

(Letter to the editors)

**Efficacy of Tacrolimus in Sjögren's Syndrome-Associated CNS Disease with
Aquaporin-4 Autoantibodies**

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Sirs: We present 2 cases of CNS disease associated with Sjögren's Syndrome (SjS) with anti aquaporin-4 water channel autoantibodies (AQP4-Ab) that were treated successfully with tacrolimus. Tacrolimus is an immunosuppressant that acts as a calcineurin inhibitor and suppresses Th2 cells [1]. Tacrolimus may also act as a neuroprotectant by reducing axonal and myelin damage, as shown in a mouse model of experimental autoimmune encephalomyelitis [2]. SjS is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands. SjS-associated inflammation sometimes spreads into the CNS (CNS-SjS), occasionally mimics relapsing-remitting multiple sclerosis (MS), and inflammation often involves the brain, spinal cord, and optic nerve [3]. Neuromyelitis optica (NMO) is also a relapsing inflammatory disease of the CNS, characterized by severe attacks of optic nerve neuritis and longitudinally extensive transverse myelitis [4]. NMO is distinguished from MS by the presence of AQP4-Ab and differences in the distribution of inflammatory lesions and pathological findings. Combination therapy with a corticosteroid and azathioprine is the current standard treatment for preventing NMO relapse [5]; however, some patients are refractory to it. Approximately 3% of patients with NMO have coexisting SLE or SjS, and CNS-SjS patients with optic nerve neuritis or longitudinal myelitis (conditions called “NMO spectrum disorder”) often present positive for AQP4-Ab [4,6,7]. To our knowledge, this is the first reported assessment of tacrolimus in patients with CNS-SjS with AQP4-Ab. This treatment was approved by the ethical committee of our university, and the patients provided written informed consent.

A 48-year-old female (Case 1, Figure) was admitted with rapidly progressive nausea, hiccups, dysphagia, and drowsiness. MRI revealed T2 hyperintensities of the

hypothalamus bilaterally and of the dorsal medulla oblongata. After 3 courses of intravenous high-dose methylprednisolone (IHMP, 1 g/day for 3 days in 1 course), she recovered completely, except for mild dysphagia. One year after the first attack, she developed limb weakness. Laboratory tests revealed high levels of anti-RO (SS-A) antibodies and positive antinuclear antibody. The Schirmer test and the Saxon test revealed decreased salivary secretion (Table). She was diagnosed with CNS-SjS [8]. She experienced 9 attacks during the entire disease course, and we started treatment with oral tacrolimus during her 9th admission. No recurrent attacks have been observed for 49 months since the start of this treatment.

A 50-year-old female (Case 2) visited our hospital with acute left visual loss and depression. She was diagnosed with retrobulbar optic nerve neuritis, but she rejected steroid therapy and was not admitted to our hospital. One year later, she was sent to our hospital by ambulance due to weakness. Physical examination revealed dysphagia, dysarthria, incomplete tetraplegia, urinary retention, and depression. MRI revealed T2 hyperintensities in the corpus callosum, thalamus, midbrain, and pons. She was diagnosed with CNS-SjS based on SjS criteria (Table), and she was treated with IHMP. Because high doses of oral steroids may exacerbate depression, we started therapy with tacrolimus (3 mg/day) to prevent relapse. No recurrence was observed for 9 months, but she could not continue the therapy due to exacerbation of depression. Two years after withdrawal, she suffered right hemiplegia, and MRI revealed a relapse lesion in the left posterior limb of the internal capsule.

The serum of both patients was positive for AQP4-Ab after the initiation of tacrolimus. Because no recurrences were observed for at least 49 months (Case 1) and 9

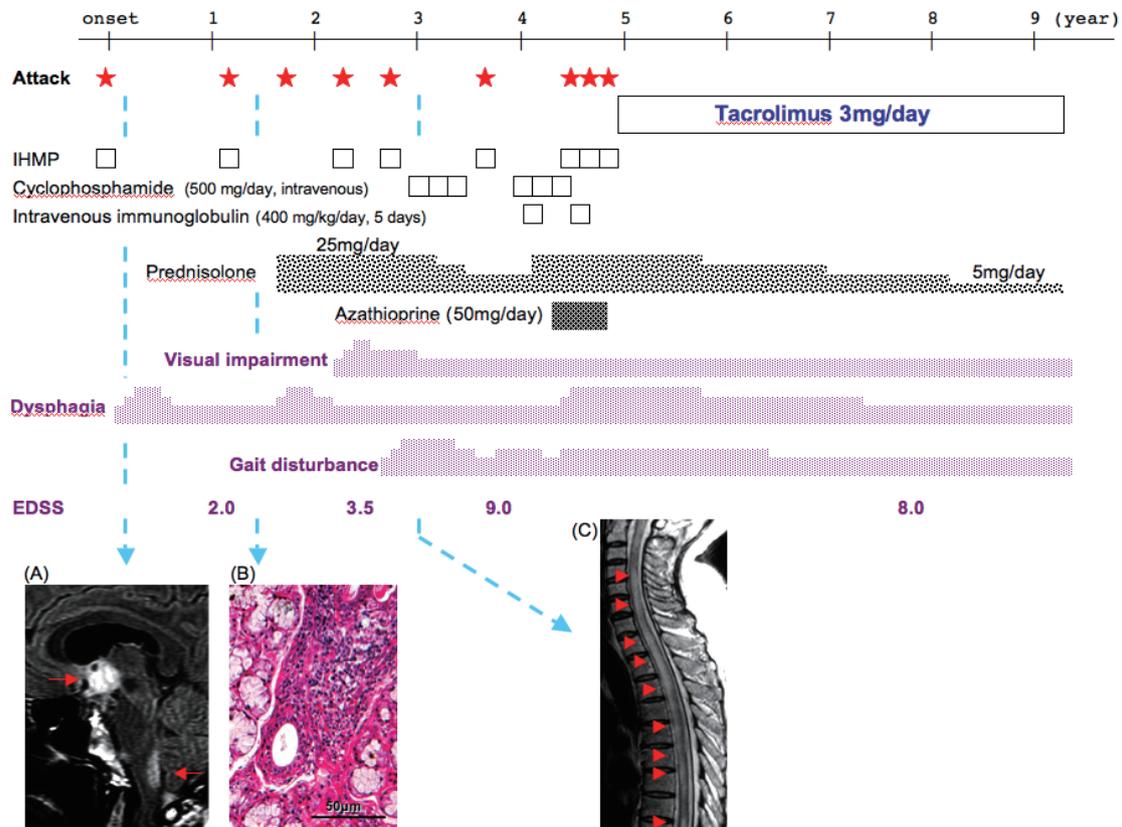
months (Case 2), we concluded that tacrolimus is effective in CNS-SjS with AQP4-Ab. Considering the pathological observations that indicate loss of AQP4 with deposition of antibody and complement in CNS lesions in NMO [9,10], we speculate that tacrolimus may act by suppressing the humoral immunity against AQP4 through Th2 inhibition.

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Figure Legend



Time course of relapse, therapies, symptoms, and images of Case 1. Stars indicate attacks. The thickness of each line represents the severity of any symptom or the dose of drug. Nine attacks had occurred in spite of therapeutic approaches, and no attacks were observed after starting tacrolimus. A: A sagittal fluid-attenuated inversion recovery (FLAIR)-weighted image at onset shows hyperintense lesions in the thalamus, the mammillary bodies and the dorsal portion of the medulla oblongata (arrows). B: A photomicrograph of a labial salivary gland biopsy at the second admission. An aggregate of lymphocytes surrounding a salivary gland. Size bar is 50 μm . C: A sagittal T2-weighted image at the fifth admission shows hyperintense lesions throughout the spinal cord (arrowheads).

IHMP = Intravenous high-dose methylprednisolone (1 g/day for 3 days in 1 course);

EDSS = Expanded Disability Status scale.

Table. Clinical Features of 2 Cases

	Patient	
	Case 1	Case 2
Age at onset, sex	48, female	50, female
Ethnicity	Japanese	Japanese
Dry mouth	+	+
Number of relapses*	9	2
MRI findings		
Optic lesion	+	+
Cerebral lesion	+	+
Pontine lesion	-	+
Medullary lesion	+	-
Longitudinal cord lesion	+	-
Autoantibodies		
ANA	+	+
SS-A	+	+
SS-B	-	+
Aquaporin-4	+	+
Diagnostic tests for SjS		
Schirmer test	+	+
Saxon test	+	+
Salivary gland biopsy	compatible for SjS	not done
Sialography	not done	compatible for SjS
CSF findings		
Cells / μ l	26	37
MBP [mg/dl, <4.0]	6.2	56.3
Oligoclonal IgG bands	-	-
Diagnosis		
Criteria of SjS	fulfilled	fulfilled
Criteria of NMO	fulfilled	not fulfilled

ANA = antinuclear antibody; MBP = myelin basic protein; NMO = neuromyelitis optica; SjS = Sjögren's Syndrome

* including first attack