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Clinical and MRI features of Japanese MS patients with NMO-IgG

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ABSTRACT

Background: NMO-IgG is a disease-specific serum marker autoantibody of neuromyelitis optica (NMO) and may distinguish NMO from multiple sclerosis (MS). NMO-IgG has also been frequently detected in Japanese patients with the optic-spinal form of MS (OSMS) suggesting that NMO and OSMS may be the same entity.

Objective: To investigate the relationship between the serological status of NMO-IgG and the clinical and MRI features in Japanese MS patients.

Methods: Serum NMO-IgG was tested in 35 Japanese patients diagnosed as MS, including 19 with OSMS, three with the spinal form of MS (SMS), and 13 with the conventional form of MS (CMS) in which the brain was involved. Their clinical and MRI findings were analyzed in reference to NMO-IgG.

Results: NMO-IgG was detected in 14 patients, 12 with OSMS (63%) and two with CMS (15%). In the 14 NMO-IgG -positive patients, longitudinally extensive (>3 vertebral segments) spinal cord lesions (93% vs. 57%) and permanent, complete blindness (no light perception) of at least one eye (50% vs. 0%) were the significant features as compared with NMO-IgG-negative OSMS. The two cases of CMS with NMO-IgG had unusual brain lesions, but in other respects had features suggesting OSMS.

Conclusion: NMO-IgG was detected in more than half of OSMS and in some CMS cases in our Japanese series. This newly discovered serum autoantibody was significantly associated with longitudinally extensive spinal cord lesions and with complete blindness, suggesting severe optic-spinal disease. Moreover, brain lesions atypical for MS might occasionally develop in NMO-IgG-positive patients with features of OSMS.

INTRODUCTION

The optic-spinal form of multiple sclerosis (OSMS) is characterized by lesions restricted to the optic nerves and the spinal cord, and is relatively common in Japan [1][2][3] and in other Asian countries.[4] Compared with the conventional form of MS (CMS) in which the brain is involved, patients with OSMS are older at onset, more often women, and mostly negative for oligoclonal IgG bands (OB) in the cerebrospinal fluid.[1][2][3] OSMS is similar to neuromyelitis optica (NMO) in many respects.

Recently, we reported that some Japanese OSMS patients as well as North American neuromyelitis optica (NMO) patients were seropositive for NMO-IgG, a unique serum IgG autoantibody.[5] In contrast, patients with CMS were usually seronegative for NMO-IgG.[5] Moreover, it is unclear whether the clinical characteristics and outcome of NMO/OSMS differ between the seropositive and seronegative patients. In the present study, we compared the clinical, laboratory and MRI features between NMO-IgG-positive and -negative patients in a larger and more diverse group of Japanese patients.

METHODS

Patients

Thirty five Japanese MS patients (19 OSMS, 3 spinal form of MS (SMS), and 13 CMS) were selected from the outpatient clinic of Tohoku University Hospital and Kohnan Hospital in Sendai, Japan and were tested for NMO-IgG. All were women except one man with OSMS and one man with CMS. Among 13 CMS patients, five had oligoclonal IgG bands (OB) which were detected by isoelectric focusing and immunofixation,[6] whereas among patients with OSMS, two were positive for OB and none with SMS was OB-positive. NMO-IgG was measured by an indirect immunofluorescence technique as previously reported.[5] Among 35 patients, 12 OSMS patients and five OB-positive CMS patients had been tested and reported previously.[5] The cases enrolled in the present study as a whole were not consecutive, since OB-positive CMS which were unlikely to be NMO-positive, as shown in our previous study,[5] were excluded except for the above-mentioned five cases.

The present study was approved by the Medical Ethics Committee of Tohoku University School of Medicine and the subjects provided written informed consent.

Diagnosis of CMS, OSMS, and SMS

All the patients fulfilled the International Panel criteria.[7] Each patient was diagnosed as having one of three subtypes of MS: OSMS, SMS, or CMS. OSMS

patients were defined as those whose symptoms were restricted to optic neuritis and myelitis and fulfilled the criteria for NMO proposed by Wingerchuk et al.[8] SMS patients were defined as those with recurrent myelitis without optic or brain lesions. CMS patients were defined as those with neither OSMS nor SMS.

Statistics

We used Fisher's exact test for comparison of the seropositive rate and Mann-Whitney U test for comparison of values between the groups. Correlations were examined by Spearman's rank correlation. $P<0.05$ was considered statistically significant.

RESULTS

Frequency of NMO-IgG

Fourteen patients were positive for serum NMO-IgG by immunohistochemistry. Among those 14 patients, 12 patients had OSMS and two had CMS. Thus, the frequency of NMO-IgG in OSMS was 63%, and that in CMS was 15%. The two CMS patients with NMO-IgG were negative for OB at multiple lumbar punctures. None of the three patients with SMS were positive for NMO-IgG.

Clinical manifestations of NMO-IgG -positive patients

Among 14 NMO-IgG-positive MS patients, transverse myelitis defined by the criteria proposed by the Transverse Myelitis Consortium Working Group[8] was found in 12 NMO-IgG -positive MS patients (86%) and permanent complete blindness (no light perception) of at least one eye was observed in seven patients (50%) (Table 1). Although the frequency of transverse myelitis was similar to that in NMO-IgG -negative-OSMS patients (71%) ($p=0.5232$), blindness was not observed in any NMO-IgG -negative patient (0%) ($p=0.0174$) (Table 1). The EDSS score did not differ between NMO-IgG-positive OSMS (median 6.0 with range 3.5 to 8.0) and -negative OSMS (median 6.0 with range 0-6.5) (Table 1).

Serum antinuclear antibodies were positive in seven patients (50%), anti SS-A or SS-B antibodies in five patients (36%) and anti-thyroid antibodies in four patients (29%). Similar frequencies of these autoantibodies were observed in the NMO-IgG-negative OSMS patients.

Interestingly, the clinical courses of two atypical CMS patients with NMO-IgG included typical optic-spinal or spinal presentation of OSMS. One patient (Case 1: 36-year-old female) developed only severe myelitis and optic neuritis, but the brain

MRI showed extensive brain lesions. The other patient (Case 2: 33-year-old female) had two episodes of transverse myelitis with the longitudinally extensive spinal cord MRI lesions (LESL) and two succeeding episodes of cerebellar ataxia and hemiparesis due to the brain lesions. Her brain MRI was normal until her third exacerbation.

MRI findings of NMO-IgG -positive patients

All 14 patients with NMO-IgG showed abnormal findings on spinal cord MRI. LESL that extended over three vertebral segments was seen in all but one patient (93%). Among the 19 OSMS patients, LESL was more commonly found in NMO-IgG -positive patients (100%) than in NMO-IgG -negative OSMS patients (57%) (p=0.0361). The lesions in the acute phase were swollen and often enhanced with gadolinium.

Brain MRI was abnormal in 10 patients with NMO-IgG (71%). Seven of these patients had medullary lesions extending from the cervical lesions, and two had small, nonspecific, asymptomatic lesions in the cerebral white matter including the periventricular region. Two patients (Case 1 and Case 2) had brain lesions atypical for MS. One patient (Case 1: 36-year-old female) showed non-enhancing lesions involving both cerebral peduncles, internal capsules, corpus callosum, and frontal white matter (Figure 1). Her whole spinal cord showed marked atrophy and multiple spinal cord lesions were scattered from C4 to Th9. Another patient (Case 2: 33-year-old female) had extensive but non-enhancing lesions involving the pons, both internal capsules and centra semiovale, corpus callosum, juxtacortical region, and both cerebellar hemispheres (Figure 1). She also had three spinal cord lesions including a long lesion extending from the Th1 to Th6 level. The other patient (Case 3: 22-year-old female), who experienced more than six episodes of optic neuritis and seven episodes of myelitis, developed an enhancing hypothalamic lesion extending to the optic chiasm (Figure 1), but she did not have any symptom attributable to the hypothalamic lesion, such as galactorrhea and amenorrhea.

DISCUSSION

NMO-IgG was detected in 14 out of 35 Japanese patients in the present study, 12 with OSMS and two with CMS. Those patients with CMS had some features suggestive of OSMS. Since the present study did not assess consecutive cases, the frequency of NMO-IgG-positive cases with atypical features, such as cerebral involvement cannot be determined. Nevertheless, NMO-IgG was detected in 63% of the OSMS patients in the present study, which is comparable to the frequency (58% of

the 12 Japanese OSMS patients) in the original study.[5]

Since 12 out of 14 NMO-IgG-positive patients were diagnosed as OSMS, as expected, the clinical characteristics of the NMO-IgG-positive patients in the present study were consistent with the previously recognized clinical features that distinguish OSMS from CMS, such as higher onset age, female predominance, and lower incidence of positive OB. NMO has been reported as a severe disease that often develops blindness and paraplegia or quadriplegia.[8][10][11] Likewise, in our NMO-IgG-positive cases, 12 patients (86%) suffered transverse myelitis and seven patients (50%) developed permanent complete blindness in at least one eye.

Comparing NMO-IgG-positive OSMS and CMS patients with the NMO-IgG -negative-OSMS patients, the majority of NMO-IgG-positive patients had LESL. Even in one NMO-IgG-positive patient without LESL, extensive spinal cord atrophy was observed, suggesting the previous existence of a longitudinally extensive spinal cord lesion. In contrast, all four OSMS patients without LESL were negative for NMO-IgG. Therefore, LESL is one of the most characteristic features of OSMS patients with NMO-IgG, although more than half of NMO-IgG-negative OSMS patients also had LESL.

Brain lesions were seen in 71% of the patients with NMO-IgG, but most were medullary lesions as an extension of cervical myelitis or non-specific cerebral white matter lesions. Meanwhile, two patients were diagnosed as having CMS as they had brain lesions in spite of optic-spinal or spinal presentation of OSMS. However, those brain lesions were extensive and atypical for classic MS; they might have been caused by the same pathomechanism as that of OSMS. Further studies are needed to clarify the characteristic features of the brain lesions in NMO-IgG-positive patients.

The neuropathological studies in OSMS and NMO suggest that dense perivascular deposition of immunoglobulins and activated complements is a key feature of the disease.[12] [13] Thus, humoral immunity probably play an important role in the pathogenesis of OSMS. The target antigen of NMO-IgG was recently identified as aquaporin-4 water channel protein.[14] At the present time, it is uncertain whether NMO-IgG is pathogenic or an epiphenomenon. Further analyses will clarify whether the binding of NMO-IgG to aquaporin-4 triggers edema and inflammatory reaction to cause severe, extensive lesions in OSMS and NMO.

Relapsing idiopathic inflammatory demyelinating diseases with longitudinally extensive spinal cord MRI lesions may represent limited or early forms of NMO/OSMS.

Table 1. Comparison of clinical, laboratory, and MRI features between NMO-IgG-positive OSMS and NMO-IgG-negative OSMS

		NMO-IgG -positive		NMO-IgG -negative	
		Total	OSMS	OSMS	P value
n		14	12	7	
Age (y)		47 ± 15	49 ± 15	46 ± 14	p=0.6418
Onset Age (y)		36 ± 13	37 ± 13	36 ± 13	p=0.7340
EDSS (median (range))		6.0 (2.0-8.0)	6.0 (3.5-8.0)	6.0 (0-6.5)	p=0.2170
Transverse myelitis		12 / 14 (86%)	11 / 12 (92%)	5 / 7 (71%)	p=0.5232
Permanent complete blindness		7 / 14 (50%)	7 / 12 (58%)	0 / 7 (0%)	**p=0.0174**
CSF marked pleocytosis (>50 cells/μl)		4 / 14 (29%)	4 / 12 (33%)	1 / 7 (14%)	p=0.6027
OB		2 / 14 (14%)	2 / 12 (17%)	0 / 7 (0%)	p=0.5088
Serum ANA		8 / 13 (62%)	6 / 11 (55%)	4 / 7 (57%)	p>0.9999
MRI	Long cord lesions (>3VS)	13 / 14 (93%)	12 / 12 (100%)	4 / 7 (57%)	**p=0.0361**
	Cerebral lesions	6 / 14 (43%)	4 / 12 (33%)	5 / 7 (71%)	p=0.1698

OSMS, optic spinal form of multiple sclerosis; SMS, spinal form of multiple sclerosis; CMS, conventional form of multiple sclerosis; n, number; EDSS, expanded disability status scale; OB, oligoclonal IgG bands; ANA, anti-nuclear antibodies; MRI, magnetic resonance imaging; VS, vertebral segments; P value, compared between NMO-IgG-positive OSMS and –negative OSMS using Mann-Whitney's U test or Fisher's exact test.

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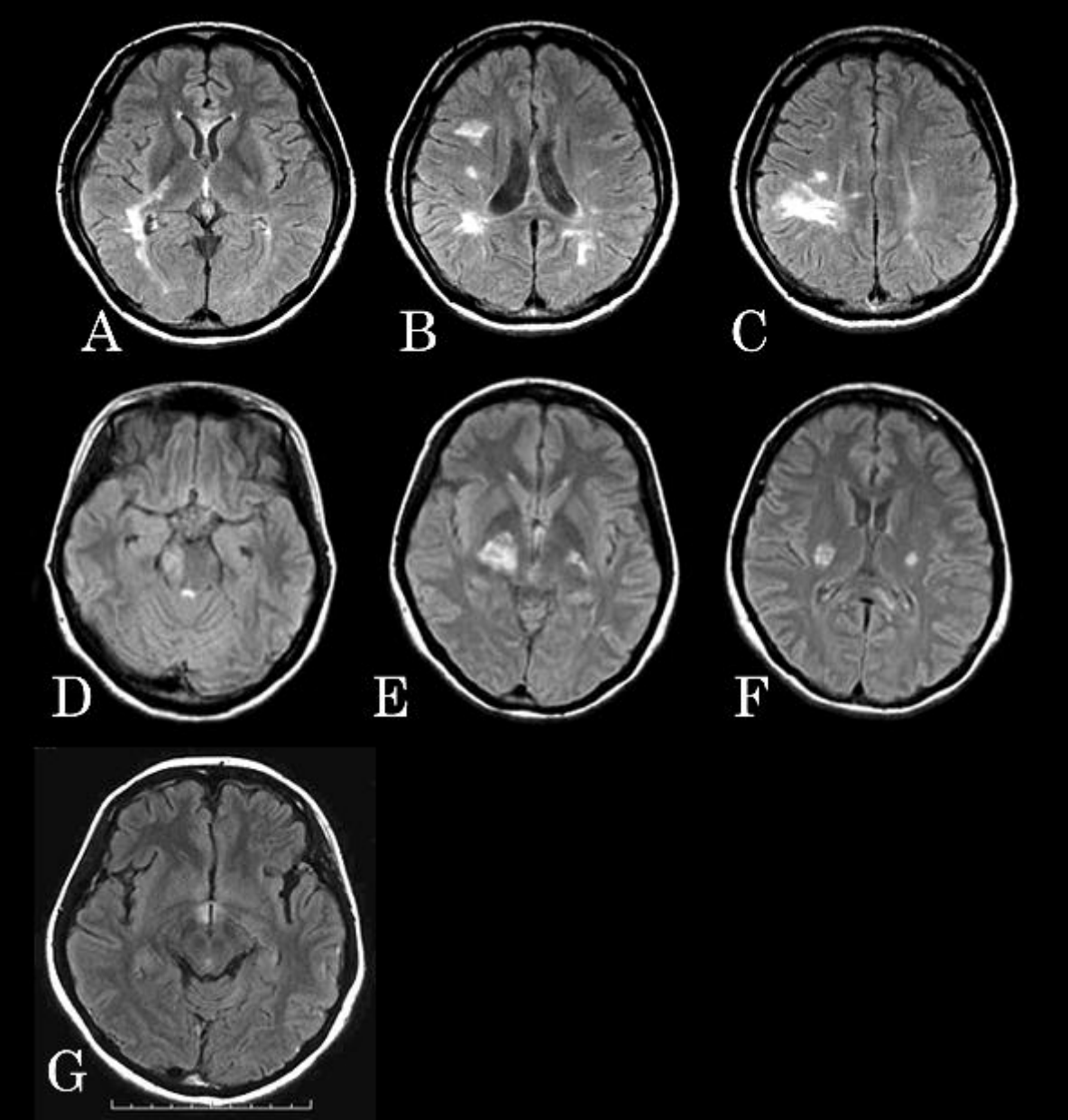
REFERENCES

1. Fukazawa T, Tashiro K, Hamada T, Moriwaka F, Matsumoto A, Shima K, et al. Multiple sclerosis in Hokkaido, the northernmost island of Japan: prospective analyses of clinical features. Intern Med 1992;31:349-52.
2. Kira J. Multiple sclerosis in the Japanese population. Lancet Neurology 2003;2:117-127.
3. Misu T, Fujihara K, Nakashima I, Miyazawa I, Okita N, Takase S, et al. Pure optic-spinal form of multiple sclerosis in Japan. Brain 2002;125:2460-8.
4. Tsai CP, Yuan CL, Yu HY, Chen C, Guo YC and Shan DE. Multiple sclerosis in Taiwan. J Chin Med Assoc 2004;67:500-5.
5. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106-12.
6. Nakashima I, Fujihara K, Sato S and Itoyama Y. Oligoclonal IgG bands in Japanese patients with multiple sclerosis. A comparative study between isoelectric focusing with IgG immunofixation and high-resolution agarose gel electrophoresis. J Neuroimmunol 2005;**159**:133-6.

7. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
8. Wingerchuk DM, Hogancamp WF, O'Brien PC and Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107-14.
9. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. Neurology 2002;59:499-505.
10. Weinshenker BG. Neuromyelitis optica: what it is and what it might be. Lancet 2003;361:889-90.
11. Bergamaschi R and Ghezzi A. Devic's neuromyelitis optica: clinical features and prognostic factors. Neurol Sci 2004;25 Suppl 4:S364-7.
12. Lucchinetti CF, Mandler RN, McGavern D, Bruck W, Gleich G, Ransohoff RM, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125:1450-61.
13. Misu T, Kakita A, Fujihara K, Nakashima I, Takahashi H and Itoyama Y. A comparative neuropathological analysis of Japanese cases of neuromyelitis optica and multiple sclerosis. Neurology 2005;64:A39-A39.
14. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS and Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;**202**:473-7.

FIGURE LEGENDS

Figure1. Axial FLAIR images of three patients with NMO-IgG.
(A, B, C) Case 1 developed extensive lesions involving the brainstem, bilateral internal capsules, bilateral superior longitudinal fasciculus, corpus callosum, and frontal white matter. None of these lesions showed gadolinium enhancement. (D, E, F) In the fourth relapse of Case 2, a continuous lesion extended from the right edge of the pons to the centrum semiovale through the internal capsule and the superior longitudinal fasciculus. A symmetric lesion extending from the left side of the pons to the internal capsule appeared at the third relapse. Lesions were also seen at the cerebellum, corpus callosum, and periventricular white matter. (G) Case 3 developed an asymptomatic hypothalamic lesion adjacent to the third ventricle, and the patient had visual impairment due to involvement of the optic chiasm by the lesion.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