Limbic Encephalitis Associated with Sjögren’s Syndrome: Report of Three Cases

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Abstract

Sjögren’s syndrome (SS) may be complicated by neurological manifestations. We herein report three women (age range 26-60 years old) who all presented with limbic encephalitis (LE) as the predominant clinical feature 3 months to 15 years after the diagnosis of SS. The 26-year-old patient also developed acute motor axonal neuropathy one week after autoimmune encephalitis. All three patients showed contrast-enhanced MRI lesions and inflammatory cerebrospinal fluid findings, while not displaying any anti-neuronal antibodies and showing a remarkable response to immunotherapy. SS is often overlooked when the symptoms are mild. Therefore, in LE cases with no identifiable cause, serological screening for rheumatologic disorders is recommended.

Key words: limbic encephalitis, autoimmune encephalitis, Sjögren’s syndrome, motor neuropathy, immunotherapy


Introduction

Sjögren’s syndrome (SS) is an autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands leading to dry eyes and mouth (1). SS may develop as a primary syndrome or secondary to other systemic autoimmune disorders. Neurologic complications occur in nearly 20% of all patients with primary SS (2, 3). Although peripheral nervous system (PNS) involvement has been widely described in several previous studies (1-5), recent studies have implicated the central nervous system (CNS) involvement as a frequent manifestation of SS (6, 7). After the introduction of the current diagnostic criteria for the SS in 2002 (8), an increased frequency of CNS involvement has been documented in SS patients (7). Nevertheless, autoimmune encephalitis (9, 10) and motor dominant neuropathy (11, 12) have only rarely been reported in relation to SS. In this report, we describe three cases with SS, two presenting with only limbic encephalitis (LE) and the third patient who developed acute motor axonal neuropathy (AMAN) after LE.

Case Reports

Case 1

A 47-year-old woman presented with a two-week history of agitation, aggression, paranoid delusions and short-term memory loss. She had started to complain of dry mouth and eyes some 3 months before presentation. On neurological examination, she was unable to stand unaided due to truncal ataxia and she also had severe dysmetria. She did not present with areflexia, sensory abnormalities or Romberg’s sign and therefore dorsal root ganglionopathy was not considered in the differential diagnosis. Brain MRI demonstrated left medial temporal lobe hyperintensity with contrast enhancement. Cerebrospinal fluid (CSF) analysis revealed mononuclear pleocytosis (22 lymphocytes/mm³), normal protein and glucose levels. The CSF cytology was normal and there were no oligoclonal bands. Electroencephalography (EEG) revealed a diffuse bilateral slow activity. The findings of

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chest X-rays, mammography and whole-body PET failed to show an underlying tumor. Panels for pathogens and anti-neuronal antibodies were negative, whereas a panel for vasculitis-rheumatologic disorders revealed SS-A and SS-B antibodies. A pathological examination of the salivary glands confirmed the diagnosis of SS. Under intravenous (i.v.) methylprednisolone (MP) (1 g/day×5 days) treatment, she showed a marked improvement of both the cerebellar and behavioral symptoms and was discharged while being administered prednisone at a tapered dose. At a follow-up visit 4 months later, she had no neurological symptoms, and her neurological examination and control MRI were normal.

Case 2

A 60-year-old woman presented with apathy, disorientation, confusion, agitation and difficulty walking. Two months before admission, she had started having episodes of vomiting and depressive symptoms and one month prior to presentation she had a single generalized tonic convulsive seizure. She had been diagnosed with SS 15 years ago by lip biopsy findings and a serological analysis and also had a history of hypertension and anemia. A neurological examination showed severe truncal ataxia. In a cranial MRI examination, FLAIR and T2-weighted scans demonstrated high signal areas in the right anterior temporal lobe and the entire left temporal lobe and T1-weighted scans with gadolinium showed contrast enhancement, primarily in the cortical regions (Figure A, B). Although CSF had no cells and both a normal protein and glucose content, oligoclonal bands were detected (pattern 2). EEG and whole-body PET were normal. Due to mild symptoms (occasional eye dryness), the patient did not receive any treatment for SS. Nevertheless, she was positive for SS-A and SS-B antibodies, but her screening panels for anti-neuronal antibodies and pathogens

Figure. MR images of case 2 before and after immunotherapy. Before immunotherapy, a FLAIR scan (A) shows high signal intensity areas in the right anterior temporal lobe and the entire left temporal lobe and T1-weighted MR scan with gadolinium (B) shows contrast enhancement in the same temporal regions. FLAIR (C) and contrast enhanced T1-weighted MR scans (D) performed after immunotherapy show a significantly decreased hyperintensity and contrast enhancement in the bilateral temporal regions.
were negative. The patient was treated with pulse i.v. MP (1 g/day × 5 days) and i.v. immunoglobulin (IVIg) 0.4 g/kg for five days and monthly repeat MP and IVIg treatments were planned. After four months of immunotherapy, her behavioral symptoms completely disappeared, her neuropsychological examination findings were normal and a neurological examination was normal, except for mild bilateral dysmetria. A control MRI examination showed significantly decreased hyperintensity and contrast enhancement in the bilateral temporal regions (Figure C, D).

**Case 3**

This 26-year-old woman presented with a 2-week history of confusion, memory loss and visual hallucinations. She had a 9-month history of SS, which had been diagnosed based on clinical features, serological findings and a pathological examination of the salivary glands. A neurological examination revealed only somnolence, but no lateralizing findings. A bedside cognitive evaluation showed an impaired executive function and an impaired verbal and visual short-term memory. Brain MRI revealed increased signals in the bilateral medial temporal lobes and contrast enhancement in the same regions. CSF studies showed mononuclear pleocytosis (43 lymphocytes/mm³) with normal protein and glucose levels. A further analysis of the CSF showed oligoclonal bands (pattern 2) and an increased IgG index (2.7). CSF cytology was negative for malignant cells. EEG and whole-body PET were normal. She was positive for SS-A and SS-B antibodies and her screening panels for anti-neuronal antibodies and CNS pathogens were negative. Treatment with i.v. MP 1 g/day for five days resulted in a dramatic improvement of all symptoms and a normalization of the MRI findings within four weeks. One week later, she was admitted again with progressive leg and hand weakness, ascending from his distal lower limbs to his proximal lower limb muscles. Her neurological examination showed muscle weakness [medical research council (MRC) 1-2/5 muscle strength] in both lower limbs and MRC 4-5/5 muscle strength in both upper limbs without any sensory loss. Her deep tendon reflexes were lost in the lower limbs and hypoactive in the upper limbs. Nerve conduction studies were suggestive of AMAN based on a reduced motor action potential amplitudes, normal motor nerve conduction velocity values and normal sensory nerve amplitude and velocity results. Needle electromyography showed signs of denervation and no myopathic motor unit potentials were observed. She was started on a five-day course of IVIg (0.4 g/kg/day), and thereafter showed a marked clinical improvement. Serial MRIs obtained over 2 years of follow-up showed normal findings and no brain atrophy. Her repeat neuropsychological and neurological examinations were also normal except for mild numbness in the legs.

In all three patients, laboratory tests revealed normal a complete blood count, sedimentation rate, general blood chemistry, vitamin B₁₂, folic acid and thyroid function tests. Serum thyroglobulin and thyroperoxidase antibodies were negative, whereas anti-SS-A and anti-SS-B antibodies were positive in all patients. Antibody screening was negative for anti-nuclear antibody (ANA), anti-Sm, anti-ds DNA, anti-RNP, anti-ScI70, rheumatoid factor, anti-anticardiolipin IgM/IgG antibody, anti-neutrophil cytoplasmic antibody (ANCA) and anti-Jo-1 antibody. None of the patients showed antibodies to Hu, Yo, Ri, Ma2, CV2, amphiphysin, N-methyl-D-aspartate receptor (NMDAR), α-amino-hydroxy-methylisoxazolepropionic acid receptor (AMPA), contactin-associated protein-like 2 (CASPR2), leucine-rich, glioma inactivated 1 (LGII), gamma-aminobutyric acid (GABA)₆ receptor and glutamic acid decarboxylase (GAD) as investigated by commercial kits (Euroimmun, Luebeck, Germany). Likewise, in all patients, CSF PCR assays for viral pathogens (varicella zoster virus, herpes simplex virus, human herpes virus-6), CSF cultures for bacterial (including tuberculosis) and fungal pathogens were negative. In all three patients, the salivary gland samples obtained by lip biopsy showed chronic sialadenitis with lymphocytic foci. There were no other systemic manifestations of SS due to the involvement of the cutaneous, pulmonary, hematologic, vascular or autonomic systems.

**Discussion**

We herein described three primary SS patients presenting with acute encephalopathy. The significant decrease in salivary and lachrymal secretion, inflammatory cell infiltration in salivary gland samples obtained by lip biopsy and the presence of anti-SS-A and anti-SS-B antibodies satisfied the diagnostic criteria for definite SS in all patients (8). Cognitive dysfunction and psychiatric symptoms were the outstanding features of encephalitis associated with primary SS. An extensive search for an underlying malignancy and alternative autoimmune, infectious and metabolic etiologies proved negative and consequently the diagnosis was established as autoimmune LE associated with SS. Our diagnosis was supported by the inflammatory CSF findings (lymphocytosis, oligoclonal bands and increased IgG index) and with a prompt and remarkable response to immunotherapy. The MRI findings were useful for demonstrating the inflammatory brain lesions in SS, which were promptly reversed in response to immunosuppression. A notable feature of the brain lesions encountered in all three SS patients was the contrast enhancement, which is very rarely seen in autoimmune and paraneoplastic encephalitis cases. Likewise, although inflammatory CSF findings are typically seen in autoimmune-paraneoplastic encephalitis, only around 30-40% of the patients with acute limbic encephalopathy present with these CSF features (13).

Neurological complications may occur in the relatively early stages of SS (1). Various neurologic conditions including motor or sensory deficits, seizures, movement disorders, headache, neuromyelitis optica, chronic progressive myelitis, dementia and cerebellar syndromes have been reported in association with SS (6, 9, 10). There have been only a few
reported cases presenting with autoimmune encephalitis, meningoencephalitis, brainstem encephalitis or meningoencephalomyelitis as the initial manifestation (9, 10, 14-16). In such cases, including our patients, memory impairment, disturbance of consciousness and orientation were common symptoms.

Peripheral nervous system manifestations of SS include cranial nerve palsies, pure or predominantly sensory polyneuropathy, sensorimotor polyneuropathy and mononeuritis multiplex (17). Our third patient developed ANAM following the clinical findings of LE. Only two cases with ANAM in association with SS have previously been reported to our knowledge (11, 12). Our patient had rapid-onset ascending quadriparesis and areflexia with preserved sensation. She had absent compound muscle action potentials on nerve conduction studies. Notably, she responded dramatically to IVlg and experienced nearly a complete recovery within a short period of time. Our third patient is the first reported case in the literature of a patient developing ANAM after LE in combination with SS-A and SS-B positivity and pathological findings consistent with SS.

The pathogenesis of neurological complications in SS remains unclear. However, neuroimaging features, CSF findings and pathological data suggest autoimmune-inflammatory mechanisms and/or vasculitic processes as potential underlying mechanisms (18). Biopsy studies of sensory ganglia and peripheral nerves suggest neuronal degeneration which is caused by lymphocytic infiltration as the leading factor in neuronopathies, mononeuropathies and axonal polyneuropathies. These changes might be caused by necrotizing vasculitis and/or anti-neuronal antibodies (e.g., ganglionic acetylcholine receptor antibodies) (19-21). Mononuclear cell infiltration has been observed in brain biopsy samples of SS patients with CNS manifestations (22). Although vasculitic processes have been proposed as an underlying mechanism (23), the clinical and imaging features of our patients were not strictly consistent with vasculitis. Nevertheless, without a proper pathological examination, primary CNS vasculitis can not be entirely ruled out. Although the pathogenic action of anti-neuronal antibodies and cross-reaction between anti-SS antibodies and neuronal antigens has also been proposed as a potential mechanism (23), these assumptions have not been reliably proven. Finally, although no persistent viral infections have been defined in SS patients with or without neurological complications, an immunological reaction triggered by as yet unknown viral pathogens might still be considered as a potential mechanism in SS-related CNS complications.

Evidently, it is not possible to definitively claim that there is a pathogenic link between SS and neurological symptoms and it is entirely probable that LE and SS co-occurrence is purely coincidental, presumably owing to a certain immunogenetic background. Also, our patients might actually be autoimmune encephalitis patients with as yet uncharacterized anti-neuronal antibodies. Nevertheless, certain common clinical features that are not constantly seen in other autoimmune encephalitis cases, such as contrast enhancement, high incidence of inflammatory CSF findings and prompt response to immunotherapy with minimal or no residual findings might suggest that LE related with SS constitute a specific syndrome with a distinctive pathogenesis.

In conclusion, although CNS or PNS manifestations often precede the diagnosis of SS, they may also be seen as early as a few months after the initial diagnosis. Neurological presentations related with SS may closely mimic paraneoplastic neurological syndromes due to their acute onset, progressive course and imaging findings suggestive of autoimmune encephalitis. Following the exclusion of metabolic, toxic, infectious etiologies and potential malignancies and after demonstrating the absence of well-characterized anti-neuronal antibodies, a diagnosis can easily be established based on medical history, salivary gland biopsy and serological screening. Therefore, even in cases with mild rheumatologic findings, antibody screening for rheumatologic disorders including SS should be performed in acute encephalopathy cases. Although LE related with SS may present with a severe and progressive course, it appears to give a dramatic response to immunotherapy. It is therefore crucial not to overlook the diagnosis of SS and consider high-dose immunosuppressive treatments, especially if there are no other identifiable causes to describe the clinical presentation.

The authors state that they have no Conflict of Interest (COI).

References