PRIMARY SJÖGREN SYNDROME PATIENT PRESENTING CENTRAL NERVOUS SYSTEM MANIFESTATIONS SUCCESSFULLY TREATED WITH CORTICOSTEROIDS

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Abstract : We treated a case of primary Sjören's syndrome with progressive central nervous systems manifestations. Central nervous system involvement in such patients is difficult to diagnose and rarely described. A 71-year-old man presenting with vertigo and vomiting was admitted to our hospital. Intension tremor developed in the left extremities and gradually spread to the right extremities, while an articulation disorder also appeared. Results of T2-weighted cranial magnetic resonance imaging on admission showed abnormally high intensity areas in the pons, medulla oblongata, and cerebellum, nearly all of which were on the left side. Laboratory findings showed a high level of serum γ-globulin, and were positive antinuclear antibodies, anti-Ro antibodies, and anti-La antibodies, while histological findings of a minor salivary gland biopsy revealed focal sialadenitis with marked lymphocytic infiltration. These serological and histopathological findings confirmed that the patient had primary Sjören's syndrome. The patient underwent pulsed intravenous methylprednisolone therapy, and blepharoptosis, miosis, kinetic tremors improved with the therapy. In addition, the intensities in T2-weighted cranial MR images in the pons and medulla oblongata disappeared, and cerebellar intensity improved. In view of the underlying autoimmune disorder, it seemed likely that the etiology of the CNS symptoms was related to inflammatory brain changes, such as from autoimmune-related vasculitis.

Key words : Sjören's syndrome, neurological involvement, central nervous system, vasculitis, corticosteroid

INTRODUCTION

Primary Sjören's syndrome (pSS), is a chronic autoimmune disorder mainly referring to keratoconjunctivitis sicca and xerostomia resulting from immune lymphocytes that infiltrate the exocrine glands, and can also involve extraglandular organ systems, including the central and peripheral nervous systems[1, 2]. Among the extraglandular manifestations of pSS, involvement of the peripheral nervous system (PNS) is a well-documented occurrence with a reported frequency of 10-20%[3, 4]. Further, the frequency of central nervous system (CNS) involvement is still a matter of discussion but reported to range from about 1-8%[3, 4, 5]. Thus, CNS involvement in pSS is considered to be less common than PNS involvement. We treated

a pSS patient that exhibited active CNS involvement, which was confirmed by evidence of abnormal signals in a cranial magnetic resonance imaging (MRI) examination. Herein, we describe our treatment of this patient with CNS involvement, who responded well to corticosteroids.

CASE REPORT

A 71-year-old Japanese man was admitted with vertigo and vomiting, which continued to worsen until he was unable to walk smoothly 1 week later. Results of the cranial MRI and magnetic resonance angiography (MRA) showed no abnormal signals.

On admission, the patient had blepharoptosis and miosis on the right side, as well as rotating nystagmus in both eyes and motor ataxia. However nuchal rigidity and Babinski sign were negative, and deep tendon reflexes in the limbs were normal. On the 6th hospital day, a kinetic tremor in the left upper limb appeared and developed, and gradually spread to the left lower, and then right upper and lower limbs. On the 11th hospital day, an articulation disorder also appeared.

T2-weighted cranial MRI on admission showed abnormal high signal intensities in the

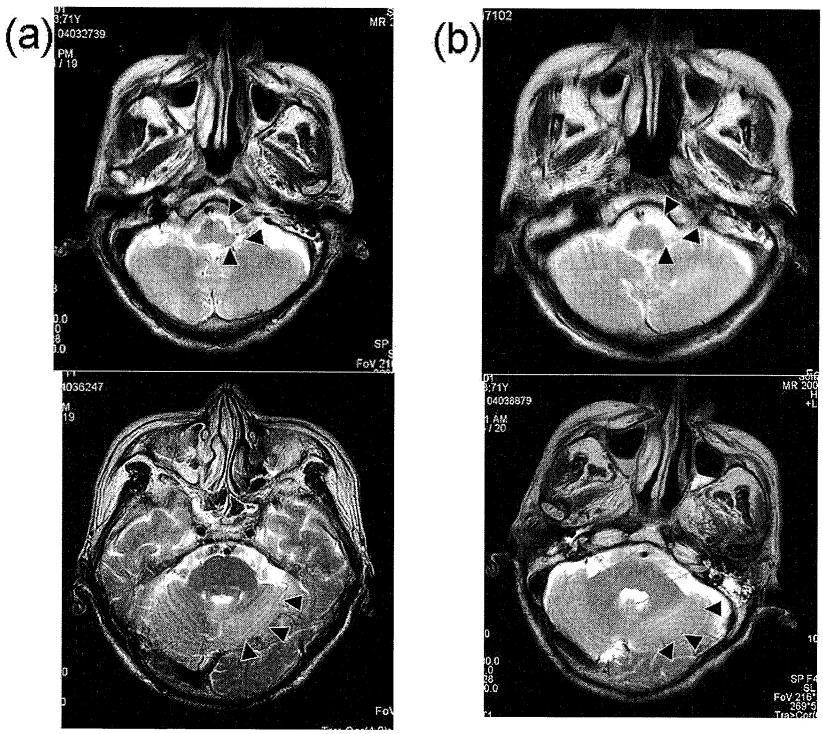

Fig. 1. T2-weighted cranial MRI findings.
(a) Upon admission, T2-weighted MRI of the brain with the neurological manifestations showed abnormally high signal intensities in the pons, medulla oblongata, and cerebellum, with nearly all on the left side.
(b) Following pulsed methylprednisolone therapy, T2-weighted cranial MRI showed the disappearance of abnormal signals in the pons and medulla oblongata. In addition, abnormal signals in the cerebellum were also improved.

pons, medulla oblongata, and cerebellum, nearly all on the left side (Fig. 1a). A cerebrospinal fluid (CSF) analysis revealed normal cytology (3 cells/3 ml), mildly elevated pressure (210 mm H_2O), and mildly elevated protein level (79 mg/dl; normal, 15–45). Laboratory findings showed an elevated erythrocyte sedimentation rate (–140 mm/hr), as well as increased serum γ–globulin (3.58 mg/dl) and serum IgG (3819 mg/dl) levels. Antinuclear antibodies were positive at 1/5210 of the speckled pattern, with anti–Ro (SS–A) at 144 U/ml, anti–La (SS–B) at 244 U/ml, and rheumatoid factor at 60 IU/ml. A syphilis test was biological false positive. Anti–cardiolipin β2GP1 antibodies and lupus anticoagulant were negative, as were anti–U1–RNP, anti–ds–DNA, anti SM, and anti–Scl–70 antibodies. C–reactive protein was at 0.2 mg/dl.

The patient did not report any sicca symptoms, such as xerophthalmia or xerostomia. However, he had a positive Schirmer's test result with 6 mm of tearing and positive Rose bengal test rests with 6 points on van Bijisterreld scoring. Histological findings from a minor salivary gland biopsy revealed focal sialoadenitis with a focus score of 3, using Greenspan's classification (Fig. 2). These serological and histological findings confirmed the patient had pSS with progressive neurological involvement[6].

We administered 3 courses of a pulse dose of intravenous methylprednisolone at 500 mg/day over 3 days, followed by oral prednisone at 30 mg/day for 2 weeks. Following that first treatment, the patient experienced an improvement in vertigo and vomiting, while

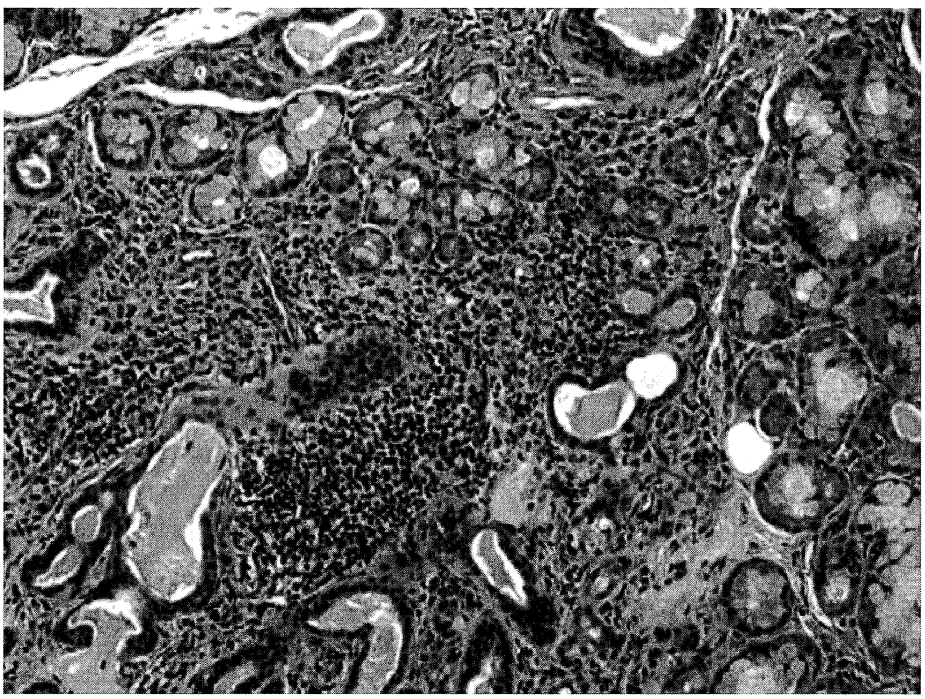

Fig. 2. Pathology of labial minor salivary gland showing a large amount of inflammatory infiltration (score of 3), interstitial fibrosis, ductal ectasia, and mild acinar atrophy (haematoxylon-eosin, original magnification: ×20).

blepharoptosis, miosis, and intention tremor also improved over the full course. Serum γ-globulin decreased to 1.1 mg/dl and IgG was decreased to a range of 1000 mg/dl, while abnormal signals in T2-weighted cranial MR images in the pons and medulla oblongata disappeared. Further, the abnormal high intensity in the cerebellum also improved (Fig. 1b).

DISCUSSION

Neurological manifestations such as involvement of the peripheral and central nervous systems are observed in approximately 20-25% of patients with pSS[3, 7, 8]. Clinical diagnosis of SS requires a high index of suspicion, especially when the first manifestations are neurologic. However, the exact prevalence remains controversial and CNS involvement especially is still a matter of discussion[3, 9]. In a cohort study of 87 Italian SS patients, some neurologic involvement was revealed in 18 patients (20%), while CNS involvement was revealed in 7 (8%)[5]. In another cohort study of 400 SS patients, some neurologic involvement was revealed in 38 patients (9.5%) and CNS involvement was found in 4 (1%)[10]. Thus, CNS involvement in pSS as seen in the patient seems to be quite rare.

Two of the main features of CNS involvement frequently seen in pSS are spinal cord involvement with severe symptoms and chronic involvement with progressive myelopathy, while other features include focal or multifocal brain involvement, which present stroke-like episodes or mimic relapsing-remitting multiple sclerosis[3]. In addition, that report noted motor neuron disease, cranial nerve involvement, optic neuritis (abnormal visual-evoked potential), cognitive impairment, seizures, and encephalitis as other related conditions involved with the CNS[3].

A brain MRI examination is useful to determine the extent of CNS involvement as well as for evaluation of reversible response to treatment in pSS cases with CNS involvement[11]. That study also reported that abnormal lesions were revealed as high intensity signals on T2-weighted images and recommending MRI as potentially more sensitive to detect CNS tissue damage than determination of clinical status.

The pathogenesis of CNS complication in pSS remains unknown. A number of studies have suggested an ischemic mechanism; however, the prevalence of multiple reversible lesions is not consistent with that suggestion. One possible etiopathogenesis of CNS damage in pSS includes mononuclear cell infiltration in the CNS, while another hypothesis includes immunologically mediated CNS vascular damage, such as antibody-mediated or immune-complex deposition vasculitis[3, 11, 12, 13]. In addition, a previous case report noted necrotizing vasculitis involving numerous small arteries and arterioles found diffusely in the cerebral cortex at autopsy[14].

For treatment of neuropathy associated with pSS, administrations of corticosteroids, immunosuppressants, plasmapheresis, D-penicillamine, cyclophosphamide, infliximab and immunoglobulin administration have been reported. Favorable therapeutic responses have been shown with each; however, randomized controlled studies are necessary to fully assess the efficacy of those treatments[3, 13]. In cases with severe CNS involvement, it has been suggested that intensive and early treatment is essential[3].

The present pSS patient initially developed neurological manifestations. Although he was free of sicca symptoms, there was a significant decrease in lacrimal secretion, evidence

of inflammatory cell infiltration in minor salivary gland biopsy results, and the presence of anti-Ro (SS-A) and anti-La (SS-B) antibodies, thus satisfying the diagnostic criteria of pSS[6]. A subacute progression of tetraplegia and cerebellar syndrome were the initial symptoms associated with pSS, and the patient had characteristic T2-weighted cranial MRI findings of well-defined multiple focal lesions involving the pons, medulla oblongata, and cerebellum. The abnormally high signals on MR images gradually disappeared and the neurological physical symptoms were improved with corticosteroid therapy. In this case, the good response of the abnormal signals to corticosteroid therapy seen with brain MRI, along with improved levels of serum γ-globulin and IgG suggested an inflammatory pathogenesis, such as vasculitis. In addition, the marked improvement demonstrated that inflammatory brain lesions in pSS patients are reversible with corticosteroid therapy.

A diagnosis of pSS with initially developed CNS involvement is sometimes difficult to obtain, especially when the patient is free of sicca symptoms. Nevertheless, CNS involvement successfully treated with corticosteroids in the present patient suggests an inflammatory pathogenesis of the brain lesions.

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