Comparison of Early Onset versus Late Onset Neuromyelitis Optica Spectrum Disorders: Clinical Characteristics and Outcomes at A University Hospital, Northeastern Thailand

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease of the central nervous system and generally follows a relapsing course, leading to neurologic disability. Older age at onset was associated with worse disease prognosis. However, there was a small number of research comparing the outcomes of patients with early-onset NMOSD (EO-NMOSD) and late-onset NMOSD (LO-NMOSD) in Thailand.

Objective: To compare clinical characteristics and outcomes between patients with EO-NMOSD (age at onset 18-49 years) and LO-NMOSD (age at onset ≥50 years).

Methods: We retrospectively analyzed data of patients diagnosed with NMOSD who visited Srinagarind Hospital between January 2015 and October 2021. Patient demographics, clinical attacks, MRI findings, laboratory data, Expanded Disability Status Scale (EDSS), and treatment were collected. A comparison of clinical characteristics and outcomes between the EO-NMOSD and LO-NMOSD was analyzed.

Results: Of 76 patients, there 44 patients were in the EO-NMOSD group, and 32 were in the LO-NMOSD group. The majority were females (90.8%), and the mean age of onset was 45.3±14.7 years. There was no significant difference in clinical characteristics between the two groups, except the CSF protein was significantly higher in LO-NMOSD than in EO-NMOSD (62 vs. 37 mg/dL, P<0.001). There was a significant positive correlation between the age of onset and EDSS on discharge date (r=0.323, p=0.004) and at six months (r=0.359, p=0.004).

Conclusion: Patients with LO-NMOSD have similar clinical characteristics but worse outcomes than EO-NMOSD.

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune central nervous system (CNS) demyelinating disorder that affects multiple areas of the CNS and generally follows a relapsing course, leading to devastating outcomes and permanent neurologic disability.[1,2] The pathophysiology of NMOSD has been well-described for many decades. A pathogenic serum IgG antibody causes it against the water channel aquaporin 4 (AQP4) that binds to the channel on astrocytes and causes inflammatory damage to astrocytes oligodendrocytes, followed by demyelination and neuronal loss.[2]

The prevalence of NMOSD varies among the studies, but it is overall more frequent in Asian and Black populations compared with White.[3,4] The average age of onset was 30-40 years, but some very early and very late-onset cases have also been reported.[5] The previous study demonstrated that older age at onset was associated with worse disease prognosis, higher mortality rate, and greater susceptibility to disability.[6] However, there was a small number of research comparing the outcomes of patients with early-onset NMOSD (EO-NMOSD, disease onset <50 years) and late-onset NMOSD (LO-NMOSD, ≥50 years), and the majority of the studies were restricted to Western populations.[7-11]

In this study, we aim to evaluate the effect of older age at onset in NMOSD patients and compare the clinical characteristics and outcomes between EO-NMOSD and LO-NMOSD in Thai populations.

Methods

Study design

This was a cross-sectional retrospective study of patients with NMOSD who visited Srinagarind Hospital between January 2015 to October 2021. This study was undertaken according to the principles of the Declaration of Helsinki. The research protocol was approved by the Ethical Committee of Srinagarind Hospital.

Participants

We retrospectively reviewed the medical records of patients diagnosed with NMOSD based on the 2015 International Panel for NMO Diagnosis (IPND) criteria.[12] The inclusion criteria included that patients must be at least 18 years old and have a disease duration longer than six months. Patients with incomplete data or incomplete follow-up were excluded.

Data collection

Patient demographics, age of onset, sex, disease duration, comorbidities, clinical attack, CSF findings, imaging, treatment, and Expanded Disability Status Scale (EDSS) on discharge date and six months follow-up were collected. Patients were classified as EO-NMOSD (age at onset, 18-49 years) or LO-NMOSD (age at onset, more than 50 years). The outcome was determined by using the EDSS score; EDSS <6 was defined as a good outcome, and EDSS ≥ 6 was defined as a poor outcome.[10]

Statistical analysis

Baseline characteristics were analyzed using mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Categorical variables were presented as percentages and frequencies. Comparison of patient characteristics using χ 2 test or Fisher's exact test for categorical variables and independent t-test or Mann-Whitney U test for continuous

variables, depending on the data. The correlation between age of onset and outcome was analyzed using Pearson's correlation. Statistical significance was defined as $p < 0.05$. All statistical analyzes were performed using STATA software version 15.0 (College Station, Texas, USA).

Results

Seventy-six patients diagnosed with NMOSD were included. The baseline characteristics were presented in Table 1. The majority were females (90.8%), and the average age of onset was 45.33±14.74 years. Comorbidities were reported in 28 patients (36.8%); the three most prevalent were hypertension (10.5%), dyslipidemia (10.5%), and diabetes mellitus (9.2%). Transverse myelitis was the most frequent clinical attack (69.7%), followed by optic neuritis (59.2%), brain stem syndrome (4%), area postrema syndrome (2.6%), and diencephalic syndrome (1.2%). For acute relapse treatment, 71 patients (93.4%) received intravenous methylprednisolone, and 19 patients (25%) were followed by plasma exchange. Most patients were prescribed prednisolone for long-term immunosuppressive (92.1%), azathioprine (54.0%), and mycophenolate mofetil (5.3%).

Table 1 Demographic data

Features	Total (n = 76)
Age at onset (years), Mean (SD)	45.33 (14.74)
Sex female, n (%)	69 (90.8%)
Comorbidities, n (%)	
- Hematologic disorders	1 (1.3%)
- Autoimmune disease	1 (1.3%)
- Thyroid disease	1 (1.3%)
- Diabetes mellitus	7 (9.2%)
- Hypertension	8 (10.5%)
- Dyslipidemia	8 (10.5%)
- Malignancy	2 (2.63)
Clinical attack, n (%)	
- Optic neuritis	45 (59.2%)
- Transverse myelitis	53 (69.7%)
- Area postrema syndrome	2 (2.6%)
- Brainstem syndrome	3 (4.0%)
- Diencephalic syndrome	1 (1.2%)
- Cerebral syndrome	0 (0.0%)
Coexisting autoimmunity, n (%)	
- ANA	15 (27.8%)
Serum NMO positive, n (%)	69 (90.8%)
CSF findings	
- CSF WBC, Median (IQR)	7.5 (22.5)
- CSF protein, Median (IQR)	45 (26.5)
- CSF/serum sugar ratio, Mean (SD)	0.559 (0.118)
Acute treatment, n (%)	
- Methylprednisolone	71 (93.4%)
- Plasma exchange	19 (25.0%)
- Methylprednisolone plus plasma exchange	19 (25.0%)
Medications, n (%)	
- Corticosteroid	70 (92.1%)
- Azathioprine	41 (54.0%)
- Mycophenolate mofetil	4 (5.3%)

Of 76 patients, 44 were in the EO-NMOSD group, the average age was 35.61±9.58 years, and 32 were in the LO-NMOSD group, the average age was 58.69±8.95 years (Table 2). The number of affected females was higher in both groups. Diabetes mellitus was reported more in LO-NOMSD than in EO-NMOSD (18.8% vs. 2.3%, p=0.037), and other comorbidities were similar in both groups. The most common clinical presentation in EO-NMOSD was optic neuritis (68.2%), while in LO-NMOSD was transverse myelitis (75%). CSF protein was significantly higher in LO-NMOSD than in EO-NMOSD (62 vs. 37 mg/dL, P <0.001). Both groups had similar spinal cord lesions in terms of length and lesion locations in the brain. Acute relapse treatment and long-term immunosuppressive were similar in both groups.

There was a positive correlation between age at onset and EDSS score on discharge date and at six months (r=0.323, 95%CI: 0.095-0.519, p=0.004, r=0.359, 95%CI: 0.111-0.565, p=0.004, respectively) (Figure 1).

Table 2 Comparison of clinical characteristics in patients with early-onset and late-onset NMOSD

Features	Early onset (N=44)	Late onset (N=32)	Difference	95% CI	P-value
Age at onset (years), Mean (SD)	35.61 (9.58)	58.69 (8.95)	23.07	18.76 to 27.39	<0.001[a]
Sex female, n (%)	42 (95.5%)	27 (84.4%)	0.11	-0.03 to 0.25	0.124[c]
Comorbidities, n (%)					
- Hematologic disorders	0 (0.0%)	1 (3.1%)	0.03	-0.03 to 0.09	0.421[c]
- Autoimmune disease	0 (0.0%)	1 (3.1%)	0.03	-0.03 to 0.09	0.421[c]
- Thyroid disease	0 (0.0%)	1 (3.1%)	0.03	-0.03 to 0.09	0.421[c]
- Diabetes mellitus	1 (2.3%)	6 (18.8%)	0.16	0.02 to 0.31	0.037[c]
- Hypertension	2 (4.6%)	6 (18.8%)	0.14	-0.01 to 0.29	0.063[c]
- Dyslipidemia	5 (11.4%)	3 (9.4%)	0.02	-0.15 to 0.12	1.000[c]
- Malignancy	1 (2.3%)	1 (3.1%)	0.01	-0.07 to 0.08	1.000[c]
Clinical attack, n (%)					
- Optic neuritis	30 (68.2%)	15 (46.9%)	0.21	-0.01 to 0.43	0.097[c]
- Transverse myelitis	29 (65.9%)	24 (75.0%)	0.09	-0.11 to 0.30	0.455[c]
- Area postrema syndrome	2 (4.6%)	0 (0.0%)	0.05	-0.02 to 0.11	0.506[c]
- Brainstem syndrome	3 (6.8%)	0 (0.0%)	0.07	-0.01 to 0.14	0.259[c]
- Diencephalic syndrome	1 (2.3%)	0 (0.0%)	0.02	-0.02 to 0.07	1.000[c]
Coexisting autoimmunity, n (%)					
- ANA	8 (24.2%)	7 (33.3%)	0.04	-0.15 to 0.22	0.541[c]
Serum NMO positive, n (%)	40 (90.9%)	29 (90.6%)	0.003	-0.129 to0.135	1.000[c]
CSF findings					
- CSF WBC, Median (IQR)	6 (19)	15 (52)	3	2 to 20	0.137[b]
- CSF protein, Median (IQR)	37 (22)	62 (54)	23	11 to 41	<0.001[b]
- CSF/serum sugar ratio, Mean (SD)	0.584 (0.100)	0.514 (0.136)	0.070	-0.001 to 0.141	0.052[a]
Acute treatment					
- Methylprednisolone	42 (95.5%)	29 (90.6%)	0.05	-0.07 to 0.17	0.644[c]
- Plasma exchange	8 (18.2%)	11 (34.4%)	0.16	-0.04 to 0.36	0.108[d]
- Methylprednisolone plus plasma exchange	8 (18.2%)	11 (34.4%)	0.16	-0.04 to 0.36	0.108[d]

Table 2 Comparison of clinical characteristics in patients with early-onset and late-onset NMOSD

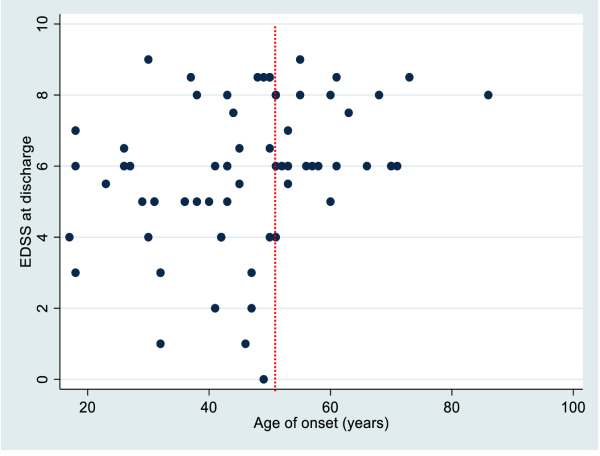
Features	Early onset (N=44)	Late onset (N=32)	Difference	95% CI	P-value
Medications					
- Corticosteroid	41 (93.2%)	29 (90.6%)	0.03	-0.10 to 0.15	0.692[c]
- Azathioprine	27 (61.4%)	14 (43.8%)	0.18	-0.05 to 0.40	0.128[d]
- Mycophenolate mofetil	3 (6.8%)	1 (3.1%)	0.04	-0.06 to 0.13	0.634[c]
MRI of brain					
- Normal	29 (65.9%)	24 (75.0%)	0.09	-0.11 to 0.30	0.394[d]
- Cortical/juxtacortical	1 (2.3%)	0 (0.0%)	0.02	-0.02 to 0.07	1.000[c]
- Periventricular	4 (9.1%)	0 (0.0%)	0.09	0.01 to 0.18	0.134[c]
- Infratentorial	8 (18.2%)	2 (6.3%)	0.12	-0.02 to 0.26	0.177[c]
- Other	2 (4.6%)	4 (12.5%)	0.08	-0.05 to 0.21	0.233[c]
Spinal cord MRI					
- Normal	17 (39.5%)	8 (25.8%)	0.14	-0.08 to 0.35	0.218[d]
- Short segment	2 (4.7%)	0 (0.0%)	0.05	-0.02 to 0.11	0.224[d]
- LETM	24 (55.8%)	23 (74.2%)	0.18	-0.03 to 0.40	0.105[d]
Spinal cord axial view					1.000[c]
- Complete	10 (41.7%)	11 (47.8%)	0.06	-0.22 to 0.35	0.671[d]
- Central	13 (54.2%)	12 (52.2%)	0.02	-0.31 to 0.27	0.891[d]
- Dorsolateral	1 (4.2%)	0 (0.0%)	0.04	-0.04 to 0.12	1.000[c]
Number of segments , Median (IQR)	6 (6)	7 (7)	1	-1 to 4	0.485[b]
GAD enhancement	29 (67.4%)	21 (65.6%)	0.003	-0.213 to 0.219	0.979[d]

[a] p-value from independent t-test, [b] p-value from Mann-Whitney U test, [c] p-value from exact method, [d] p-value from z-test

1.1 EDSS on discharge date

r = 0.323, 95%CI: 0.095 to 0.519, p-value = 0.004

(Pearson's correlation)



1.2 EDSS at follow-up 6 months

r = 0.359, 95%CI: 0.111 to 0.565, p-value = 0.004

(Pearson's correlation)

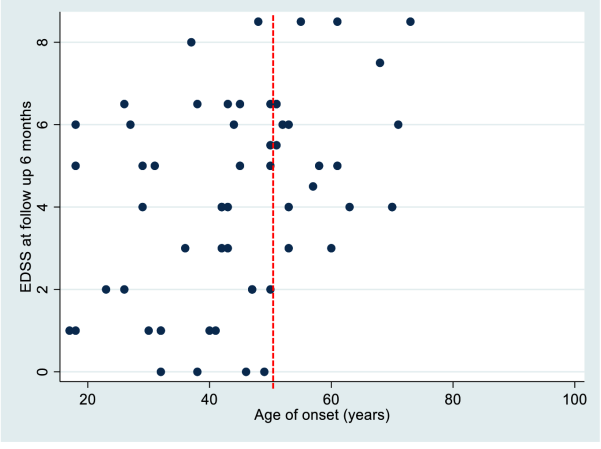


Figure 1 Correlation between age of onset and outcome

Discussion

We included 76 patients diagnosed with NMOSD and classified into EO-NMOSD group and LO-NMOSD group, using a cut point of age at onset of 50 years.[9] The previous studies showed transverse myelitis was more common in LO-NMOSD, and optic neuritis was more common in EO-NMOSD, the same with our study.[11,13] Interestingly, significantly higher levels of CSF protein in LO-NMOSD group correlated with age; Carl P et al. stated that age-related reduction in CSF turnover caused higher levels of CSF protein in the elderly.[14] Our study discovered no significant differences in the spinal cord lesions and the locations of the brain lesions between EO-NMOSD and LO-NMOSD, but some earlier studies reported longer spinal cord lesions and more severe myelitis in LO-NMOSD.[8]

This study emphasized the correlation between age of onset and outcomes; we demonstrated that patients with older age at onset had worse clinical outcomes, like the results from previous studies.[8,9,16] Maria et al. also reported that late-onset patients had a higher disability rating after follow-up; for every 10-year increase in age at disease onset, the risk of requiring a cane to walk (EDSS score of 6.0) increased by 63% (hazard ratio [HR] 1.63, 95%CI1.35-1.92, p <0.001).[9] The association of older age with a lower or impaired mechanism of reparation has also been suggested in some reports.[15] During aging, there is a substantial decline in the ability to resist immune and inflammatory responses and a corresponding decline in the generation of protective immune responses, leading to a deficient anti-inflammatory process.[15] Furthermore, earlier research discovered that LO-NMOSD had a worse response to immunosuppressive medication and higher side effects because of additional comorbidities.[5] Age-related comorbidities were another factor that contributed to poor outcomes and the risk of complications, our study also found a prevalence of diabetes mellitus in LO-NMOSD more than in EO-NMOSD. These processes probably synergistically influence morbidity and disability, but they are more likely to be age-related than NMOSD-related. Unfortunately, our investigation failed to find any meaningful prognostic differences between the two groups. It was similarly challenging to pinpoint prognostic variables in a previous study.[8]

Our study's limitations were that we collected data from only a single center and had a small population, and the study design was retrospective; some data might have been missed.

Conclusion

The current study revealed that patients with LO-NMOSD have similar clinical characteristics but worse outcomes than EO-NMOSD. Further studies in multi-centers with larger populations need to confirm and evaluate the prognostic factors.

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