Factors Associated with Clinical Outcomes of NMOSD Patients in King Chulalongkorn Memorial Hospital

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Abstract

Background: Since the discovery of aquaporin-4 IgG (AQP-4) antibody in 2004. The incidence of neuromyelitis optica spectrum disease (NMOSD) in Thailand continue to rise. However, the local demographic and clinical data of this disease is still scarce.

Objective: To present data on NMOSD patients with regard to demographics, clinical presentation, laboratory investigation, and treatment outcome.

Methods: We reviewed records of 49 patients diagnosed with NMOSD with positive AQP-4 antibody test results who received treatment at King Chulalongkorn Memorial Hospital between January 2010 and September 2019. We retrieved data on demographics, underlying illnesses, laboratory test results, clinical characteristics, treatment prognosis, and related complications. Statistical analyses included descriptive analyses and univariate and multivariate logistic regression analyses of factors associated with EDSS score improvement and relapse of NMOSD.

Results: Patients were mostly female (87.8%) with the mean (±SD) age of 44.46 ± 16.16 years. Patients had 57.4% reduction in EDSS score after treatment compared to before treatment. One-third (36.7%) of patients relapsed within the first year of treatment, with the mean (± SD) duration to first relapse was 12.8 ± 19.3 months. Increase in EDSS score was associated with adverse events during course of treatment (Adjusted OR = 5.73; 95% CI 1.51-21.81). Relapse of disease was associated with only bilateral optic neuritis (Adjusted OR = 16.92; 95% CI 1.87-152.77).

Discussion and Conclusion: We presented factors associated with clinical outcomes of NMOSD

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patients from the tertiary care hospital in Thailand. This can be useful for prognostic assessment and management of each patients. Our study excluded NMOSD patients without AQP-4 antibody test results, and the potential selection bias due to this exclusion should be taken into consideration.

Keywords: Neuromyelitis optica spectrum disease, AQP4-IgG, Outcome, Expanded Disability Status Scale

Introduction and Objectives

Neuromyelitis optica spectrum disease (NMOSD), previously known as Devic's disease or neuromyelitis optica (NMO), is now classified as an inflammatory disorder of the central nervous system leading to astrocytopathy.[1,2] It had been characterized by demyelination and axonal damage mediated by NMO-IgG; the antibody to water channel aquaporin-4 (AQP-4) that predominant at the astrocyte footplates. Florid demyelination and inflammation usually target optic nerves, spinal cord, and area postrema.[3] The classic clinical manifestations comprised of visual loss, transverse myelitis, hiccups and intractable vomiting. Through the disease course, relapsing is typical with variable degrees of recovery over weeks to months. Also, there are some reports that NMOSD is associated with other autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, Hashimoto thyroiditis, pernicious anemia, and myasthenia gravis.[4,5]

The rationale for treatment of acute and recurrent attacks in NMOSD is based upon evidence that humoral autoimmunity plays a role in the pathogenesis of NMOSD and is driven by the increase in morbidity and mortality in untreated patients. High-dose glucocorticoids, such as intravenous methylprednisolone, given for three to five consecutive days is recommended for an initial treatment. In patients with aggressive symptoms, unresponsive to glucocorticoids, therapeutic plasma exchange[6,7] and Rituximab (a monoclonal antibody directed against the CD20 antigen) are the suggested rescue treatment. Furthermore, intravenous immunoglobulin is prescribed in some case reports.[8] An attack prevention is indicated due to the natural history of stepwise deterioration from recurrent attacks and accumulated disability. Long-term immunotherapy has been showed effectiveness in reduction of relapse and decrease disease morbidity.[9] Clinical response is evaluated from the patient symptoms at follow up and Expanded Disability Status Scale (EDSS) is recorded for the accumulation of disability.

In Thailand, there are limited published data on the demographics and clinical characteristics of NMOSD. This may be due to low number of diagnosed cases and limitations in laboratory investigations. This study aims to present data on patient demographics, clinical characteristics, treatment, and factors associated with clinical outcomes of NMOSD patients in King Chulalongkorn Memorial Hospital (KCMH).

Materials and Methods

Fifty-six records of the adult NMOSD patients with positive AQP-4 antibody admitted to (KCMH) during January 2010 and September 2019 were reviewed. The study was approved by Human Subjects Ethics Committee of the Faculty of Medicine, Chulalongkorn University IRB no. 508/62. Seven cases were not eligible for this study due to unconfirmed laboratory results and/or incomplete medical records. Details of demographic data, underlying medical illness, clinical presentations,

laboratory investigations, treatment, and related complications were recorded in the case report form. Severity and disability before and after treatment were graded by using EDSS and modified Ranking Scale (mRS). Dosage of corticosteroid was divided, into very high (>1.6 mg/kg/d prednisolone equivalent), high (>0.5 mg/kg/d, but ≤1.6 mg/kg/d prednisolone equivalent), medium (>0.125 mg/kg/d, but ≤0.5 mg/kg/d prednisolone equivalent), and low dose (≤0.125 mg/kg/d prednisolone equivalent).

Statistical analyses

SPSS version 23.0 software (SPSS Inc., Chicago IL) was used for statistical analysis. Descriptive data were analyzed using means and standard deviation (SD), median and interquartile range, or frequency and percentages according to types of data. Multivariate logistic regression analyses was used to identify factors associated with two dependent categorical variables such as an improvement of EDSS score, disease relapse and calculated adjusted odds ratios (ORs) with 95% confidence interval (95% CI). All tested were 2-tailed at 95% level of confidence.

Results

Forty-nine patients were included into our study (Table 1) with mean (±SD) age of 44.46 ± 16.16 years. Most of the patients were between 41 to 60 years of age (44.9%) with female predominance (87.8%). A considerable proportion of patients had thyroid disorders, and systemic autoimmune disease comorbidities (e.g. SLE, Sjögren syndrome, myasthenia gravis). One-fifth of the patients (21.3%) had been previously diagnosed as multiple sclerosis. The most common presenting symptoms were transverse myelitis (40.3%), followed by unilateral optic neuritis (26.4%). The mean (± SD) time from first symptom to treatment was 41.3 ± 67.9 days. Before receiving treatment, most patients had mRS score of 4 and median (± SD) EDSS score of 5.5 ± 1.91. After treatment, there was a 57.4% reduction in median (± SD) EDSS score of 4.5 ± 2.87, The mean (± SD) number of annualized relapse rate was 0.6 ± 0.5 attacks. One-third of patients had relapsed within the first year after treatment (36.7%). The mean (± SD) duration to first relapse was 12.8 ± 19.3 months despite receiving immunosuppressive agents.

CSF examination showed mean white blood cells (WBC) count of 25.9 ± 72.6 cell/mm3, all of which were lymphocytes, while the protein level was 48.3 ± 34.3 mg/dL and sugar level was 69.1 ± 25.5 mg/dL. Examination of AQP-4 antibodies found the mean seroconversion time of 23 ± 26.8 months. The magnetic resonance imaging (MRI) of the brain was performed in 87.5% of the patients with 67.3% met the NMOSD criteria. 87.8% of patients received spinal MRI, most of whom had the disease at the cervical and thoracic levels, 38.6% and 29.8% respectively.

Most patients (89.4%) received acute phase treatment with methylprednisolone, pulse regimen. Only 10% received plasma exchange and 10% received intravenous immunoglobulin combined with intravenous methylprednisolone. No patient received rituximab. For the maintenance phase, nearly all patients (97.9%) received treatment with high dose oral prednisolone. with the average duration of treatment 2.9 ± 3.4 months, then 11.2 ± 16 months for the medium dose and 6 ± 13.4 months for low dose corticosteroids. Regarding immunosuppressive agents, most patients received azathioprine (80.9%). The authors found adverse events in 40.8% of patients who received treatment, most commonly urinary tract infection. There was no mortality observed in our study.

Table 1 Patients' characteristics and univariate analyses of factors associated with EDSS score improvement and relapsing of disease

Characteristics	Patient, N (%)	P-value	
		EDSS improvement	Relapsing of disease
Gender		0.638	0.999
• Female	43 (87.8)		
• Male	6 (12.2%)		
Age (mean, years)	44.46±16.16	0.551	0.886
• 15-25	6 (12.2%)		
• 25-40	12 (24.5%)		
• 41-60	22 (44.9%)		
• 61-80	8 (16.3%)		
• More than 81	1 (2%)		
Underlying disease			
• Previously diagnosed as multiple sclerosis	10 (21.3%)	0.286	0.999
• Thyroid disorders	7 (14.9%)	0.438	0.691
• Rheumatologic diseases	3 (6.4%)	0.999	0.999
• Malignancy	3 (6.4%)	0.999	0.551
• Human immunodeficiency infection	2 (4.3%)	0.500	0.999
• Previously diagnosed as optic neuritis	2 (4.3%)	0.999	0.145
• Myasthenia gravis	1 (2.1%)	0.426	0.999
• Others[a]	19 (40.4%)	0.264	0.602
Clinical presentation			
• Transverse myelitis	29 (40.3%)	0.923	0.179
• Unilateral optic neuritis	19 (26.4%)	0.999	0.879
• Brainstem syndrome	10 (13.9%)	0.154	0.066
• Bilateral optic neuritis	8 (11.1%)	0.050	0.004
• Area postrema syndrome	4 (5.6%)	0.567	0.636
• Diencephalic syndrome	2 (2.8%)	0.500	0.515
mRS score (median)	4±1.12		0.434
EDSS score before treatment (median)	5.5±1.91		
EDSS score latest (median)	4.5±2.87		
EDSS score change			0.132
• Improvement	27 (57.4%)		
• No improvement	20 (42.5%)		
Time between first event to myelitis (mean, days)	35.9±132.4	0.276	0.807
Time to receive treatment (mean, days)	41.3±67.9	0.146	0.412
Length of hospital stay (mean, days)	8.1±6	0.915	0.243
Annualized relapse rate	0.6±0.5	0.220	
Duration to first relapse (mean, months)	12.8±19.3	0.184	
• Relapse at first years after treatment	18 (36.7%)		
• Relapse at second years after treatment	1 (2%)		
Duration time of following up (mean, months)	46.8±35.5	0.623	0.989
Investigation			
Lumbar puncture done	39 (83%)		
• WBC (mean, cell/mm3)	25.9±72.6	0.508	0.880
• Lymphocyte predominance	35 (100%)		
• Protein (mean, mg/dL)	48.3±34.3	0.338	0.398
• Sugar (mean, mg/dL)	69.1±25.5	0.604	0.36
Oligoclonal band positive	22 (44.9%)	0.327	0.999
Time for seroconversion of AQP-4 Ab (mean, months)	23±26.8	0.284	0.999

Table 1 Patients' characteristics and univariate analyses of factors associated with EDSS score improvement and relapsing of disease (cont.)

Characteristics	Patient, N (%)	P-value	
		EDSS improvement	Relapsing of disease
Brain MRI	42 (87.5%)		
• Fitted in NMO criteria	33 (67.3%)	0.259	0.379
• Asymptomatic FLAIR positive	25 (58.1%)	0.232	0.873
• Anterior retrobulbar optic neuritis	3 (6.1%)	0.567	0.053
• Posterior retrobulbar optic neuritis	28 (57.1%)	0.561	0.117
Spinal cord MRI	43 (87.8%)		
• Cervical lesion	22 (38.6%)	0.999	0.639
• Thoracic lesion	17 (29.8%)	0.437	0.274
• Cervico-medullary lesion	2 (3.5%)	0.999	0.999
• Lumbosacral lesion	1 (1.8%)	0.999	0.999
• No lesion	10 (17.5%)	0.999	0.276
Acute phase treatment			
• Intravenous methylprednisolone	42 (89.4%)	0.377	0.072
• Plasma exchange	10 (21.3%)	0.286	0.276
• Intravenous immunoglobulin	10 (21.3%)	0.723	0.276
• Rituximab	0 (0%)		
Long-term immunosuppressive agents			
• Prednisolone prescribed	46 (97.9%)	0.999	0.999
• High dosage duration (mean, months)	2.9±3.4		
• Medium dosage duration (mean, months)	11.2±16		
• Low dosage duration (mean, months)	6±13.4		
• Last dosage (mean, mg/day)	9.6±14.5		
• Azathioprine prescribed	38 (80.9%)	0.465	0.720
• Treatment duration (mean, months)	32.6±29.6		
• Last dosage (mean, mg/day)	81.99±37.1		
• Mycophenolate Mofetil prescribed	15 (30.6%)	0.318	0.339
• Treatment duration (mean, months)	32.3±29.1		
• Last dosage (mean, mg/day)	1066.6±578.3		
• Methotrexate prescribed	2 (4.2%)	0.999	0.521
• Treatment duration (mean, months)	75.5±84.1		
• Last dosage (mean, mg/week)	5±3.5		
Adverse events	20 (40.8%)	0.017	0.555
• Infection[b]	15 (30.6%)	0.180	0.210
• Drug related events[c]	12 (24.5%)	0.105	0.743
• Death	0 (0%)		

mRS = modified Rankin Scale, EDSS = Expanded Disability Status Scale, AQP4 antibody = aquaporin 4 antibody, FLAIR = Fluid attenuation inversion recovery

[a]Including systemic/metabolic disease (e.g. hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, anemia, epilepsy), autoimmune encephalitis, venous thrombosis

[b]Including urinary tract infection, cutaneous abscess, chronic sinusitis, herpes dermatitis, candida stomatitis

[c]Including steroid induced avascular necrosis, steroid myopathy, drug induced bone marrow dysfunction, drug induced hyperglycemia, drug induced transminitis

Outcome measurement

In the multivariate analyses, adverse events during treatment [OR = 5.31; 95% CI = 1.51-18.69] were associated with higher odds of increase in EDSS score. Demographic factors, underlying disease, time to treatment from onset symptom, annualized relapse rate, duration to first relapse, CSF result, method of acute treatment, and selection of long-term immunosuppressive agents were not associated with increase in EDSS score. Bilateral optic neuritis [OR, 16.92; 95% CI, 1.87-152.77] was the only factor associated with relapsing of the disease.

Discussion

Most of the patients included in the study were predominantly female with the female-to-male ratio of 7.2:1 that was similar to other studies.[10-13] Majority of patients were between 41-60 years of age, slightly higher than other countries (32.6-45.7 years).[14,15] Thyroid disorder was the most frequent comorbidity (14.9%). Eight point five percent of patients had systemic autoimmune diseases (SLE, Sjögren syndrome, and myasthenia gravis) corresponding to previous reviews.[4,5,16] Most common clinical presentations of NMOSD in this study were transverse myelitis (40.3%) and optic neuritis (37.5%), which concordant to reports from Thai[17], The United States[18], Morocco[19], and Italy.[20] Unlike findings from Japan and England[13,21], there was no association between optic neuritis and older age in this study.

Several previous studies in NMOSD patients have reported that female gender, older age of onset, positive AQP-4 status, choice of immunotherapy (e.g. azathioprine, mycophenolate mofetil, or rituximab), and delayed plasma exchange (especially more than 5 days after symptom onset) were associated with higher risks of disease relapse and disability.[22-27] In our study, we found strong association between adverse events during treatment and worse EDSS outcome. These results were different from Wingerchuk et al.[23] which emphasized that history of autoimmune diseases and higher attack frequency during the first 2 years of disease were associated with poor outcome. Patients with adverse events during treatment had 5.7-times higher odds of little-to-no improvement than those without the events. It might be possible that adverse events contributed to delayed use of long-term immunosuppressive agent, hindering the symptoms control.

Bilateral optic neuritis, especially posterior part, was the only factor that had statistically significant association with relapse rate of NMOSD in our patients. This was similar to the previous studies from Thailand[7,17], but differed from other ethnicities (Caucasian, African, Asian, and Hispanic).[23,24,27] This finding emphasized a crucial recognition of NMOSD patients presenting with bilateral optic neuritis to be promptly received highly effective acute phase treatments, and proper long-term immunosuppressive agents in order to decrease relapse that might resulted in better outcome.

Our study had several limitations. Firstly, it was a retrospective study. Thus, there were some incomplete documentations. Secondly, the follow-up interval was different between patients and the sample size was quite small. Thirdly, our study did not include patients who were diagnosed as NMOSD but without AQP-4 antibody results, potentially introducing selection bias. Lastly, this study was conducted in a single tertiary care

center located in Bangkok, the capital city of Central Thailand. Therefore, these findings may not represent patients from all of the country.

Conclusion

Neuromyelitis optica spectrum disease (NMOSD) is a relatively rare disease in medical practice. Without appropriated treatment, patients tended to have neurological deficits resulted in morbidity and may increase mortality rate. Several factors could affected the outcome of NMOSD patients such as gender and age group. However, in our Thai retrospective cohort, bilateral optic neuritis was the most important risk factor that related to poor prognosis. This should raise awareness for clinicians and suggested promptly aggressive treatment in NMOSD patients with bilateral optic neuritis.

Acknowlegdement

I would like to show my gratitude to all NMOSD patients of KCMH for their contributions, and also Assistant Professor Abhinbhen W. Saraya, my research supervisor, for guidance, enthusiastic encouragement, useful critiques of this research work.

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