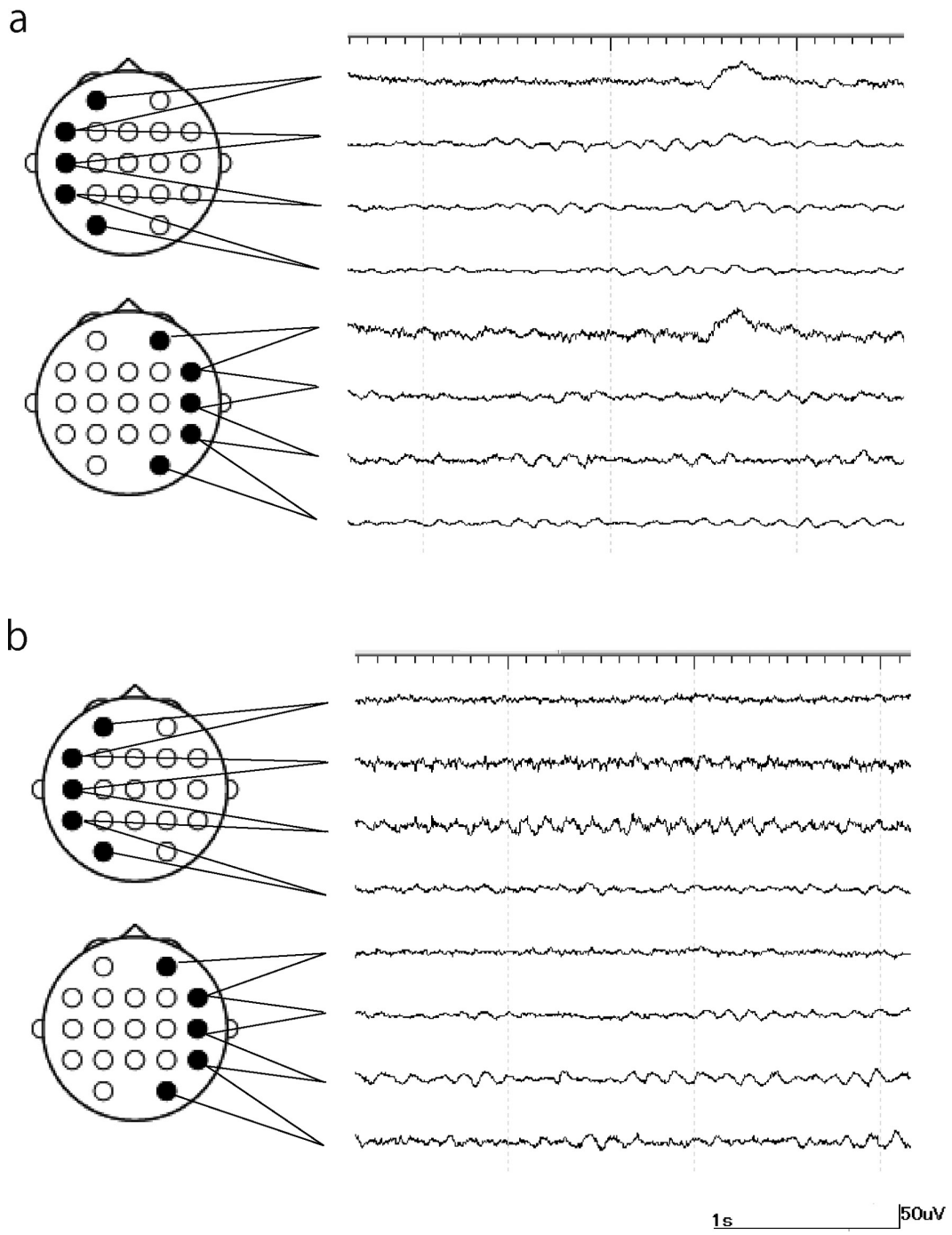

Fig. 3. Electroencephalography recorded before (a) and 7 months after immunosuppressive therapies (b). Slow wave activity (6.5-7.5 Hz) was improved to 8-9 Hz and delta power activity disappeared after immunosuppressive treatments.

testing was performed.

Cerebrospinal fluid (CSF) findings were as follows: white cell count 1 cell/μL (reference value $\leqq$ 4), protein 120 mg/dL (reference value 10-40), IgG 20.6 mg/dL (reference value 0.5-4.0), IgG index 0.597 (reference value < 0.8) and interleukin-6 (IL-6) < 8 pg/ml. Cerebral blood flow was evaluated with single photon emission computed tomography (SPECT), which showed hypoperfusion of the both hemispheres with slight left-sided dominancy (Fig. 2). Electroencephalography (EEG) demonstrated a slow wave activity (6.5-7.5 Hz) and an increase in delta power activity (Fig. 3a). The diffuse brain hypoperfusion did not account for left-sided hemiplegia; hence, we considered that this hemiplegia was not caused by conventional TIA with stenosis of blood vessels or brain embolization. The temporal hemiplegia seemed to be a focal neurologic symptom. Given the diffuse brain damage and the diagnosis of SS, however, we considered that the patient's neurologic symp-

toms were due to autoimmune-mediated mechanisms.

After sufficient informed consent, immunosuppressive treatments were started with prednisolone (PSL) (1 mg/kg/day = 50 mg/day) and intravenous cyclophosphamide. After starting immunosuppressive therapy, the temporal hemiplegia did not reappear. At 7-month follow-up, the brain hypoperfusion was improved as indicated on SPECT (Fig. 2), and the delta power activity disappeared on the EEG (Fig. 3b). After 10 administration of cyclophosphamide pulse therapy (total 5 g), azathioprine (50 mg/day) was started; the PSL was decreased and maintained at 3 mg/day. At 8-year follow-up, the patient's neurologic symptoms had not recurred. Informed consent was obtained from the patient.

Discussion

In this case report, we describe a patient with pSS who experienced repeat episodes of temporal hemiplegia with a TIA-like presentation. The differential diagnosis of TIA is broad and includes brain tumors, CNS infection, trauma, hypoglycemia, migraines, multiple sclerosis, subarachnoid hemorrhage, and vertigo (Simmons et al. 2012). Although the patient's primary symptom was left-sided hemiplegia, the cerebral blood flow scintigraphy showed diffuse and EEG showed abnormal waves. The finding of hypoperfused brain lesions was inconsistent with the hemiplegia site; therefore, it was determined that she was not experiencing a conventional TIA. Neuropsychiatric systemic lupus erythematosus (NPSLE) involves diffuse brain lesions and cognitive impairment (Schwartz et al. 2019), and a wide range of neurologic involvement is also observed in pSS patients (Mekinian et al. 2020).

Although the pathophysiology of CNS involvement in pSS has yet to be elucidated, it can be caused by microvascular ischemic changes on brain associated with vasculitis and inflammatory cell infiltration (Jeltsch-David and Muller 2014). However, in this case, EEG recording during an episode of hemiplegia was not performed; therefore, the TIA-like symptom may be considered to be caused by epilepsy (Nadarajan et al. 2014), which is associated with NPSLE (Grasso et al. 2021). The pathogenesis of NPSLE involves brain-reactive autoantibodies, cell-mediated inflammation, and pro-inflammatory cytokines (Schwartz et al. 2019). Among these cytokines, IL-6 in brain was neurotoxic and associated with proconvulsive effects in animal models (Li et al. 2011) as well as functional diagnostic factor (Hirohata et al. 2009). Although our patient had low IL-6 in CSF, measuring the cytokine levels just after a neurological attack would help in clarifying the pathomechanism of neurological symptoms. Although neurological symptoms were compatible to NPSLE, this patient did not develop skin rash, joint symptom, hematological disorder, and disease-specific autoantibodies, therefore not meeting the diagnostic criteria for SLE (Aringer et al. 2019). CSF analysis showed albuminocytological dissociation in this patient. However, demyelinating diseases, such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy were unlikely because of the absence of peripheral neuropathy. This albuminocytological dissociation of CSF may indicate the dysfunction of blood brain barrier (Brooks et al. 2019). Brain MRI of our patient revealed no significant lesions. While CNS involvement in Sjögren's syndrome associated with vascular lesions and infarction show abnormalities in MRI (Ferreiro et al. 1987), some patients with non-focal/diffuse CNS disease had no abnormal MRI findings in pSS (Soliotis et al. 2004) and SLE (Luyendijk et al. 2011). These brain lesions are invisible in conventional MRI but might be detected in quantitative MRI (Luyendijk et al. 2011). Since this patient had no risks for atherosclerosis and embolism, we considered that this TIA-like symptom was caused by an autoimmune mechanism, and we then started her on immunosuppressive therapy.

The treatment for CNS involvement in pSS has yet to be established. Moreover, to the best of our knowledge, to date, no double-blind, placebo-controlled studies have been performed in this population. Thus, the treatment of CNS involvement in pSS is typically based on case reports, uncontrolled studies, and similar reports of other rheumatic disease, such as SLE (Bougea et al. 2015; Kampylafka et al. 2016). In this context, we selected high-dose steroids and cyclophosphamide, which were remarkably successful as an induction therapy for treatment of NPSLE (Bertsias et al. 2010).

Several cases with TIA in SS have been reported (Binder et al. 1988; Nagahiro et al. 1996; Sakata et al. 2014). In two cases (Nagahiro et al. 1996; Sakata et al. 2014), blood vessel stenosis occurred and treatment with bypass surgery was successful. In five cases (Binder et al. 1988), the treatment details were not described. To our knowledge, our case is the first report in which TIA-like symptoms of SS was successfully treated with immunosuppressive therapies.

This case suggests that pSS should be considered in the differential diagnosis for patients who present with TIA-like symptoms associated with diffuse brain damage on SPECT and/or EEG. In such a case, the patient should be examined for sicca symptoms and autoantibodies. The immunosuppressive therapies may be effective to treat the neurologic symptoms of SS.

Conflict of Interest

The authors declare no conflict of interest.

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