SHORT REPORT

Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG

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This study investigates the relation between the serological status of NMO (neuromyelitis optica)-IgG and the clinical and MRI features in Japanese patients with multiple sclerosis. Serum NMO-IgG was tested in 35 Japanese patients diagnosed with multiple sclerosis, including 19 with the optic–spinal form of multiple sclerosis (OSMS), three with the spinal form of multiple sclerosis (SMS), and 13 with the conventional form of multiple sclerosis (CMS), which affects the brain. NMO-IgG was detected in 14 patients, 12 with OSMS and 2 with CMS. In these patients, longitudinally extensive (>3 vertebral segments) spinal cord lesions (93% *v* 57%) and permanent, complete blindness (no perception of light) in at least one eye (50% *v* 0%) were the noticeable features as compared with NMO-IgG-negative OSMS. The two patients having CMS with NMO-IgG had unusual brain lesions, but in other respects had features suggesting OSMS. NMO-IgG was detected in more than half the number of patients with OSMS and in some patients with CMS. This newly discovered serum autoantibody was markedly associated with longitudinally extensive spinal cord lesions and with complete blindness, suggesting severe optic–spinal disease.

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

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

METHODS

Patients

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

This study was approved by the Medical Ethics Committee of Tohoku University School of Medicine and the participants provided written informed consent.

Diagnosis of CMS, OSMS and SMS

All the participants fulfilled the International Panel criteria for multiple sclerosis.[7] Each participant was diagnosed as having one of three subtypes of multiple sclerosis: OSMS, SMS or CMS. Patients with OSMS were defined as those whose symptoms were restricted to optic neuritis and myelitis and who fulfilled the criteria for NMO proposed by Wingerchuk *et al*.[8] Patients with SMS were defined as those with recurrent myelitis without optic or brain lesions. Patients with CMS were defined as those with neither OSMS nor SMS.

Statistics

We used Fisher's exact test for comparison of the seropositive rates and Mann–Whitney U test for comparison of values between the groups. Correlations were examined by Spearman's rank correlation. Values of $p<0.05$ were considered significant.

RESULTS

Frequency of NMO-IgG

Fourteen patients were positive for serum NMO-IgG by immunohistochemistry: 12 patients had OSMS and 2 had CMS. Thus, the frequency of NMO-IgG in OSMS was 63% and that in CMS was 15%. The two patients with CMS who were positive for NMO-IgG were negative for oligoclonal IgG bands at multiple lumbar punctures. None of the three patients with SMS was positive for NMO-IgG.

Abbreviations: CMS, conventional form of multiple sclerosis; LESL, longitudinally extensive spinal cord MRI lesions; NMO, neuromyelitis optica; OSMS, optic–spinal form of multiple sclerosis; SMS, spinal form of multiple sclerosis

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

	NMO-IgG positive		NMO-IgG negative	
	Total (n = 14)	OSMS (n = 12)	OSMS (n = 7)	p Value
Age, years (SD)	47 (15)	49 (15)	46 (14)	0.642
Age at onset, years (SD)	36 (13)	37 (13)	36 (13)	0.734
EDSS, median (range)	6.0 (2.0–8.0)	6.0 (3.5–8.0)	6.0 (0–6.5)	0.217
Transverse myelitis	12 (86%)	11 (92%)	5 (71%)	0.523
Permanent complete blindness	7 (50%)	7 (58%)	0 (0%)	**0.017**
CSF marked pleocytosis (>50 cells/μl)	4 (29%)	4 (33%)	1 (14%)	0.603
OB	2 (14%)	2 (17%)	0 (0%)	0.509
Serum ANA	8/13 (62%)	6/11 (55%)	4 (57%)	>0.999
MRI				
Long-cord lesions (>3VS)	13 (93%)	12 (100%)	4 (57%)	**0.036**
Cerebral lesions	6 (43%)	4 (33%)	5 (71%)	0.1698

ANA, anti-nuclear antibodies; CMS, conventional form of multiple sclerosis; EDSS, Expanded Disability Status Scale; OB, oligoclonal IgG bands; OSMS, optic–spinal form of multiple sclerosis; p Value, compared between NMO-IgG-positive OSMS and NMO-IgG-negative OSMS using Mann–Whitney U test or Fisher's exact test; SMS, spinal form of multiple sclerosis; VS, vertebral segments.
Values in bold are significant ($p<0.05$).

Clinical manifestations of NMO-IgG-positive patients

Among the 14 NMO-IgG-positive patients, transverse myelitis defined by the criteria proposed by the Transverse Myelitis Consortium Working Group[9] was found in 12 NMO-IgG-positive patients with multiple sclerosis, and permanent complete blindness (no perception of light) in at least one eye was observed in 7 patients (table 1). Although the frequency of transverse myelitis was similar to that in NMO-IgG-negative patients with OSMS (71%, $p = 0.5232$), blindness was not observed in any NMO-IgG–negative patient (0%, $p = 0.0174$; table 1). The Expanded Disability Status Scale score did not differ between NMO-IgG-positive OSMS (median 6.0 with range 3.5–8.0) and NMO-IgG-negative OSMS (median 6.0 with range 0–6.5; table 1).

Seven (50%) patients were positive for serum antinuclear antibodies, 5 (36%) patients for anti SS-A or anti SS-B antibodies and 4 (29%) patients for anti-thyroid antibodies. Similar frequencies of these autoantibodies were observed in the NMO-IgG-negative patients with OSMS.

Interestingly, the clinical courses of two atypical patients with CMS who were positive for NMO-IgG included typical optic–spinal or spinal presentation of OSMS. One patient (case 1: 36-year-old woman) developed only severe myelitis and optic neuritis, but the brain MRI showed extensive brain lesions. The other patient (case 2: 33-year-old woman) had two episodes of transverse myelitis with the longitudinally extensive spinal cord MRI lesions (LESL) followed by two episodes of cerebellar ataxia and hemiparesis due to the brain lesions. Her brain MRI was normal until the 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 patients but one. Of the 19 patients with OSMS, LESL was more commonly found in NMO-IgG-positive patients (100%) than in NMO-IgG-negative patients with OSMS (57%, $p = 0.036$). 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 had medullary lesions extending from the cervical lesions, and two had small, non-specific, asymptomatic lesions in the cerebral white matter, including the periventricular region. Two patients (cases 1 and 2) had brain lesions atypical for multiple sclerosis. One patient (case 1: 36-year-old woman) showed non-enhancing lesions associated with both cerebral peduncles, internal capsules, corpus callosum and frontal white matter (fig 1). The patient's whole spinal cord showed marked atrophy, and multiple spinal cord lesions were scattered from C4 to Th9. Another patient (case 2: 33-year-old woman) had extensive, but non-enhancing lesions of the pons, both internal capsules and centra semiovale, corpus callosum, juxtacortical region and both cerebellar hemispheres (fig 1). She also had three

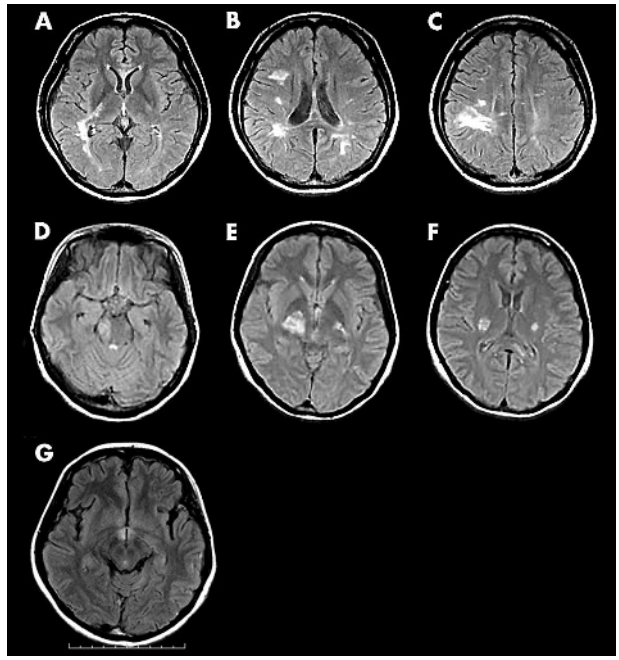

Figure 1 Axial fluid-attenuated inversion recovery images of three patients with neuromyelitis optica-IgG. (A–C) Case 1 developed extensive lesions in the brainstem, bilateral internal capsules, bilateral superior longitudinal fasciculus, corpus callosum and frontal white matter. None of these lesions showed gadolinium enhancement. (D–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.

spinal cord lesions, including a long lesion extending from the Th1 to Th6 level. The other patient (case 3: 22-year-old woman), who experienced more than six episodes of optic neuritis and seven episodes of myelitis, developed an enhancing hypothalamic lesion extending to the optic chiasm (fig 1), but she did not have any symptom attributable to the hypothalamic lesion, such as galactorrhoea and amenorrhoea.

DISCUSSION

NMO-IgG was detected in 14 of 35 Japanese patients in this study, 12 with OSMS and two with CMS. The patients with CMS had some features suggestive of OSMS. As this study did not assess consecutive patients, the frequency of NMO-IgG-positive patients with atypical features, such as cerebral involvement cannot be determined. Nevertheless, NMO-IgG was detected in 63% of the patients with OSMS in this study, which is comparable to the frequency (58% of the 12 Japanese patients with OSMS) in the original study.[5]

As 12 of the 14 NMO-IgG-positive patients were diagnosed with OSMS, as expected, the clinical characteristics of the NMO-IgG-positive patients in this study were consistent with the previously recognised clinical features that distinguish OSMS from CMS, such as higher age at onset, predominance in women and lower incidence of positive oligoclonal bands. NMO has been reported as a severe disease that often results in blindness and paraplegia or tetraplegia.[8 10 11] Likewise, in our 14 NMO-IgG-positive patients, 12 had transverse myelitis and 7 developed permanent complete blindness in at least one eye.

On comparing NMO-IgG-positive patients with OSMS and CMS with the NMO-IgG-negative patients with OSMS, we found that most of the 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 patients with OSMS without LESL were negative for NMO-IgG. Therefore, LESL is one of the most characteristic features of patients with OSMS positive for NMO-IgG, although more than half of the NMO-IgG-negative patients with OSMS also had LESL.

Brain lesions were seen in 71% of the patients with NMO-IgG, but most were medullary lesions, which were 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 despite optic–spinal or spinal presentation of OSMS. The brain lesions, however, were extensive and atypical for conventional multiple sclerosis and may have been caused by the same pathomechanism as that for 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 their activated complements is a key feature of the disease.[12 13] Thus, humoral immunity probably has 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 present, it is uncertain whether NMO-IgG is pathogenic or is an epiphenomena. Further analyses will clarify whether the binding of NMO-IgG to aquaporin-4 triggers oedema 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 or OSMS.

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