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Japanese cases of neuromyelitis optica spectrum disorder associated with myasthenia gravis and a review of the literature

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ABSTRACT

Background: The incidence of concurrent myasthenia gravis (MG) and neuromyelitis optica spectrum disorder (NMOSD) is higher than what chance predicts, yet it remains unclear why MG and NMOSD appear concurrently.
Objective: The purpose of the present study was to examine the clinical features of the concurrence of these diseases.
Methods: Clinical details were analyzed retrospectively.
Results: Three (0.5%) out of 631 MG patients had confirmed ($n=2$) or suspected ($n=1$) NMOSD. Two of these patients were women. All showed early-onset MG (EOMG) that preceded NMOSD and were positive for acetylcholine receptor antibody (AChR-Ab). Two patients were tested for aquaporin 4 antibody (AQP4-Ab) and were positive. Two patients were treated with a thymectomy that preceded NMOSD. Two patients had decreased frequency of regulatory T (Treg) cells. We identified in the literature 46 patients with both MG and NMOSD. Our results of female predominance, EOMG, MG preceding NMOSD, and positive AChR-Ab are consistent with previous descriptions.
Conclusions: This is the first report to examine the frequency of NMOSD in Japanese patients with MG. The reduction and/or dysfunction of Treg cells may be one cause of NMOSD development in MG.

1. Introduction

Neuromyelitis optica (NMO) is an inflammatory autoimmune disease characterized by monophasic or relapsing attacks of optic neuritis (ON) and myelitis. In many NMO patients, aquaporin 4 antibody (AQP4-Ab) and NMO-IgG are present in the serum and CSF. Wingerchuk et al. [1] proposed that neuromyelitis optica spectrum disorder (NMOSD), which is limited to ON or longitudinally extensive myelitis with titers for AQP4-Ab/NMO-IgG, has common pathological condition of NMO. NMO patients often have concurrent autoimmune disease, such as Sjögren syndrome and systemic lupus erythematosus (SLE), and the concurrence of NMOSD and myasthenia gravis (MG) has been reported recently [2–19]. It remains unclear, however, why MG and NMOSD appear concurrently. In the present report, we attempt to identify the causes of concurrent MG and NMOSD by examining our cases and cases previously reported in the literature.

2. Materials and methods

Clinical details were analyzed retrospectively. The NMO/NMOSD diagnosis was made according to the diagnostic

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Table 1
Present and previous cases of concurrent MG and NMOSD MG: myasthenia gravis, NMO: neuromyelitis optica, NMOSD: neuromyelitis optica spectrum disorder, NA: not available, AChR: acetylcholine receptor, AQP4: aquaporin 4, *The onset of NMOSD preceding thymectomy in only one case [17].

Author/year	Number of cases	Diagnostic NMO or NMOSD	AChR-Ab	AQP4-Ab	Thymectomy	Thymic histology
O'Riordan et al. (1996) [2]	1	NMO	1 positive	Not done	NA	NA
Isbister et al. (2003) [3]	1	NMOSD suspected	1 positive	Not done	1	1 Hyperplasia
Antoine et al. (2004) [4]	1	NMO	1 positive	Not done	1	1 thymoma
Furukawa et al. (2006) [5]	2	2 NMO	2 positive	2 negative	1	1 hyperplasia
Gotkine et al. (2006) [6]	1	NMOSD	1 positive	1 positive	1	NA
Kister et al. (2006) [7]	4	4 NMO	4 positive	2 positive 1 negative 1 not done	4	3 hyperplasia 1 NA
Ikeda et al. (2007) [8]	1	NMO	Negative	Not done	1	1 hyperplasia
Bichuetti et al. (2008) [10]	1	NMO	NA	Not done	1	NA
Kay et al. (2008) [11]	1	NMO	1 positive	1 positive	0	
Uzawa et al. (2009) [12]	2	2 NMO	2 positive	2 positive	2	1 hyperplasia 1 NA
Kohsaka et al. 2009 [13]	1	NMOSD	1 positive	1 positive	1	1 hyperplasia
Etemadifar et al. (2011) [14]	1	NMO	1 positive	1 positive	0	
Jarius et al. (2012) [15]	10	6 NMO, 4 NMOSD	9 positive 1 not done	10 positive	6	3 hyperplasia 2 normal 1 thymitis
Hironishi et al. (2012) [16]	1	NMOSD suspected	1 positive	1 negative	1	1 hyperplasia
Leite et al. (2012) [17]	16	9 NMO, 7 NMOSD	16 positive	16 positive	11*	8 hyperplasia 3 normal
Ogaki et al. (2012) [18]	1	NMO	1 positive	1 positive	1	NA
Tsujii et al. (2012) [19]	1	NMOSD	1 positive	1 positive	1	1 hyperplasia
Present cases	3	2 NMOSD, 1 NMOSD suspected	3 positive	2 positive 1 not done	2	1 thymoma 1 normal
Total	49	30 NMO, 16 NMOSD, 3 NMOSD suspected	46 positive	38 positive	35	21 hyperplasia, 2 thymoma 1 Thymitis, 6 normal

criteria revised in 2006 and in agreement with the NMOSD criteria described by Wingerchuk et al. [1]. We examined records of MG patients treated at 6 neurological centers in Japan. We evaluated the frequency of $CD4^+CD25^+CD127^{low/-}$ regulatory T (Treg) cells among peripheral $CD4^+$ T cells. In addition, we examined cases reported in the literature between January 1990 and December 2012 in which MG and NMO/NMOSD were diagnosed in the same patient (Table 1). These cases were identified with a PubMed search using the terms "neuromyelitis optica," "myelitis," "optic neuritis," "multiple sclerosis," and "myasthenia gravis." Clinical information was obtained after the patients had given their informed consent, and the study was approved by the Institutional Review Board of each hospital.

3. Statistical analysis

Statistical analysis was performed using the JMP 10 statistical software package (SAS institute). Comparisons between groups were performed with Student's *t*-test. Statistical significance was determined by p values < 0.05.

4. Case report

4.1. Case 1

A Japanese woman developed dysarthria and weakness of the extremities at age 25. The diagnosis of generalized MG was confirmed by elevated AChR-Ab titer and a positive edrophonium test. She underwent thymectomy at age 29, and thymic histology was normal. After thymectomy, her symptoms gradually improved; thus, prednisolone treatment was stopped. At 49 years of age, she was admitted to our hospital with a gait disturbance. A neurological exam revealed paresis in both legs, decreased sensation below the T5 level. Laboratory tests for anti-nuclear antibody (ANA), anti-SS-A, B antibodies, and anti-DNA antibody were negative. The proportion of Treg cells among peripheral $CD4^+$ T cells was decreased (7.3%; normal range $10.0 \pm 1.5\%$). The CSF contained 7 leukocytes/μl and 38 mg/dl of protein. Spinal MRI revealed a longitudinal signal with an increased T2 intensity below C5 (more than 3 vertebral segments) (Fig. 1). Brain MRI was normal. A diagnosis of NMOSD was made, based on the positive serum AQP4-Ab findings. High-dose intravenous methylprednisolone pulse (HIMP) was initiated, and her neurological symptoms gradually improved. After 2 years, she was able to walk unassisted under maintenance therapy with prednisolone.

4.2. Case 2

A Japanese woman developed diplopia and ptosis at age 47. A MG diagnosis was confirmed by elevated AChR-Ab titer and a positive edrophonium test, and she was started on prednisolone. She developed extremity weakness at age 61 under prednisolone treatment. Chest CT did not show any thymic abnormality. At 70 years of age, she experienced acute vision loss in the left eye. She was diagnosed with ON and was treated with HIMP. Although her visual acuity improved, her disability persisted. Two years later, she was admitted to our hospital due to a relapse of ON in her right eye; she was under prednisolone treatment at that time. Neurological examination revealed right eye blindness. Laboratory tests for ANA and anti-DNA antibody were negative. Spinal MRI results were normal, brain MRI revealed ON for the right eye. She was treated with HIMP, but showed little improvement. Therefore, prednisolone treatment was continued. Nine years after developing ON in the right eye, she showed positive results for serum AQP4-Ab and was diagnosed with NMOSD. Follow-up examination conducted when she was 79 showed decreased proportion of Treg cells among peripheral $CD4^+$ T cells (6.0%).

4.3. Case 3

A Japanese man developed diplopia, ptosis, and dysarthria at age 41. A diagnosis of generalized MG was confirmed by elevated AChR-Ab titer and a positive edrophonium test. Chest CT showed thymic abnormality, and he underwent thymectomy. Thymic histology