Clinical and magnetic resonance imaging features of multiple sclerosis with autoreactive antibodies in Ishikawa Prefecture, Japan

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Abstract

Previous reports of multiple sclerosis (MS) with autoantibodies might include neuromyelitis optica (NMO). We investigated the frequency of autoreactive antibodies (AR) in both MS and NMO. Systemic lupus erythematosus (SLE)-associated autoantibodies such as anti-Sm antibodies, anti-single stranded-DNA antibodies and lupus anticoagulant were only identified in MS, whereas SLE itself is more commonly associated with NMO. Moreover, when magnetic resonance imaging features between autoreactive antibody-positive (AR(+))MS and -negative (AR(-))MS were compared, AR(+)MS cases showed significantly fewer than 3 periventricular lesions compared to AR(-)MS cases. These results may indicate different pathogenetic mechanisms underlying AR(+)MS and AR(-)MS.

Key words; neuromyelitis optica, systemic lupus erythematosus, lupus anticoagulant, anti-Sm antibodies, anti-single stranded DNA antibodies

1. Introduction

Multiple sclerosis (MS) is considered a Th1-mediated autoimmune disease of the central nervous system (CNS) and is characterized by phases of remission and relapse (Martin et al., 1992; Hafler and Weiner, 1995). To date, no specific biomarker for MS has been identified, which may indicate the heterogeneous pathogenesis of MS. Subpopulations of MS are often discussed from clinical or immunological perspectives (Takahashi et al., 2001; Weinshenker et al., 2005; Satoh et al., 2006). The relationship of MS to other autoimmune diseases has also been discussed; that is, autoantibodies common in other autoimmune diseases can also be found in patients with MS. For example, anti-nuclear antibodies (ANA) are detected in 20 to 26% of MS cases (Collard et al., 1997; Tourbah et al., 1998; de Andres et al., 2001; De Keyser, 1988), anti-SS-A antibodies in 2 to 7% of MS cases (Tourbah et al., 1998; de Andres et al., 2001) and anti-cardiolipin antibodies in 2% of MS cases (de Andres et al., 2001).

In contrast, the opticospinal form of MS (OSMS) has been characterized in Japan and other Asian countries (Nakashima et al., 2006; Kira, 2003). Since both OSMS and neuromyelitis optica (NMO) characteristically involve the optic nerves and the spinal cord, the differences between these diseases has been discussed especially in Japan (Matsuoka et al., 2008). The development of magnetic resonance imaging (MRI) technology and the discovery of anti-aquaporin-4 (AQP4) antibodies have resulted in the revision of diagnostic criteria for NMO in 2006 (Wingerchuk et al., 2006). Recently, some groups have reported that the OSMS in Japan is consistent with NMO in that the AQP4 antibody can be identified in both populations (Nakashima et al., 2006; Lennon

et al., 2004). Moreover, NMO is more commonly associated with other systemic autoimmune diseases, such as SLE or Sjögren syndrome (SjS), compared to typical MS (Pittock et al., 2008). These associations indicate that NMO patients may be included in previous reports regarding the identification of autoreactive antibodies in MS.

The purpose of this study was to investigate the frequency with which autoreactive antibodies can be identified in both MS and NMO followed by comparisons of the clinical and magnetic resonance imaging (MRI) features found in both autoreactive antibody-positive MS and antibody-negative MS.

2. Methods

2.1 Subjects

Enrollment for this study began in January 2010 and was completed in December 2011. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of the Iou Hospital and Kanazawa University. Inclusion criteria for subjects with MS included: (1) 2 or more attacks and objective clinical evidence of 2 or more lesions; (2) brain and spinal cord MRI; (3) complete analysis of a broad panel of autoreactive antibodies (ANA, anti-AQP4, anti-double stranded DNA antibodies (dsDNA), anti-single stranded DNA antibodies (ssDNA), anti-ribonucleoprotein antibodies (RNP), anti-SS-A/Ro antibodies (SS-A), anti-SS-B/La antibodies (SS-B), anti-Sm antibodies (Sm), PR3-anti-neutrophil cytoplasmic antibodies (ANCA), MPO-ANCA, anti-cardiolipin antibodies (aCL), anti-cardiolipin-beta-2 glycoprotein I antibodies (aCLb2GPI), anti-topoisomerase I antibodies (Scl-70), anti-thyroid

peroxidase antibodies (aTPO), anti-thyrogloblin antibodies (aTG), lupus anticoagulant (LAC), and rheumatoid factor (RF)). NMO, defined by the revised NMO criteria by Wingerchuk in 2006, was also included when all inclusion criteria were fulfilled. Exclusion criteria included: (1) primary or secondary progressive MS; (2) clinically isolated syndrome (CIS); and (3) immunosuppressive treatment within the last 6 months prior to blood sampling.

2.2 Autoreactive antibodies

Autoreactive antibodies were measured using a commercially available laboratory assay. The majority of testing was performed at the clinical laboratory of Kanazawa University. The fluorescence antibody method (FA) was used for measurement of ANA and anti-AQP4. Enzyme-linked immunosorbent assay (ELISA) was used for measurement of dsDNA, ssDNA, RNP, Sm, SS-A, SS-B, PR3- ANCA, MPO-ANCA, aCL, aCLb2GPI, and Scl-70, and chemiluminescence enzyme immunoassay (CLEIA) was used for measurement of aTPO and aTG. LAC was measured using the dilute Russell's viper venom time (dRVVT) assay and kaolin clotting time (KCT) assay. RF was measured by nephelometry. High positive cut-off values for ANA (1:160 serum dilution) and RF (15 IU/ml) were used to exclude 95% of normal individuals (Tan et al., 1997). Normal range for dsDNA, ssDNA, RNP, Sm, SS-A, SS-B, PR3- ANCA, MPO-ANCA, aCL, aCLb2GPI, and Scl-70, aTPO, aTG and LAC were also set to exclude at least 95% of normal individuals. To exclude temporary positivity, auto-reactive antibodies were defined as "positive" when detected at least twice in tests

performed at least 12 weeks apart, with the exception of aAQP4. aAQP4 was considered “positive” with at least 1 positive result.

2.3 Cerebrospinal fluid collection

Cerebrospinal fluid (CSF) was collected from patients in relapse, prior to treatment with methylprednisolone. Myelin basic protein (MBP) was measured using radioimmunoassay (RIA). The oligoclonal band (OB) was measured by isoelectric focusing electrophoresis as previously reported. In brief, both CSF and serum samples were diluted with phosphate-buffered saline (PBS). Diluted CSF and serum samples were applied to isoelectric focusing (IEF) gel and prefocused. After the IEF run, specific IgG bands were precipitated in gel by immunofixation and the immunoprecipitate was silver-stained. An OB was defined as 2 or more distinct bands in the CSF sample, but not visible in the paired serum sample. MBP and OB were each considered “positive” with at least 1 positive result.

2.4 MRI acquisition and examination

A 1.5 or 3T MRI scanner was used to collect the following image sequences: (1) fluid attenuated inversion recovery (FLAIR); (2) T2-weighted spin echo; and (3) post-contrast T1-weighted spin echo.

2.5 Statistical analysis

Fisher’s exact test was used for comparison of MRI and CSF data and the

Mann-Whitney U-test was used for comparison of values between the groups. Values of $p < 0.05$ were considered significant. All quantitative data are presented as mean (SD). Statistical calculations were performed using SPSS 18.0 software (IBM, Armonk, NY).

3. Results

3.1 Demographics of MS and NMO patients

A total of 47 patients fulfilled the inclusion criteria for MS and 10 patients among them met the revised NMO criteria. Table 1 shows the clinical characteristics of the study population. Nine patients with NMO (90%) were aAQP4 positive and 8 of them (80%) showed the contiguous T2-weighted signal abnormality on spinal MRI extending 3 or more vertebral segments. The 37 patients with MS (female/male: 25/12) had disease onset at the age of 30.1 (11.3) years (range 3−60), mean disease duration of 9.9 (9.8) years (range 1−42) and a mean expanded disability status scale (EDSS) of 2.8 (2.8) (range 0−7.5). The 10 patients with NMO (female/male 8/2) had mean disease onset at the age of 42.3 (13.5) (range 22−65), mean disease duration of 12.5 (12.8) years (range 3−45), and a mean EDSS of 4.7 (3.6) (range 1−9.5). Six of the patients with MS received beta-interferon therapy, while the other patients did not receive any disease-modifying therapy.

3.2 Frequency and distribution of autoreactive antibodies

The distribution of subtypes of autoreactive antibodies in patients with MS and NMO is shown in Table 2. Fifteen (41%) patients with MS and 7 (70%) patients with NMO were

positive for 1 or more autoreactive antibodies. Although RF, SS-A, aTG, and aTPO were demonstrated in both groups, all of these autoreactive antibodies were detected with a higher frequency in NMO. In contrast, ANA, Sm, ssDNA and LAC were only positive in MS, while PR3-ANCA was only positive in NMO. When LAC was positive in patients with MS it was only demonstrated with the KCT assay, not the dRVVT assay. No patients in either group were positive for RNP, SS-B, aCL, aCLb2GPI, MPO-ANCA, Scl-70, or centromere antibodies. Finally, anti-mitochondrial antibodies (AMA) were positive in a single patient with MS and thyroid receptor-stimulating antibodies (TRs) were positive in 2 patients with NMO.

3.3 Association with autoimmune diseases

Overall, 9 (24.3%) patients with MS had an association with other autoimmune diseases (OAD). Hashimoto thyroiditis (4) was the most common. Psoriasis, ulcerative colitis (UC), anti-phospholipid syndrome (APS), primary biliary cirrhosis (PBC), and Sjögren syndrome (SjS) were each identified in a single patient. In patients with NMO, 6 of 10 (60.0%) had associated OAD, most commonly SjS (2/10) and Graves' disease (2/10). Systemic lupus erythematosus (SLE) and Hashimoto thyroiditis were each identified in a single patient.

3.4 Clinical correlation between AR(+)MS and AR(-)MS

The comparison of clinical features and CSF data between autoreactive antibody positive-(AR(+)) and negative-(AR(-)) patients with MS is shown in Table 3. No

difference was found in age of onset, disease duration and EDSS. The 15 patients with AR(+)MS (female/male 10/5) had mean disease onset at the age of 32.5 (11.3) years (range 18−60), mean disease duration of 9.9 (10.5) years (range 1−42), and a mean EDSS of 2.7 (3.0) (range 0−7.5). The 22 patients with AR(-)MS (female/male 16/6) had mean disease onset at the age of 28.4 (11.4) years (range 22−65), mean disease duration of 12.5 (12.8) years (range 1−38), and a mean EDSS of 2.9 (2.6) (range 0−9). Cerebrospinal fluid analysis was performed in the 14 (93%) patients with AR(+)MS and the 17 (77%) patients with AR(-)MS. The frequency of OB and MBP was similar in the AR(+)MS and AR(-)MS groups.

3.5 Correlation with MRI findings between AR(+)MS and AR(-)MS

The comparison of MRI findings between patients with AR(+)MS and AR(-)MS is shown in Table 4. Five (33%) patients with AR(+)MS fulfilled the MRI criteria from the 2005 revision of MS diagnostic criteria, which is a significantly low proportion compared to the AR(-)MS group (16 of 22; 73%) ($p = 0.023$). The number of patients with AR(+)MS with more than 3 periventricular lesions was significantly lower than the AR(-)MS group. In contrast, when the MRI criteria from the 2010 revision of MS diagnostic criteria were used, there was no difference between the AR(+)MS and AR(-)MS groups ($p = 0.198$).

4. Discussion

The frequency of autoreactive antibodies found in the current study, except for aCL,

was similar to those found in previous reports (Collard et al., 1997; Tourbah et al., 1998; de Andres et al., 2001; De Keyser, 1988; Takahashi, 2010). Although previous studies have reported an increased aCL titer in both MS and NMO (Fukazawa et al., 1993; Garg et al., 2007), no patients in either group showed “positive” aCL results in this study. This difference may be explained by aCL often showing temporary positivity, as described in the diagnostic criteria for APS (Miyakis et al., 2006). ANA and RF can be seen in a few healthy individuals, but a high positive cut-off value for ANA, 1:160 serum dilution, would likely exclude 95% of normal individuals (Tan et al., 1997). Since 4 (11%) patients with MS were ANA-positive in this study, it is likely that a patient with MS can become ANA-positive more easily than a healthy individual. Surprisingly, no patient with NMO was ANA-positive, although we expected higher frequency of ANA in the patients with NMO than with MS. However, when we used a low positive cut-off value for ANA, 1:40 serum dilution (expecting 32% positive in healthy individuals), 9 (24%) patients with MS and 4 (40%) patients with NMO became positive for ANA. This frequency of ANA in NMO patients was similar to that in a previous report (Pittock et al., 2008). Moreover, in this study, the sample size of NMO group is too small to clarify the frequency of ANA in patients with NMO. Using a cut-off value of 15 IU/mL for RF should also exclude 95% of normal individuals and since 2 (5%) patients with MS were RF-positive in this study, it is likely that RF-positivity occurs in a patient with MS at a similar frequency to that in healthy individuals.

In agreement with the results of this study, MS associated with gastrointestinal

autoimmune diseases, such as UC, Crohn's disease, and PBC has been previously reported, but NMO has not been associated with these diseases (Pokorny et al., 2007; Pontecorvo et al., 1992; Cohen et al., 2008). In this study, SLE, the representative systemic autoimmune disease, was only shown in NMO. Although SjS and autoimmune thyroid diseases were shown in both MS and NMO, organ-specific autoimmune diseases seem to be somewhat related to MS and systemic autoimmune diseases seem somewhat related to NMO. Interestingly, SLE-associated autoantibodies such as Sm, ssDNA, and LAC were seen only in patients with MS in this study, whereas SLE itself has a higher incidence in NMO than in MS. It is well known that type 1 interferon would promote not only the production of autoantibodies but also induction of drug-induced SLE (Neau et al., 1996; Crispín et al., 2005; Bronaci-Nikolic B et al., 2009; Sladkova V et al., 2011). In our study, although 6 of 37 patients with MS received beta-interferon therapy, only a single patient was ssDNA positive without positivity of any other autoreactive antibodies. These data indicate that SLE-associated autoantibodies such as Sm, ssDNA, and LAC in the patients with MS are independent of beta-interferon therapy. Among autoantibodies related to APS, aCL has been reported mainly in relation to NMO, not MS (Fukazawa et al., 1993; Takahashi, 2010b). The relationship between LAC in MS and aCL in NMO remains unknown. Sm, ssDNA, and LAC may be associated with CNS involvement but not SLE itself.

None of the patients in either the MS or NMO group had RNP, MPO-ANCA, Scl-70, or centromere antibodies. These results are supported by the fact that previous studies rarely report an association of MS with mixed connective tissue disease (MCTD),

vasculitis, or systemic sclerosis (SSc) specifically associated with these autoreactive antibodies (Takahashi, 2010a).

In Asia, including in Japan, NMO is more commonly diagnosed than that in western countries. Moreover, the opticospinal form of MS is more common than typical MS. NMO and MS along with other collagen diseases, are considered contraindications for interferon therapy. Immune modulating therapy must also be chosen carefully in patients with MS with autoreactive antibodies, especially SLE-associated autoantibodies (Sm, aCL, and LAC).

In this study, the MRI criteria from the 2005 revised MS diagnostic criteria was used to distinguish typical MS from NMO or MS with autoreactive antibodies. Interestingly, the number of patients with AR(+)MS with more than 3 periventricular lesions was significantly lower than in the AR(-)MS group. The periventricular plaque forms a lesion around a subependymal vein in the early stage (Adams et al., 1987). Autoimmune cells of AR(+)MS may be different form those of AR(-)MS, with respect to their affinity for the epithelium cells of the subependymal vein; this may indicate heterogeneity of pathogenesis of MS. Moreover, the MRI criteria from the 2010-revised McDonald criteria for MS was unable to detect a distinction and included all patients with NMO and 80% of patients with MS with autoreactive antibodies. Specifically, a diagnosis of MS included 27% of the AR(+)MS group by the 2005-revised MRI criteria and 73% by the 2010-revised MRI criteria. These results indicate that the presence of autoreactive antibodies, including aAQP4, should be carefully monitored, especially in Japan.

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Table 1. Demographic characteristics

	MS	NMO
No. of patients	37	10
Sex (female/male)	25/12	8/2
Age, years (SD)	40.3 (12.2)	51.0 (13.3)
Age at onset, years (SD)	30.1 (11.3)	42.3 (13.5)
Disease duration, years (SD)	9.9 (9.8)	12.5 (12.8)
EDSS, mean (SD)	2.8 (2.8)	4.7 (3.6)
DMT	6	0

EDSS, Expanded Disability Status Scale; DMT, disease modifying therapy (beta-interferon)

Table 2. Frequency (%) and distribution of autoreactive antibodies in MS and NMO

Autoreactive antibodies	MS (n = 37)	NMO (n = 10)
Positive autoreactive antibodies	15(41%)	7(70%)
ANA	4(11%)	0(0%)
RF	2(5%)	2(20%)
RNP	0(0%)	0(0%)
SS-A	1(3%)	2(20%)
SS-B	0(0%)	0(0%)
Sm	1(3%)	0(0%)
ssDNA	2(5%)	0(0%)
dsDNA	0(0%)	0(0%)
aCL	0(0%)	0(0%)
aCLb2GPI	0(0%)	0(0%)
LAC	5(14%)	0(0%)
PR3-ANCA	0(0%)	1(10%)
MPO-ANCA	0(0%)	0(0%)
aTG	6(16%)	3(30%)
aTPO	6(16%)	3(30%)
Scl-70	0(0%)	0(0%)
Centromere	0(0%)	0(0%)
others	AMA 1(3%)	TRs 2(20%)

ANA, antinuclear antibodies; RF, Rheumatoid factor; RNP, anti-ribonucleoprotein antibodies; SS-A, anti-SS-A/Ro antibodies; anti-SS-B/La antibodies (SS-B), Sm, anti-Sm antibodies; ssDNA, anti-single stranded DNA antibodies; dsDNA, anti-double stranded DNA antibodies; aCL, anticardiolipin antibodies; aCLb2GPI, anticardiolipin-beta-2 glycoprotein I antibodies; LAC, lupus anticoagulant; PR3-ANCA, PR3-anti-neutrophil cytoplasmic antibodies; MPO-ANCA, MPO-anti-neutrophil cytoplasmic antibodies; aTPO, anti-thyroid peroxidase antibodies; aTG, anti-thyrogloblin antibodies; Scl-70, anti-topoisomerase I antibodies; Centromere, anti-centromere antibodies; AMA, anti-mitochondrial antibodies; TRs, anti-thyroid receptor stimulating antibodies.

Table 3. Comparison of clinical features and CSF markers between AR(+)MS and AR(-)MS

	AR(+)MS	AR(-)MS	†p -value
No. of patients	15	22	
Sex (female/male)	10/5	16/6	
Age, years (SD)	42.4 (14.1)	38.8 (10.8)	0.545
Age at onset, years (SD)	32.5 (11.3)	28.4 (11.4)	0.377
Disease duration, years (SD)	9.9 (10.5)	10.0 (9.6)	0.791
EDSS, mean (SD)	2.7 (3.0)	2.9 (2.6)	0.531
DMT	1	5	
OB	6/14 (43%)	5/17 (29%)	0.477
MBP	5/14 (36%)	4/17 (29%)	0.693

CSF, cerebrospinal fluid; AR(+)MMS, autoreactive antibodies-positive MS; AR(-)MS, autoreactive antibodies-negative MS; EDSS, Expanded Disability Status Scale; DMT, disease modifying therapy (beta-interferon); OB, oligoclonal band; MBP, myelin basic protein; †p-value represent a comparison between AR(+)MS and AR(-)MS using the Mann-Whitney U test or the Fisher's exact test. Values in bold are significant ($p < 0.05$)

Table 4. Comparison of MRI features between AR(+)MS and AR(-)MS

	AR(+)MS	AR(-)MS	†p-value
McDonald 2005	5/15 (33%)	16/22 (73%)	**0.023**
>9 T2 or >1 enhanced lesion	6/15 (40%)	14/22 (64%)	0.193
>1 infratentorial lesion	11/15 (73%)	15/22 (68%)	0.516
>1 juxtacortical lesion	8/15 (53%)	18/22 (82%)	0.08
>3 periventricular lesion	6/15 (40%)	17/22 (77%)	**0.038**
McDonald 2010	11/15 (73%)	20/22 (91%)	0.198

†p-value represents a comparison between AR(+)MS and AR(-)MS using the Fisher's exact test. Values in bold are significant ($p < 0.05$)