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Prognostic value of auto-antibodies to extractable nuclear antigens in neuromyelitis optica

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Abstract

Background: Compared with the Western population, central demyelinating disorders are relatively rare while the data on the prognostic value of autoantibodies together with clinical characteristics and cognitive dysfunction has rarely been explored in neuromyelitis optica (NMO) and multiple sclerosis (MS). *Methods:* Nineteen patients with MS and 14 with NMO underwent clinical profiling and cognitive assessment. According to serology tests, they are divided into four subgroups for further analysis. *Results:* There was higher frequency of aquaporin-4 immunoglobulin G. sero-positivity (64.3% vs. 10.5%; p=0.003) and antinuclear antibodies (ANA) and/or antibodies to extractable nuclear antigens (anti-ENA) in NMO compared to MS (42.9% vs. 5.2%; p=0.026). The presence of anti-ENA represented a unique clinical phenotype, with longer segment of myelitis (p=0.049), female preponderance, and an inverse correlation between age-of-onset and annual relapse rate (ρ= -0.88, p=0.021). Among patients with anti-ENA positivity, comprehensive serology panels revealed Sjögren's syndrome A antibodies as the most common (83%), in contrast to limited clinical documentation of Sjögren's syndrome (16%). There was no significant difference in cognitive assessment by anti-ENA status. MS and NMO represent two different serologic entities.
Conclusions: Anti-ENA may have prognostic value for its linkage to a unique clinical phenotype, which has longer initial segment of myelitis, female preponderance, and higher annual relapse rate on earlier age-of-onset, but has limited clinical impact on cognition. Further studies are warranted to investigate whether anti-ENA represents an epiphenomenon of myelitis or simply a systemic inflammatory state.

INTRODUCTION

The presence of aquaporin-4 immunoglobulin G (AQP4-IgG) in neuromyelitis optica (NMO) highlights the humoral immunity dysfunction and diagnostic value of serum biomarkers in the spectrum of acquired central nervous system (CNS) demyelinating diseases.[1] Patients with NMO often have accompanying autoimmune disorders, most commonly, but not limited to *systemic lupus erythematosus (SLE)*[2-3], Sjögren's syndrome[2,4-5,6], and anti-phospholipid syndrome.[3,7] In NMO, the co-existence of anti-nuclear antibodies (ANA)[8-9], extractable nuclear antigens (ENA) auto-antibodies[4-5], and anti-phospholipid antibodies[8] is often considered unfavorable, with a link between myelopathy[5] and optic neuritis[4,8] often reported.

Although multiple sclerosis (MS) is primarily categorized as an acquired demyelinating disease with cellular immunity derangement, co-existing Sjögren's syndrome A antibodies (SSA) or anti-phospholipid antibodies have been reported.[10-11] However, their impact on cognition remains uncertain.

Overlapping clinical symptoms such as optic neuritis and myelitis in MS and NMO often pose diagnostic challenges.[12] Based on the different immunologic mechanisms of NMO and MS, the detection of co-existing auto-antibodies may extend the diagnostic repertoire if they have predictive value in clinical outcomes. Moreover, a link between serum auto-antibodies and cognitive presentations in NMO and MS has not yet to be established in Asian populations.

The aim of the present study was to investigate the clinical significance of four groups of co-existing auto-antibodies[4,5,8,9] on clinical outcomes in patients with MS and NMO.

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METHODS

Subjects

Nineteen MS and 14 NMO patients were recruited. Demographic, clinical features, cognitive testing, neuro-imaging, and laboratory data, including AQP4-IgG status, were collected. The diagnosis of NMO was based on the revised criteria by Wingerchuk *et al*.[1], while MS was diagnosed using the McDonald's revised criteria[13] and the Barkhof criteria.[14] Cognitive assessment and serology sampling were performed during the remission stage, while brain or spine MRI was performed within three months. Co-existing autoimmune conditions were recorded after consultations with rheumatologists aside from the diagnosis of SLE[15] or Sjögren's syndrome.[16] The Institutional Review Board of Chang Gung Memorial Hospital approved the study.

The exclusion criteria, which removed confounding factors in cognitive evaluation, were an Expanded Disability Status Scale (EDSS)[17] score >7.5 and failure to pass the visual attention tests[18] or prolonged visual evoked potentials bilaterally (108 ms) or visual acuity <20/100 prior to cognitive testing.[19]

Serology tests

For statistical analysis, serology data were categorized into four groups according to similar inflammatory processes or disease entities.[20]

Group 1 included ANA (reference <1:160) and anti-ENA screening. Serum samples positive for anti-ENA screening were further tested for anti-SSA/Ro, anti-SSB/La, anti-Sm, anti-U1RNP, anti-Jo-1, and anti-Scl-70.

Group 2 included anti-double strand DNA (cut-off value 12 IU/ml), immunoglobulin (reference: IgG, 700-1600 mg/dL; IgA, 70-400 mg/dL; IgM, 40-230 mg/dL), and complement (hypo-complementemia was defined as C3 <90 mg/dL or C4 <10 mg/dL).

Group 3 included anti-phospholipid antibodies (lupus anti-coagulants reference 31-40 seconds; cut-off values: anti-cardiolipin antibodies >15 GPL/ml; anti-$\beta_2$glycoprotein >15 U/ml).

Group 4 included the thyroid-gland specific anti-thyroglobulin and anti-microsomal antibodies (both cut-off values >1:100).

Cognitive assessment

General intellectual function was assessed using the mini-mental state examination (MMSE).[21] Clinical dementia rating[22] and EDSS[17] were used to evaluate cognitive capacity and physical function, respectively. Visuo-spatial ability was assessed using the modified Rey-Osterrieth Complex Figure Test[23] and Visual Object and Space Perception Battery.[24]

Statistical analysis

Categorical variables were compared using the chi-square test. Differences in continuous variables between groups were analyzed using the Kruskal-Wallis one-way analysis of variance, with Bonferroni correction. Spearman correlation analysis was performed to check the correlation between continuous variables. All statistical analyses were conducted using the Statistical Package for Social Sciences software package (version 13 for Windows®, SPSS Inc, Chicago, IL). Statistical significance was set at $p<0.05$.

RESULTS

Demographic data

Based on the demographic and serologic data of the 33 patients (Table 1), the average follow-up period from diagnosis to the study was 31±10.9 months. All patients with NMO were female, which was significantly different compared to the MS group ($\chi^2=6.547$, $p=0.01$). Although there was no difference in EDSS between the MS and NMO groups, the NMO group had better cognitive capacity based on the clinical dementia rating sum of the box scores ($p=0.016$). Clinically, there were higher incidences of optic neuritis (ON) and myelitis in the NMO group than in the MS group (ON: $\chi^2=7.781$, $p=0.005$; myelitis: $\chi^2=4.342$, $p=0.049$).

Auto-antibodies by clinical diagnosis

AQP4-IgG sero-positivity was significantly higher in the NMO group than in the MS group (64.3% vs. 10.5%; $\chi^2=8.623$, $p=0.003$). Comparing the four serology groups, there was a higher sero-positivity for ANA and anti-ENA in the NMO group than in the MS group ($\chi^2=6.816$, $p=0.026$). Five NMO and one MS patients were sero-positive for anti-ENA ($\chi^2=4.051$, $p=0.044$). The ANA and anti-ENA positivity were highly inter-correlated ($\rho = 0.796$, $p<0.001$). However, there was no significant difference in Groups 2 to 4 antibodies between the MS and NMO groups.

Auto-antibodies by myelitis or optic neuritis

The patients were dichotomized by presence of

Table 1: Demographic and serology data by clinical diagnosis and characteristic of patients with multiple sclerosis (MS) or neuromyelitis optica (NMO)

	Clinical Diagnosis		Clinical Characteristics			
	MS n=19	NMO n=14	Myelitis (+) n=28	Myelitis (-) n=5	ON (+) n=25	ON (-) n=8
Age (year)	35.8 (9.7)	42.6 (13.8)	38.3 (12.0)	41.2 (12.3)	41.6 (12.1)	29.8 (5.1)*
Age of onset (year)	30.1 (11.1)	34.6 (15.1)	30.7 (12.6)	37.8 (13.1)	34.5 (13.7)	24.3 (4.9)*
Sex (M/F)	7/12	0/14*	3/25	4/1*	4/21	3/5
Education (year)	12.8 (3.5)	11.8 (5.4)	12.4 (4.6)	11.6 (2.9)	11.5 (4.6)	14.5 (2.5)
Expanded Disability Status Scale	3.4 (1.7)	4.8 (2.1)	4.1(1.9)	4.0 (2.5)	4.5 (1.9)	2.1 (0.8)
Mini-Mental Status Examination	24.8 (5.9)	27.3 (3.7)	26.1 (5.4)	24.2 (2.4)	24.9 (5.5)	28.8 (1.8)*
Clinical Dementia Rating Sum of the Box	2.2 (3.9)	0.0 (0.1)*	1.2 (3.3)	1.8 (2.3)	1.6 (3.5)	0.2 (0.4)
Optic neuritis (ON)	11	14*	21	4	25*	0
Myelitis	14	14*	28*	0	21	7
Aquaporin-4 immunoglobulin G positive	2	9*	11	0	10	1
Group 1 ANA ≥ 1:160 or Anti-ENA(+)	1	6*	7	0	6	1
Group 2 C3, C4, IgG/A/M, anti-dsDNA	8	5	11	2	10	3
Group 3 Anti-phospholipid antibodies	4	5	8	1	5	4
Group 4 Thyroid-specific antibodies	0	2	2	0	2	0

*p<0.05 comparing between groups ;
Note: Anti-phospholipid antibodies included lupus anti-coagulants, anti-cardiolipin antibodies, anti-$\beta_2$glycoprotein; data are presented as mean (standard deviation)

clinical myelitis (Table 1). There was a female preponderance in the myelitis group (χ^2=12.186, p=0.04). Interestingly, trends of AQP4-IgG and ANA/anti-ENA sero-positivity were also identified in the myelitis group.

Patients with optic neuritis [ON(+)] (Table 1, right column) were older at disease onset and at examination compared to those without ON [ON(-)]. The ON(+) group had lower MMSE scores, which was unrelated to age (β= -0.047, p=0.677). There were no differences in autoantibody profiles between the ON(+) and ON(-) groups.

Comparison of clinical features according to anti-ENA status

Further examining the clinical significances of anti-ENA antibodies (Table 2), patients positive for anti-ENA had significantly longer segments of myelitis (p=0.049). However, there was no difference in serology profiles and cognitive performance.

Clinical presentation of patients with positive anti-ENA antibody

Based on the clinical presentations of the six patients who were positive for anti-ENA (Table 3), there was a female preponderance and an inverse correlation between age of onset and annual relapse rate (β= -0.841, p=0.036). Except for an isolated case with anti-U1RNP (25.3 U/ml), all had anti-SSA (n=5, 83%).

In neuro-imaging assessment, longitudinal transverse myelitis tended to appear as enhanced intra-medullary lesions in the cervical and/or thoracic levels (n=4, 67%). The most commonly involved intracranial area was the peri-ventricular (n=5, 83%) area, with or without juxtacortical lesions.

DISCUSSION

The present study has two major findings regarding serum auto-antibodies in patients with NMO and MS. First, the presence of both ANA and anti-ENA (Group 1) is highly correlated with the diagnosis of NMO. Patients with anti-ENA antibodies have a higher prevalence of myelitis, characterized by longer segment involvement at the cervical-thoracic level. Aside from myelitis, the presence of anti-ENA does not predict cognitive performances in patients with MS or NMO. Second, earlier disease onset is predictive of higher annual relapse rate in the patients sero-positive for anti-ENA and whose initial presentation all include myelitis.

Although SSA is the major co-existing autoantibody in anti-ENA screening in our study, only one patient has been diagnosed with Sjögren's

Table 2. Comparisons of patients based on anti-extractable nuclear antibodies (anti-ENA) status

	Anti-ENA(+) n=6	Anti-ENA(-) n=27
Clinical features		
Age (year)	39.3 (15.0)	38.6 (11.5)
Sex (M/F)	0/6	7/20
Education (year)	11.2 (5.9)	12.5 (4.0)
Expanded Disability Status Scale	4.4 (2.7)	4.0 (1.8)
Annual relapse rate (/year)	1.6 (1.0)	1.0 (0.8)
Focal neurological features		
Optic neuritis	5	20
Weakness	5	26
Numbness	6	24
Intra-nuclear ophthalmoplegia	1	2
Neurogenic bladder/bowel	3	10
Cerebellar ataxia	0	5
Brainstem signs	1	7
Myelitis total length (vertebral segment)	7 (5.8)	3 (3.8)*
Serology groups		
AQP4-IgG (+)	3	8
Group 2 C3, C4, IgG/A/M, anti-dsDNA	2	11
Group 3 Anti-phospholipid antibodies	2	7
Group 4 Thyroid-specific antibodies	1	1
Cognitive performance		
Mini-Mental Status Examination	28.5 (2.8)	25.2 (5.3)
Clinical Dementia Rating Sum of the Boxes	0.0 (0.0)	1.6 (3.4)
Rey-Osterrieth recognition (1)	1.0 (0.0)	0.8 (0.4)
Visual Object and Space Perception (10)	7.7 (2.4)	7.9 (2.7)

*$p<0.05$
Data are presented as mean (standard deviation)

syndrome. Therefore, the co-existence of other auto-antibodies does not necessarily point to a clinical diagnosis of an autoimmune disorder. Although autoimmune diseases like SLE[2-3], Sjögren's syndrome[2,6], and anti-phospholipid antibody syndrome[3,7] may manifest as NMO, the incidence is rare. Similarly, only a small portion of the patients with NMO (2/14, 14%) in this study fit the criteria of other extra-neural autoimmune diseases.[2] Different sero-positive rates of AQP4-IgG and ANA/anti-ENA (65 % vs. 43%) suggest that the presence of anti-ENA antibodies does not necessarily imply the co-existence of AQP4-IgG, and vice versa.

Transverse myelitis has been associated with ANA and SSA in a previous case series [25-26], characterized by female preponderance, recurrent clinical course, and co-morbid optic neuritis. This raises a reasonable suspicion of NMO under the revised diagnostic criteria [1]. This study documents the clinical impact of anti-ENA on spinal cord involvement, even though its relationship with cognitive performance is not pronounced. Since the study design is based on serum samples during the remission stage, the existence of anti-ENA appear to be in accordance with baseline immunity rather than the biomarkers during the flare-up.

In our case 4 and 6, concurrent diagnosis of NMO and rheumatic disease were made (Table 3). The interrelationships between NMO and rheumatologic disease raised important diagnostic implications. The overlapping between NMO or NMO-spectrum with other systemic autoimmune diseases including SLE or Sjögren's syndrome were reported in Japan[27-29] or Western society.[30,31] Based on the high specificity of aquaporin-4 antibody[32], the presence of aquaporin-4 antibodies in the context of serological autoantibodies may secure the diagnosis of NMO coexisting with rheumatologic disease as in our case 6. Considering the low sensitivity of aquaporin-4 antibodies, it remained unclear whether patients

Table 3: Clinical presentation of the patients with positive anti-extractable nuclear antibody (anti-ENA)

Case No./Sex/Age (Year)/onset age (year)	Dx	EDSS	Annual Relapse Rate	First attack	Anti-ENA	Associated serology abnormality	Autoimmune disease	Brain lesions	Initial Spinal lesion characteristics
1/F/29/27	MS	1.5	1.6	Myelitis	SSA	IgG/anti-thrombin III	None	Peri-ventricular/ juxtacortical	C4 and T9 with enhancement
2/F/24/16	NMO	7.5	3.6	Myelitis	RNP	None	None	Peri-ventricular	C2-T12 with enhancement
3/F/30/24	NMO	1.5	1.6	Myelitis with ON	SSA/SSB	Anti-microsomal antibodies, AQP4-IgG	None	Occipital peri-ventricular	C1 and T2-4
4/F/37/36	NMO	6.5	1.6	Myelitis	SSA	Lupus anticoagulant	SLE	Peri-ventricular/ juxtacortical	C4-T7 and T10-L1 with enhancement
5/F/58/45	NMO	6.5	0.5	Myelitis	SSA	AQP4-IgG	None	Peri-ventricular	T4-6
6/F/50/48	NMO	3	0.7	Myelitis	SSA/SSB	C3, C4, IgG, and lupus anticoagulant, AQP4-IgG	SS and SLE	Right cerebellar peduncle	C3-T11 with enhancement

EDSS, Expanded Disability Status Scale; AQP4-IgG, aquaporin-4 immunoglobulin G; SSA, Anti-Ro antibody; SSB, Anti-La antibody; RNP, anti-ribonucleoprotein; MRI, Magnetic resonance imaging; Dx, diagnosis; SLE, systemic lupus erythematous; SS, Sjögren's syndrome

with sero-negative for aquaporin-4 antibodies and who experience a single attack of myelitis or optic neuritis may determined to have NMO. However, a repeated attack of myelitis and optic neuritis, as in our case 4, is still likely to have NMO coexisting with the SLE.[32] For other patients with seonegative aquaporin-4, careful clinical follow-up and recheck the diagnostic criteria of other associated symptoms aside from optic neuritis and myelitis is recommended.

In summary, the presence of anti-ENA or ANA in the CNS demyelinating disease indicates longer segments of myelitis and higher annual relapse rate in patients with earlier disease onset. The initial presentation is predominantly myelitis in the cervical or thoracic regions. The co-existence of anti-ENA auto-antibodies in patients with NMO does not necessarily imply a clinical diagnosis of an extra-neural autoimmune disorder, and its correlation with cognition is not pronounced.

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DISCLOSURE

Conflict of interest: None

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