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Clinical characteristics of disabling attacks at onset in patients with neuromyelitis optica spectrum disorder

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ABSTRACT

Background: Individual attacks of neuromyelitis optica (NMO) are generally severe enough to cause disability even after the onset attack. We aimed to elucidate the clinical characteristics of disabling attacks at the onset of NMO.

Methods: We investigated the clinical characteristics at onset and at first relapse in patients with NMO or NMO spectrum disorder with seropositive for the anti-aquaporin-4 antibody. A disabling attack at onset (DAO) was defined as an onset attack in which, at best recovery (allowing up to one year), patients were unable to walk without assistance or were left functionally blind in at least one affected eye.

Results: Fifty-seven patients were enrolled (53 females; onset age, 41.9 ± 14.8 years). Ten patients (17.5%) had a DAO; four had become unable to walk without assistance following myelitis, and six had severe visual impairment following optic neuritis despite rescue treatments. Attack severity at nadir was the only clinical factor predicting a DAO (odds ratio, 2.120; 95% CI, 1.162–3.869; $P = 0.014$). The use of immunosuppressants delayed the interval to the first relapse ($P = 0.003$).

Conclusion: Our study showed characteristics of NMO onset attacks that caused severe disability. However, no clinically modifiable factors predicted disabling attacks, except attack severity.

1. Introduction

Neuromyelitis optica (NMO) is an autoimmune relapsing inflammatory disorder of the central nervous system (CNS) characterized by optic neuritis, myelitis, and distinctive brain lesions [1]. An antibody against the main water channel protein in the CNS, aquaporin-4 (AQP4), is thought to be pathogenic and is detected in 60–80% of patients with NMO [2].

NMO is widely regarded to be more severe than multiple sclerosis (MS).[1] A secondary progressive phase in which the disabilities associated with MS accumulate is rare, whereas the disability in NMO is the cumulative result of incomplete recovery from each individual attack [3]. There is remarkable variability in the prognosis of patients with NMO, which could be a reflection of the variability in the severity of, and potential recovery from, individual NMO attacks [4].

In CNS inflammatory diseases, the initial attack is considered to be of particular importance. In MS, several studies have related the severity and recovery of the initial attack with subsequent attacks. Patients with relapsing-remitting MS had relatively localized relapses, which might be under separate biological or genetic control from the initial attack [5–8]. In NMO, onset location can predict the location of subsequent attacks [9], and some patients with NMO could develop severe disabilities even after the onset attack [4]. However, there are no reports on the clinical characteristics and treatment profiles of NMO attacks at onset, which could contribute to initial attack severity and recovery.

In this study, we aimed to elucidate the clinical characteristics of initial attacks and other factors predicting subsequent residual disability in patients with NMO spectrum disorder (NMOSD).

2. Material and methods

2.1. Patients and methods

We retrospectively reviewed patients who were registered in the CNS Inflammatory Disease Registry at the Samsung Medical Center from 2007 to 2014. All patients were diagnosed as having NMO or

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NMOSD with positive anti-AQP4 antibodies [1,10]. Patients were excluded from the study on the basis of the following criteria: (a) an anti-AQP4 antibody test, performed using a cell-based indirect immunofluorescence assay as described previously [11], yielded negative results or was not done; (b) the clinical characteristics of the initial attacks and the first relapses were not evaluated or were unknown; and (c) the duration of follow-up was less than a year after disease onset.

We evaluated the initial attacks and first relapses of all patients. Data were collected regarding age at each attack, sex, time to first relapse after onset, clinical presentation, disability, type of acute treatment, time to treatment after symptom onset, and use of immunosuppressants. Considering their clinical symptoms and MRI lesions together, patients were classified into six clinical presentations: optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, diencephalic syndrome, cerebral syndrome, and combined [12].

An attack was defined as an acute episode of neurological symptoms lasting 24 h or more that happened at least 30 days after any previous attack. The disability of each attack was scored using the Expanded Disability Status Scale (EDSS) score. Attack severity was defined as the highest EDSS score within 1 month after symptom onset of an individual attack, and attack recovery was defined as the lowest EDSS score within 1 year of the initial attack. Each initial attack was defined as a disabling attack at onset (DAO) when the best EDSS score within a year included the inability to walk without assistance (an EDSS score of 6 or above) or functional blindness (20/200 vision or worse) in at least one affected eye. The patients were divided into two groups according to the presence or absence of a DAO.

2.2. Statistical analysis

Appropriate summary statistics were used to describe categorical and continuous variables. Continuous data are shown as mean and standard deviation, or median and inter-quartile range (IQR). Categorical variables are presented with absolute and relative frequencies. We analyzed the differences between the groups (DAO versus without DAO) using a chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or a Mann-Whitney *U* test for continuous variables. Multivariate logistic regression analysis was performed to evaluate the independent contribution of factors that influenced the presence of a DAO. Results are given as the odds ratio (OR) with a 95% confidence interval (CI). Factors that were evaluated with a multivariate analysis are presented in Supplementary Table 1. The time between symptom onset and acute treatment, the type of acute treatment, and total amount of intravenous methyl-prednisolone (IVMP) were considered as modifiable predictors.

The time to first relapse after onset attack was estimated by Kaplan-Meier survival curves. The effect of the use of immunosuppressants on time to first relapse was evaluated by log-rank tests. A value of $P < 0.05$ was considered significant. All statistical analyses were performed using commercially available software (SPSS for windows, version 19.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Fifty-seven patients were finally enrolled, 53 (93.0%) of whom were female. Mean age at onset was 41.9 ± 14.8 years, and the mean follow-up duration was 69.6 ± 61.2 months. Forty-three patients (75.4%) experienced a relapse. The median time to this first relapse after onset was 12.0 months (IQR, 4.6 to 22.4). Acute myelitis was the most common clinical presentation at onset (38.6%), followed by optic neuritis and area postrema syndrome (31.6% and 12.3%, respectively). Twenty patients had comorbid autoimmune diseases (35.1%), with Sjogren's syndrome being the most common one (13/20, 65.0%) (Table 1).

3.2. Clinical characteristics and treatment profile of initial attack

EDSS scores of the initial attack at nadir and at recovery were 3.0 (IQR 2.8 to 4.0) and 1.5 (IQR 1.0 to 2.0). Ten patients (10/57, 17.5%) had a DAO. Of the patients with a DAO, six presented with optic neuritis, and three presented with acute myelitis. One patient had acute myelitis and optic neuritis in rapid succession at onset. Patients presenting with brain region-related clinical syndromes affecting the area postrema, brainstem, or cerebrum had no DAO (Table 2). The clinical and radiological features of all individual patients with a DAO are detailed in Table 3. The EDSS score at nadir in patients with myelitis presentation was significantly higher than that of patients with optic neuritis or area postrema syndrome presentations ($P = 0.016$ and $P = 0.028$, respectively). The neurological disability assessed by the EDSS score in patients with myelitis presentation tended towards being worse at recovery, but this was not statistically significant (Fig. 1).

Most of the patients in this study were treated with IVMP during the acute stage at onset and at the first relapse (78.9% and 87.2%, respectively). Four patients at onset (7.0%) and one patient at the first relapse (2.6%) underwent subsequent plasma exchange based on the physician's discretion. Between patients with and without a DAO, the types of acute treatment were not significantly different. The total dose of methyl-prednisolone and the median time between symptom onset and acute treatment were not different (4.2 ± 1.7 and 4.6 ±

Table 1
Baseline characteristics of patients.

	Total	Patients without disabling attack at onset	Patients with disabling attack at onset	*P* value
	N = 57	*N* = 47	*N* = 10	
Females, n (%)	53 (93.0)	44 (93.6)	9 (90.0)	0.548
Age at onset, year (SD)	41.9 (14.8)	41.7 (14.3)	42.7 (17.5)	0.845
Follow-up duration, months (SD)	69.6 (61.2)	73.4 (61.5)	51.9 (59.3)	0.224
Number of attacks (SD)	5.0 (5.3)	5.3 (5.5)	3.3 (4.1)	0.206
EDSS at last follow-up (SD)	3.3 (2.4)	2.9 (2.2)	5.2 (2.4)	0.005
Autoantibodies				
Anti-AQP4 antibody, n (%)	57 (100)	47 (100)	10 (100)	
Anti-nuclear antibody, n (%)	33/50 (66.0)	28/40 (70.0)	5 (50.0)	0.277
Anti-SSA or SSB antibody, n (%)	19/51 (37.3)	17/41 (41.5)	2 (20.0)	0.287
Associated autoimmune disease				0.722
Sjogren's syndrome, n (%)	13 (22.8)	11 (23.4)	2 (20.0)	
Systemic lupus erythematosus, n (%)	3 (5.3)	3 (6.4)	0	
Other[a], n (%)	4 (7.0)	3 (6.4)	1 (10.0)	
CSF findings				
WBC count in CSF, /μl (SD)	24.5 (62.3)	24.9 (65.9)	21.3 (14.4)	0.092
Protein level in CSF, mg/dl (SD)	51.3 (42.5)	45.7 (30.2)	97.5 (93.3)	0.306

AQP4, aquaporin-4; CSF, cerebrospinal fluid; SD, standard deviation; SSA, anti-Ro antibody; SSB, anti-La antibody; WBC, white blood cell.
[a] Antiphospholipid antibody syndrome, mixed connective tissue disease, autoimmune Hashimoto's thyroiditis and myasthenia gravis.