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Short Communication

The clinical and prognostic value of antinuclear antibodies in NMO-IgG seropositive neuromyelitis optica spectrum disorder

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ABSTRACT

In neuromyelitis optica spectrum disorders (NMOSD), the clinical and long-term prognostic value of antinuclear antibodies (ANAs) is unclear. We analyzed registry data of NMO-IgG seropositive NMOSD patients ($n = 74$) according to ANA presence. The ANA-positive group ($n = 32$) demonstrated more frequent other autoantibodies (anti-SSA/Ro, anti-SSB/La, antiphospholipid, and anti-double stranded DNA antibodies) than did the ANA-negative group ($n = 42$). Clinically, annual relapse rates, and average lesion extents on MRI during attacks were comparable between the two groups (median follow-up of 7 years). The development of a poor outcome (walking with unilateral aid) also did not differ. In conclusion, although common, ANAs were not associated with a benign/malignant disease course in our NMOSD cohort.

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSDs), of which diagnostic marker is antibodies to aquaporin-4 (NMO-IgG), are severe inflammatory disease characterized by recurrent optic neuritis (ON) and transverse myelitis (TM). NMOSD patients often have antinuclear antibodies (ANAs) that target macromolecular components of the cell nucleus (Pisetsky, 2017). The clinical significance of ANAs is yet to be elucidated. Interestingly, a recent study suggested that ANAs might be a protective marker in NMOSD because their presence was associated with less frequent attacks (Masuda et al., 2016). However, a cross-sectional study in NMOSD patients found that ANAs were not related to specific neurologic manifestations (Pittock et al., 2008). Here, we aimed to evaluate the clinical and prognostic value of ANAs in NMO-IgG seropositive NMOSD patients with an independent cohort. Since the previous study (Masuda et al., 2016) did not consider ANA titers or detailed magnetic resonance imaging (MRI) findings in the evaluation, we added these components for the current analysis.

2. Materials and methods

2.1. Subjects

The registries of two university hospitals (Asan Medical Center (Seoul, South Korea) and Ulsan University Hospital (Ulsan, South Korea)) were reviewed retrospectively between January 2007 and June 2017. Data from seropositive NMOSD patients (with NMO-IgG), who fulfilled the published criteria (Wingerchuk et al., 2015) were analyzed. This study was approved by the Institutional Review Boards of both hospitals, which waived the requirement for informed patient consent because of the retrospective nature of the study.

2.2. NMO-IgG and ANA

NMO-IgG was detected by indirect immunofluorescence (Lennon et al., 2004). If sera tested positive at a 1:60 dilution, it was serially titrated to 1:960 (Lim et al., 2013). ANAs were measured using a pre-standardized kit (Zeus Scientific, USA). Sera were screened at a 1:40 dilution, and positive sera were titrated to 1:1280.

2.3. Studied variables

Patients were classified according to the presence of ANA at their first visit to our center. Clinical characteristics and MRI findings during attacks were compared between the groups. Patients with disease duration < 1 year were not included in the annual relapse rate (ARR) calculation. For MRI findings, the number of vertebral segments and optic nerve segments (Becker et al., 2010) involved during an attack

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Table 1
Clinical characteristics, imaging findings, and prognosis according to the presence of antinuclear antibodies.

	ANA− NMOSD	ANA+ NMOSD	
	(*n* = 42)	(*n* = 32)	*p*-value
Age at onset (years)	38 [28–47]	31.5 [25–49]	0.365
Female	37 (88.1)	30 (93.8)	0.691
Disease duration (years) to the sampling of ANA	2.0 [0–15.5]	6.0 [0–18.3]	0.698
Follow-up duration in our center (years)	6.8 [3.8–9.2]	6.7 [2.5–10.8]	0.892
Onset attack, %			0.064
ON	15 (35.7)	13 (40.6)	
TM	26 (61.9)	14 (43.8)	
ADEM or ADEM-like (including brainstem attacks)	0 (0.0)	4 (12.5)	
Simultaneous ON and TM	1 (2.4)	1 (3.1)	
Autoantibodies			
NMO-IgG titer	400 [105–600]	960 [240–1920]	0.007
Anti-SSA/Ro antibody	4 (11.8) (*n* = 35)	18 (64.3) (*n* = 28)	< 0.001
Anti-SSB/La antibody	0 (0.0) (*n* = 35)	12 (42.9) (n = 28)	< 0.001
Antiphospholipid antibody	0 (0.0) (*n* = 30)	5 (19.2) (*n* = 26)	0.017
Anti-double stranded DNA antibody	0 (0.0) (*n* = 23)	8 (33.3) (*n* = 24)	0.004
Systemic disease			
Systemic lupus erythematosus	0 (0.0)	4 (12.5)	0.031
Sjogren syndrome	0 (0.0)	6 (18.8)	0.005
CSF findings			
CSF, cell (> 10/μL)	8 (27.6)	5 (23.8)	0.764
CSF elevated protein > 0.60 g/l, n (%)	15 (48.4) (*n* = 29)	5 (22.7) (*n* = 19)	0.058
CSF oligoclonal bands, n (%)	3 (10.3) (*n* = 29)	1 (5.3) (*n* = 19)	> 0.999
CSF IgG index > 0.68, n (%)	8 (27.6) (*n* = 29)	5 (23.8) (*n* = 19)	> 0.999
Disease couse			0.528
Monophasic	9 (21.4)	5 (15.6)	
Relapsing	33 (78.6)	27 (84.4)	
Sequential ON and/or TM (ON → TM or TM → ON)	25 (59.5)	17 (53.1)	0.582
Simultaneous ON and TM (at any time)	5 (11.9)	1 (3.1)	0.226
MRI findings during attacks			
TM, lesion segments per attack	5.8 [4.0–7.1]	6.0 [3.9–8.6]	0.454
TM, lesions ≥3 segments (at any time)	31 (73.8)	28 (87.5)	0.147
TM, lesions ≥6 segments (at any time)	30 (71.4)	20 (62.5)	0.416
ON, lesion segments per attack	2.0 [1.6–3.0]	2.0 [1.0–2.8]	0.280
Annual relapse rate			
ARR from onset to sampling	0.15 [0.00–0.43]	0.02 [0.00–0.37]	0.951
ARR during follow-up	0.40 [0.28–0.66]	0.32 [0.20–0.47]	0.861
of TM	0.31 [0.23–0.58]	0.24 [0.15–0.43]	0.423
of ON	0.00 [0.00–0.12]	0.00 [0.00–0.13]	0.886
Clinical status at the last visit			
EDSS	3.5 [2.5–6.5]	3.5 [3.0–6.0]	0.865
EDSS > 6.0	12 (28.6)	8 (25.0)	0.732
Visual acuity fixed as < 0.1 at least one eye	10 (23.8)	9 (28.1)	0.674
Treatment*			
Duration to the first immune-modulating agent (months)	15 [2–54]	23 [6–71]	0.154
Steroid	41 (97.6)	30 (93.8)	0.575
Azathioprine	35 (83.3)	27 (84.4)	0.904
Mycophenolate mofetil	14 (33.3)	11 (34.4)	0.925
Interferon	17 (40.5)	10 (31.3)	0.414
Rituximab	5 (11.9)	7 (21.9)	0.249

Data are expressed as number (n, %) for categorical variables, median (IQR) for continuous variables.
ADEM = acute disseminated encephalomyelitis; ANA = antinuclear antibody; ARR = annual relapse rate; DNA = deoxyribonucleic acid; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; NMO = neuromyelitis optica; ON = optic neuritis; TM = transverse myelitis.
* During follow-up.

was investigated from the perspective of TM and ON, respectively. Clinical statuses at the last visit were examined with the Expanded Disability Status Scale (EDSS) score; poor outcome was defined by the presence of EDSS ≥6.0 (walking with unilateral aid) and/or of poor visual acuity (< 0.1).

2.4. Statistical analysis

ANA groups were compared using the Chi-square or Fisher's exact tests (categorical variables) and Mann-Whitney *U* test (continuous variables). Spearman's rho was used to measure the degree of correlation between NMO-IgG and ANA titers. Time to an EDSS score of 6.0 was displayed using Kaplan-Meier curves; data were compared between the ANA groups using the log-rank test. Variables with two-tailed *p* values of < 0.05 were considered significant. All statistical analyses were performed using SPSS (version 21) software (SPSS Inc., Chicago, IL).

3. Results

During the study period, 82 patients were diagnosed with NMO-IgG seropositive NMOSD. Of these, 74 (90.2%) patients who underwent ANA tests were enrolled. The median age at onset was 36.0 years (interquartile range [IQR], 26.0–48.0), and the median follow-up was 6.7 years (IQR, 3.6–9.5).

ANAs were detected in 32 (43.2%) patients. Onset age and proportion of female patients were comparable between the ANA-positive and negative groups (Table 1). The type of onset attack was also not

significantly different. With regard to autoantibodies, the ANA-positive group was more likely to have higher NMO-IgG titers. Moreover, patients with a high NMO antibody titer tended to have a higher ANA level, although the correlation was weak (Spearman rho = 0.391, $p = .002$). The median NMO-IgG titer was 1:480 (IQR, 1:240–1:960) and the median ANA titer in the ANA-positive group was 1:160 (IQR, 1:40–1:400). The ANA-positive group also had other autoantibodies more frequently such as anti-SSA/Ro, anti-SSB/La, antiphospholipid, and anti-double stranded DNA antibodies (Table 1). Accordingly, these patients had more frequent systemic diseases such as systemic lupus erythematosus and Sjogren syndrome. However, findings in cerebrospinal fluid were comparable between the ANA groups.

Clinically, relapses developed in > 80% (60/74) of patients; 165 TM, 32 ON, and 6 simultaneous TM and ON were recorded in the registry. Forty-three patients experienced both TM and ON (37 with sequential attacks only, 5 with both sequential and simultaneous attacks, and 1 with a simultaneous attack only) in their disease courses. On MRI studies, median lesion segments in the spinal cord for each TM attack was 5.9 (IQR, 4.0–8.0), while median lesion segments in the optic nerve for each ON attack was 2.0 (1.1–3.0). Longitudinal extensive TM (≥3 segments or more) was evident in 59 (79.7%) patients. Between the ANA groups, the extent of MRI lesions during attacks were not significantly different. ARRs were similar before and during follow-up, regardless of TM or ON. Accordingly, clinical status at the time of the last visit (including the EDSS, frequency of poor visual acuity, and EDSS ≥6.0) was also comparable. Kaplan-Meier analysis revealed no significant difference between the ANA groups in the EDSS 6.0 achievement rate (Fig. 1).

With respect to treatment regimens, steroid was most frequently used during the disease course. Interferons, known to be ineffective for NMOSD (Kim et al., 2012), had been administered to a number of patients before a definite NMOSD diagnosis was made. Between the ANA groups, the disease duration up until the first immune-modulating therapy, and the frequency of treatment methods during follow up were comparable.

4. Discussion

In this study, > 40% of NMO-IgG seropositive NMOSD patients were ANA-positive. Patients with high NMO-IgG tended to have ANAs and other non-organ specific autoantibodies. However, the presence of ANA did not alter the long-term disease course, regardless of ANA titers.

NMO-IgG often occur with other autoantibodies (Jarius et al., 2011; Masuda et al., 2016; Park et al., 2015; Pittock et al., 2008; Wingerchuk and Weinshenker, 2012). Current evidence suggests that this co-existence develops in patients that are susceptible to humoral autoimmunity (Wingerchuk and Weinshenker, 2012). Theoretically, autoantibodies other than NMO-IgG may augment cellular immune response. In addition, these autoantibodies may induce vascular damage, thereby rendering the central nervous system more accessible to aquaporin-4 antibodies (Jarius et al., 2011). However, cross-sectional studies found no evidence that they were directly related to neurologic manifestations of NMOSD (Jarius et al., 2011; Park et al., 2015; Pittock et al., 2008). A recent study rather showed that ANAs are a protective marker in NMOSD; their presence was associated with less frequent attacks up until the time of ANA sampling (Masuda et al., 2016).

Here, we examined the long-term prognostic value of ANA in NMO-IgG seropositive NMOSD. Clinical characteristics did not differ between the ANA groups, as determined by ARR, the extent of disease during attacks (MRI findings), and clinical status at the last visit. ANAs were not associated with benign or malignant NMOSD prognosis. ANAs may be a non-specific marker which is not enough to manifest their effect on the prognosis. ANAs are known to be observed in up to 20–30% of the healthy population (Pisetsky, 2017). As in the case of systemic lupus erythematosus, specific autoantibodies other than ANA may be more influential (Hahn, 1998; Pisetsky, 2017). However, the small number of such cases in this study prevented us from evaluating the value of those autoantibodies; future studies in NMOSD patients with a larger panel of autoantibodies are warranted.

Several limitations should be noted. Small numbers of NMOSD patients and the retrospective design indicate that the results should be interpreted cautiously. Moreover, all patients were ethnically Korean; our results may not be more generally applicable.

In conclusion, as in previous studies, ANAs were often observed and were associated with the presence of other autoantibodies. However, the presence of ANA was not related to a benign/malignant disease course in our NMOSD cohort.

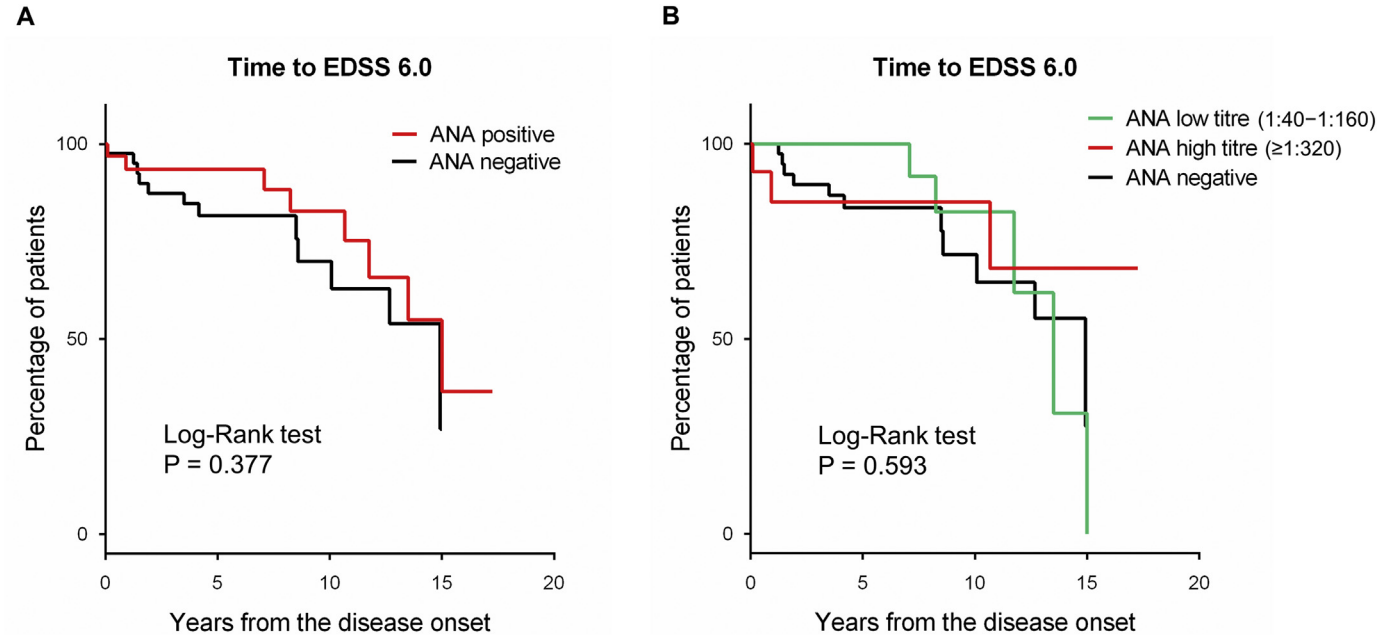

Fig. 1. Time to an Expanded Disability Status Scale (EDSS) score of 6.0, according to (A) the presence of antinuclear antibodies (ANAs) and (B) the ANA levels. The high-titer group was defined as having ANA titers higher than the median level (1:160).

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None.

Declaration

The authors declare no conflicts of interest.

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