Rhombencephalitis as an Initial Manifestation of Primary Sjögren's Syndrome: A Case Report and Review of the Literatures

San-Feng Chen, Ming-Jang Chiu, Jen-Jen Su

Abstract-

Purpose: We present a case report and a comprehensive review of the literature concerning aseptic meningoencephalitis and Sjögren's syndrome (SS).

Case Report: We report a 44-year-old woman of primary SS with initial presentation of aseptic meningoencephalitis and a reversible magnetic resonance image (MRI) lesion in the medulla. The diagnosis of primary SS based on ocular dryness, lacrimal hyposecretion, secretory and excretory dysfunction from sialocintigraphy, and positive anti-SS-A antibodies. Corticosteroid and cyclophosphamide therapies reversed the neurological deficits and the MRI lesion.

Conclusion: Primayr SS may have variable manifestations in the central nervous system which may precede the classic sicca symptoms. SS should be investigated in cases of aseptic meningoencephalitis even without clinical signs of xerostomia or xerophthalmia. MRI is useful in demostrating brain lesions and in evaluating treatment efficacy of the SS.

Key Words: Sjögren's syndrome, meningoencephalitis, anti-Sjögren's syndrome A antibody, anti-Sjögren's syndrome B antibody

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INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease, which may be either primary or secondary to other connective tissue diseases. The pathology of SS is characterized by mononuclear cell infiltration and destruction of salivary and lacrimal glands, leading to xerostomia and xerophthalmia[1]. Peripheral nervous system (PNS) involvement is a well-documented occurrence with a frequency of 10-20%[2,4]. However, prevalence of the central nervous system (CNS) involvement is still a controversial issue, with a frequency ranging from 1.5% to 25%[5,6]. Since meningoencephalitis in primary SS is treatable, it is important to understand its clinical features in order to make a differential diagnosis of meningoencephalitis. We report a patient with primary SS, who presented with aseptic meningoencephalitis and a reversible magnetic resonance image (MRI) lesion in

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CASE REPORT

The 44-year-old woman suffered from progressive dizziness, nausea, and vomiting for 2 weeks before admission, she later developed an unsteady gait with deviation to the right side and occasional vertigo and diplopia. She also complained of numbness in the lower part of her face. Neurological examination revealed that the patient was in a state of clear consciousness. She displayed mild weakness with scores of manual muscle test (MMT) 4+ /5 in bilateral lower limbs. She was normal in all modalities of sensory test including pinprick, light touch, temperature, and joint position sense. She had overt dysphagia, thus a nasogastric tube was inserted. Head magnetic resonance image (MRI) showed an abnormal high signal intensity (SI) at the left medulla oblongata without definite contrast medium enhancement (Figure 1A & B). Brain tumor was suspected. After admission, she developed progressive weakness and became bed-ridden on the 5th day of hospitalization. Her muscle power reduced to MMT 0/5 (right upper limb), 2/5 (right lower limb), 3/5 (left upper limb), and 2/5 (left lower limb). Generalized hyper-reflexia was found. Methylprednisolone, 40 mg, every 8 hours, was given by intravenous injection for clinical deterioration. However the clinical condition did not improve after steroid therapy.

Follow-up MRI identified an ill-defined lesion with a fluffy margin and mild mass effect in the left medulla oblongata with minimal peripheral enhancement. But there was no evident intrathecal lesion or focal SI change in the cervicothoracic cord. Inflammatory or demyelinating lesion was then considered (Figure 1C & D). Since she had poor response to steroid therapy, plasma exchange therapy was performed which did not improve her muscle power significantly.

Visual evoked potential (VEP) study showed absence of goggle VEP from the left eye. The somatosensory evoked potential study showed a prolonged central conduction time from both median nerves compatible with a central lesion. A nerve conduction velocity (NCV) study showed markedly reduced compound muscle action potentials in nearly all sampled nerves, reduced sensory action potentials and mildly slowed sensory conduction velocity in some nerves. The F-wave study showed normal responses in the left tibial nerve, prolonged minimal latency in the right tibial nerve, and absence of F-waves in all other sampled nerves. The findings suggested a motor-predominant axonal polyradiculoneuropathy. The results of cerebrospinal fluid were unremarkable with normal cell count (L/N 3/0), normal level of protein (43 mg/dL) and no malignant cells.

The patient developed multi-lobar pneumonia. Chest X-ray showed patchy lesions and increased infiltration in the bilateral lung fields. Chest computed tomography scans showed patchy ground glass opacity in both lungs and consolidation in the right lung (Figure 2). Dyspnea progressed in the patient and she received intubation, ventilator support and finally tracheotomy. Follow-up chest x-ray did not show obvious improvement after antibiotic adjustment. Interstitial lung disease caused by the autoimmune process was highly considered. Therefore, we gave her steroid pulse therapy with intravenous methylprednisolone of 1000 mg per days for 5 days followed by oral steroid therapy. The dyspnea improved and the ventilator weaning program was then successful.

Because of the possible association between brainstem encephalitis and interstitial lung disease, we started a series of autoimmune examination, which revealed normal anti-nuclear antibody, normal complement[3,4] but positive anti-Sjogren's syndrome A (anti-SSA) antibody. The Schirmer test showed no tears after 5 min. Tc-99m sialoscintigraphy showed secretory and excretory dysfunction of bilateral salivary glands. Tracing back her history, the patient suffered from dry mouth and dry eyes for several years. The patient was then diagnosed with primary SS with aseptic meningoencephalitis, on the basis of the positive clinical and serological tests, Schirmer test, and sialoscintigraphy. For disease modification, the patient was treated with cyclophosphamide (500 mg) by intravenous infusion. The nasogastric tube and Foley catheter were both removed smoothly, and the

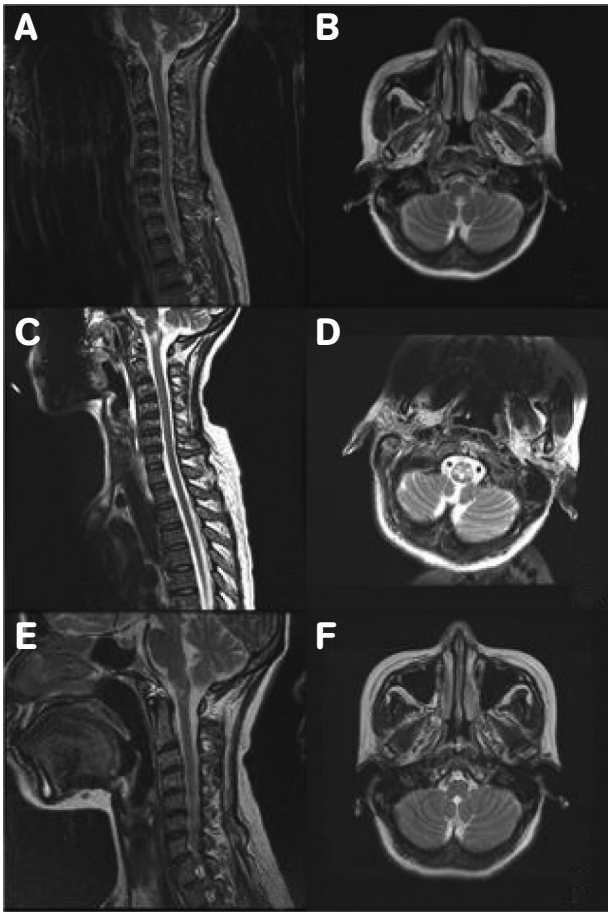

Figure 1. (A,B) T2WI magnetic resonance image (MRI) of head shows an abnormal high signal intensity (SI) at the left medulla at the onset of the neurological deficit. (C,D) T2WI MRI of head shows an ill-defined lesion of high SI with fluffy margin and mild mass effect in the medulla oblongata when the motor function deteriorated. (E,F) T2WI MRI of head shows faint patches of increased SI without definite mass effect 2 years after the episode.

tracheotomy was closed later. Her muscle power almost fully restored after rehabilitation. The patient took one tablet of hydroxychloroquin twice a day after discharge with gradual tapering of oral steroid. During the regular follow-up at our outpatient clinic, there was no recurrence of meningoencephalitis or any other manifestation of SS in the following 2 years. Follow-up head MRI 2 years after the episode did not show any new lesion (Figure 1E & F).

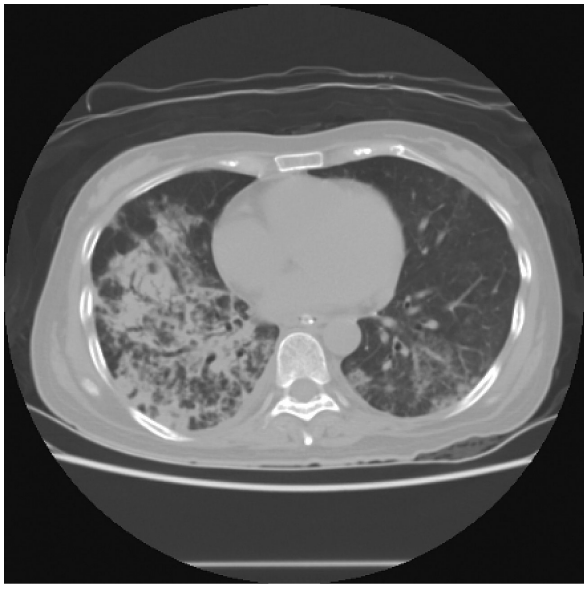

Figure 2. Chest CT without contrast enhancement shows patchy ground glass opacities at both lungs and consolidation at right lung.

DISCUSSION

Among the extra-glandular manifestations of primary SS, involvement of CNS has been described as non-existing to quite common depending on the diagnostic and inclusion criteria used by the study[7]. CNS lesion of primary SS could be monofocal, multifocal or diffuse involvement with wide-spectrum clinical manifestations of neuropsychiatric and spinal cord symptoms. Its clinical course could be insidious onset, remitting course, or progression [4]. Meningoencephalitis as the initial manifestation of patients with primary SS has been reported in few cases (Table). Acute rhombencephalitis with fever and bilateral hearing loss secondary to SS was reported in one patient [12]. In Kurne at al's series five SS patients presenting transverse myelopathy, two patients developed additional lesions in the brainstem and one had them in the cerebellum[13].

Cerebral vasculitis has been considered to be the pathologic mechanism of CNS manifestation of primary SS. Necrotizing vasculitis, involving numerous small arteries and arterioles, was observed in a patient with

Table. *Review of literature for primary Sjögren's syndrome with CNS involvement. (NR: not recorded)*

Author (et al)	Patient no	Sex	Age	Diagnosis	Symptoms	Country	Year	Reference
Rafai MA	5	F	43	4 chronic myelopathy, 1 aseptic meningoencephalitis	Confusional syndrome in the one with meningoencephalitis	Maroc	2009	29
Béjot Y	1	F	53	Bilateral optic neuropathy with aseptic meningitis	Rapidly progressive visual loss	France	2008	26
Kurne A	5	F	10-52	Transverse myelopathy, 2 cerebrum/brainstem lesion; 1 cerebrum/cerebellum lesion	NR (just MRI and diagnosis in figure)	Turkey	2008	13
Hoshina T	1	F	16	Meningoencephalitis, Cervicothoracic myelitis 2 months later	Disturbed consciousness, urine retention, parethesia	Japan	2008	30
Lin CC	`	F	59	Cervical cord atrophy	Neck/arms numbness	Taiwan	2008	36
Azeroual A	1	F	54	Cerebellar syndrome	NR (article in France)	Maroc	2007	11
Moutaouakil F	1	F	25	Aseptic meningoencephalitis	Mental confusion	Maroc	2005	31
Hirohata M	1	F	50	Aseptic meningoencephalitis	Disturbed consciouness	Japan	2005	14
Devos D	1	NR	NR	Acute rhombencephalitis associated with hearing loss	NR (article in France)	France	2002	12
Nishida H	1	F	64	Aseptic meningoencephalitis	Conscioussness loss	Japan	1999	32
Miyachi T	1	F	76	Aseptic meningoencephalitis	Disturbed consciouness	Japan	1997	33
Giordano MJ	1	F	55	Cerebritis complicated by bilateral superior cerebellar artery occlusion and diffuse subarachnoid hemorrhage.	Lethargy, dysarthria, dyaphagia, diplopia, right hemiparesis	USA	1995	17
Gerraty RP	1	F	18	Aseptic meningoencephalitis	NR (no full text)	Australia	1993	15
Peña-Sagredo JL	3	1M 2F	NR	1 focal meningoencephalitis 2 previous diagnosed definite MS	NR (article in Spanish)	Spain	1993	34
Caselli RJ	1	F	56	Dementia	Cognitive change	USA	1993	2
Kawashima N	1	F	48	Subcortical dementia	Cognitive change	Japan	1993	10
Alexander EL	5	NR	NR	Aseptic meningoencephalitis, 4 recurrent	NR (no full text)	USA	1983	9
Alexander GE	5	NR	NR	5 aseptic meningoencephalitis, 1 recurrent, 3 myelopathy	NR (no full text)	USA	1981	8

primary SS at necropsy[16]. Severe necrotic arterial vasculitis and thrombus formation was noted in another patient of chronic Sjögren's cerebritis complicated by bilateral superior cerebellar artery occlusion and diffuse subarachnoid hemorrhage[17]. On the other hand, Caselli et al reported five cases of steroid-responsive encephalopathy and proposed the term nonvasculitic autoimmune inflammatory meningoencephalitis[18], which was also described in patients with SS, systemic lupus erythematosus, and Hashimoto's disease[19]. Gerraty et al presented a fatal case of aseptic meningoencephalitis in an 18-year-old woman with primary

SS, in whom there was no evidence of cerebral vasculitis at autopsy[15].

The NCV study of our patient showed motor-predominant axonal polyradiculopathy. This is rather unusual in patients with multiple sclerosis or clinical isolated vasculitis syndrome. The patient did not have any other CNS lesion in neuroimage follow-up. Multiple sclerosis was not favored after 2-year follow-up. Her autoimmune profile revealed only positive anti-SS-A antibody but no antibodies for systemic lupus erythematous, rheumatoid arthritis, or other autoimmune diseases. Therefore neurological complications due to other autoimmune diseases were excluded from the diagnosis. In patients with neuromyelitis optica (NMO) / optic-spinal form of multiple sclerosis, autoantibodies involving SSA and ANA are occasionally detected[20-22]. Neuropathological characteristics of NMO were as follows: 1) the involved sites adjacent to the third and fourth ventricles and in the posterior limb of the internal capsule, 2) unique configurations, such as the longitudinal course from the internal capsule to the midbrain, large cerebral or cerebellar lesions over 3 cm, and cavity-like formation[28]. Our patient did not fulfill the neuropathological criteria of NMO[23,24]. VEP study showed absence of goggle VEPs from the left eye of our patient. Optic neuropathy has been reported as the rare symptom of primary SS [25,26]. The patient was diagnosed with primary SS according to the criteria of the European Community[27]. We concluded that her neurological symptoms were due to SS. The clinical picture of SS often shows spontaneous remission, whenever overt neurological symptoms occur or the clinical course become progressive, high-dose corticosteroid and cytotoxic agent may be indicated. Our patient received plasma exchange for deteriorating muscle power, prednisolone pulse therapy for interstitial lung disease, followed by cyclophosphamide. She remained in stable condition and did not have any new neurological symptoms till the day of this report.

In conclusion, primary SS may have variable CNS manifestation and could precede the classic sicca symptoms[35]. SS should be investigated in cases of aseptic meningoencephalitis even without clinical signs of xerostomia or xerophthalmia. Our patient showed an isolated occurrence of meningoencephalitis without any other manifestation of SS for at least 2 years. MRI is useful in demonstrating brain lesions and in evaluating treatment efficacy of SS.

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