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Long-term disability in neuromyelitis optica spectrum disorder with a history of myelitis is associated with age at onset, delay in diagnosis/preventive treatment, MRI lesion length and presence of symptomatic brain lesions

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Abstract

Background.—Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) that preferentially targets the spinal cord and optic nerves. Increasing disability is accrued with each inflammatory attack. Disability has been shown to be an independent predictor of poor quality of life in those with NMOSD. Factors associated with increasing disability need further systematic investigation.

Methods.—We performed a multi-center retrospective chart analysis of aquaporin-4 (AQP4) seropositive NMOSD patients with a history of myelitis seen at five large referral centers for

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patients with NMOSD worldwide for whom thorough records including relapse history and corresponding imaging were available. Potential contributors to long-term disability were extracted including demographics, radiographic findings, and clinical characteristics. Multivariable regression modeling was conducted to determine correlates of disability in patients with NMOSD, as measured by the Expanded Disability Status Scale (EDSS).

Results.—One hundred eighty-two AQP4 seropositive patients (88% female) were included in this analysis. Multiple regression modeling revealed that older age at disease onset, delay in diagnosis/preventive treatment, length of longest acute myelitis lesion and presence of symptomatic brain/brainstem lesions were associated with increased disability when holding other variables constant.

Conclusion.—While age at onset is a factor that cannot be controlled in NMOSD, we can reduce the delay in diagnosis/preventive treatment and reduce future relapses in the brain/brainstem and spinal cord. Delay in diagnosis/preventive treatment and imaging variables that contributed to increased disability support the need for improved measures for early, accurate diagnosis and management of NMOSD, and aggressive treatment of acute relapses.

Keywords

Devic's; disability; NMOSD; EDSS; MRI

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) associated with the highly specific aquaporin-4 antibody (AQP4-Ab) which preferentially targets the spinal cord, optic nerves and brainstem leading to blindness and paralysis.^{1,2} NMOSD is distinct from multiple sclerosis (MS) and other demyelinating CNS diseases in that NMOSD causes destruction of astrocytes and irreparable cell death which leads to more severe disability and a poorer prognosis.^{3,4} Because NMOSD is only rarely associated with a progressive phase of disease, permanent damage accrues with each inflammatory attack and leads to increasing disability.⁵ Disability has been shown to be an independent predictor of poor quality of life in those with NMOSD,^{6,7} yet a comprehensive assessment of factors that are associated with accrual of disability need to be examined systematically in this population. In order to identify what most contributes to the accrual of disability, we performed an investigation into demographic, radiographic and clinical characteristics that correlate with disability in patients with NMOSD. Awareness of the treatable factors that contribute most to disability may reduce accrual of disability.

Materials and Methods

This was a retrospective chart analysis of patients who met 2015 diagnostic criteria for NMOSD⁸ seen at any of five NMOSD centers worldwide: the Johns Hopkins University NMO Clinic (Baltimore, USA), Research Institute and Hospital of National Cancer Center (Goyang, South Korea), John Radcliffe Hospital, University of Oxford (Oxford, UK), NeuroCure Clinical Research Center at Charite University Hospital (Berlin, Germany) and Neuroclinica (Medellin, Colombia). Local review boards at each site approved the use of

human subjects for this analysis, as required. The study was approved by Johns Hopkins Institutional Review Board (NA_00041032), and shared data were de-identified.

Participants:

To increase homogeneity of our cohort, only AQP4-Ab seropositive patients were included in this analysis. All patients were seen on average every 6 to 12 months at each site. For inclusion, patients needed to have been followed for at least 1 year and records needed to be complete such that all predictor variables could be collected for each patient, including Magnetic Resonance Imaging (MRIs) with and without gadolinium from each relapse, acute relapse treatment data, and clinical notes that included a physical examination that enabled retrospective calculation of a remission disability score, as assessed by the Expanded Disability Status Scale (EDSS), from the most recent follow-up visit. Patients were included if remission EDSS calculation was outside of the context of a new clinical event by at least 6 months and had a corresponding remission MRI. Patients at each site were started on NMOSD-specific immunotherapy at the time of NMOSD diagnosis confirmation,⁹ such that delay in diagnosis was equivalent to delay in initiation of preventive treatment. Because of the emphasis of EDSS on mobility, those patients without a history of myelitis were excluded.

Materials & Design:

Demographic, clinical and radiographic data were extracted from each participant's health record. Relapses were defined as a new or worsening neurologic symptom lasting at least 24 hours associated with a change in exam localizing to the CNS and not explainable by fever, infection or metabolic condition, and were confirmed by MRI if clinically indicated.¹⁰ Remission from acute events was defined as greater than 6 months from last event. Demographic data was captured at the same time point as remission EDSS score. Treatment score was calculated to account for 1) number of events and 2) type of treatment received. Published data suggest that patients receiving steroids alone recover to approximately one-third of their baseline function, whereas those additionally receiving plasma exchange recover to approximately two-thirds.¹¹ As such, the score was tabulated based on treatment received and subsequent predicted recovery per acute event, and event scores were added together to calculate a total treatment score per patient. All study variables collected are listed in Table 1, with dimensions of categorical variables noted; all other variables were linear.

Statistical Analysis:

Simple regressions were calculated for each study variable against EDSS to determine which factors were independently associated with long-term disability. This analysis was extended into a multivariable regression where the best-fit model examined the impact of the interaction among variables on EDSS. Only those variables with a p-value of <0.1 in the simple regressions were included in the multivariable analysis. Significant variables were identified ($p < 0.05$). Because collinearity among predictor variables may increase the variance of the coefficient estimates, collinear predictor variables were not used in multivariable regression modeling if correlation was greater than 0.6. Data analysis was conducted using STATA 15.

Results

One hundred eighty-two seropositive NMOSD patients met inclusion criteria (US: 64; S. Korea: 47; UK: 39; Germany: 18; Colombia: 14). As expected, most patients were female (88%). Mean age at onset of disease was 39.2 years. Disease duration in this cohort was a median 9.0 years (IQR 7.9; mean 9.7; SD 5.9), with disease duration extending >3 years in 94% of our patient cohort, 5 years in 77%, and 10 years in 43%. At time of follow-up, the median EDSS was 4.0 (Table 2).

Simple regression analyses resulted in several variables that trended toward significance ($p < 0.1$; Table 1): age at onset ($p < 0.000$), delay in diagnosis/preventive treatment ($p = 0.033$), longest acute T2 spinal cord lesion length ($p = 0.000$), additive number of T2 cord segments affected at remission ($p = 0.004$), presence of T1 hypointensity within myelitis lesions ($p < 0.000$), and presence of brain/brainstem lesions (versus normal brain: asymptomatic lesions, $p = 0.06$; symptomatic, $p = 0.076$). None of these predictor variables were found to be collinear suggesting that each of them was an independent variable that can contribute to disability. However, collinearity was found between race and site, with 86% of patients of Latin descent, 84% of patients of Asian descent and 79% of patients of African descent each coming from a single site. Because of the lack of racial variability among sites, the low number of patients of Latin descent and the inability to distinguish which variable may contribute to differences in EDSS, neither race nor site were used as an explanatory variable in a multivariable regression despite significant findings. However, both variables were controlled for in the analysis due to their potential impact on EDSS. Multivariable analysis revealed that increased age at disease onset, delay in diagnosis/preventive treatment, length of longest acute myelitis lesion and presence of symptomatic brain/brainstem lesions were associated with increased disability when holding other variables constant (Table 3). The impact on disability was such that there was a corresponding: 0.6 increase in EDSS score per decade increase in age at disease onset ($p = 0.000$), 0.9 increase in EDSS score per decade increase in delay of diagnosis/initiation of preventive immunotherapy ($p = 0.006$), 0.16 increase in EDSS score per spinal cord segment in the longest acute lesion ($p = 0.000$), and 0.91 increase in EDSS score in those with history of symptomatic brain or brainstem lesions ($p = 0.023$) compared to those without brain or brainstem lesions.

Discussion

This retrospective analysis examined correlates of disability in patients with NMOSD. The characteristics that most strongly emerged as contributors to disability are age of NMOSD onset, delay in diagnosis/time to initiation of preventive immunotherapy, length of longest spinal cord lesion (by MRI), and attacks in the brain and brainstem. These findings build on previous investigations into disability in NMOSD, which includes the seminal study by Wingerchuk et al.¹² This investigation highlighted the natural history of disability accrual in NMOSD over time, reporting that 60% of surviving relapsing patients were functionally blind in at least one eye and half were mono- or paraplegic. Since this time, correlates of disability have been examined, and suggest that delayed onset age of NMOSD is associated with increased disability in both adjusted and unadjusted analyses.^{13,14} Another study reported increased disability in patients with NMOSD who had brainstem involvement,

specifically in the medulla.¹⁵ The current study builds on these and other previous investigations through its comprehensive consideration of multiple demographic, clinical, and radiographic explanatory variables in an adjusted analysis.

Higher disability in those patients who presented at an older age may be a result of increased severity of attacks, poorer healing after an attack or reduced neuroplasticity. While age at disease onset is clearly not a modifiable risk factor, having the knowledge that outcomes are worse in those who present at an older age may influence aggressiveness of disease management in those who present at an older age.

Delay in diagnosis/preventive treatment is also associated with increased disability, and can be targeted as a modifiable risk factor. Previous multi-center analyses found that 29–42.5% of patients diagnosed with NMOSD had been misdiagnosed with MS allowing their NMOSD diagnosis, and subsequently initiation of preventive immunotherapy, to be delayed.^{16,17} It is well-established that many treatments for MS can exacerbate NMOSD disease, thus increasing relapse severity and/or frequency and contributing to further disability.^{18–22} Fortunately, diagnostic delay has been reduced in recent years largely due to the specificity of the AQP4 antibody biomarker.^{17,23}

An imaging variable that contributes to increased disability is acute T2 lesion length, supporting the need for aggressive treatment of acute relapses and expedient initiation of preventive immunotherapy. T2 lesion length has previously been shown to correlate with higher nadir disability,²⁴ and the current study suggests that this correlation endures beyond the acute period. Aggressive treatment of acute inflammatory events with plasma exchange has been shown to more effectively improve recovery than those relapses treated with high-dose steroids alone.^{11,25} Taken together, the findings suggest that careful consideration of early escalation of acute therapies to plasma exchange may reduce long term disability in NMOSD. A second imaging variable that emerged is the presence of symptomatic brain/brainstem lesions. While only 4.3% of patients with NMOSD present with brain or brainstem lesions,¹⁶ these attacks are correlated with a higher level of disability.¹⁵ Early use of preventive immunotherapy to reduce the risk of additional relapses in the brain and brainstem may be especially beneficial.

This retrospective analysis was limited by the data available. Aside from neurological disability, pain has been shown to contribute to disability and impact quality of life among patients with NMOSD.^{5,6,26} Pain scores were not reliably recorded across all centers and hence excluded from the analysis. Due to the widespread and intractable nature of pain in NMOSD, understanding how the presence and severity of pain affects disability status, and subsequent quality of life, is of interest for future research. Low vitamin D has also been shown to correlate with higher disability in AQP4 positive patients.²⁷ However, these data were also not reliably collected across all centers and could not be included in the current analysis. Future research should include these data, given that vitamin D is involved in multiple immunologic pathways, acts as a disease modifying agent in other CNS autoimmune diseases,^{27,28} and has the potential to do so in NMOSD as well.^{27,30,31} Furthermore, we did not account for length of time between symptom presentation and attainment of acute MRI. Time lapse to MRI may differ across sites and may influence acute

lesion length.³² Lastly, this study was limited by sample size. Because NMOSD is a rare disease, adequate powering of studies is difficult; this is particularly true in one that investigates multiple risk factors where comprehensive data collection is necessary, as in this study. This was mitigated by including multiple sites to increase patient numbers and by including only those variables that reached a significance level less than 0.1 in the multivariable regression; the approach of choosing international sites with diverse populations further allows for greater generalizability.

In conclusion, increased age at diagnosis, delay in diagnosis/preventive treatment, longer acute lesion length in the spinal cord and presence of symptomatic brain/brainstem lesions are the primary contributors to disability in NMOSD when controlling for other factors. Early diagnosis, appropriate patient follow-up and aggressive treatment of NMOSD may reduce long term disability by impacting those variables which can be directly or indirectly modulated.

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Highlights

- One hundred eighty-two seropositive NMOSD patients from international sites were included for analysis of contributors to long-term disability
- Multivariable regression modeling determined that correlates of disability in NMOSD included increased age at disease onset, delay in diagnosis/preventive treatment, length of longest acute myelitis lesion and presence of symptomatic brain/brainstem lesions
- These contributors to disability over time support the need for improved measures for early diagnosis and aggressive treatment.

Table 1.

Variables assessed with simple regression analyses with results.

Characteristic	p-value	95% Confidence interval
Demographic:		
Age at Onset *	0.000	0.022, 0.064
Sex	0.940	-2.39, 2.58
Race (Site) [†]		
• Caucasian descent (constant; from all Western sites)		
• Asian descent (84% from Korea)	0.103	-0.148, 1.59
• African descent (79% from USA)	0.144	-1.46, 0.215
• Latin descent (86% from Columbia)	0.001	1.035, 3.799
Clinical:		
Duration of disease	0.161	-0.017, 0.099
Delay in diagnosis *	0.033	0.006, 0.140
Total number of inflammatory events	0.578	-0.054, 0.096
Annualized relapse rate	0.846	-0.910, 0.746
Relapse treatment score	0.987	-0.111, 0.109
Duration of multiple sclerosis disease modifying treatment	0.603	-0.14, 0.241
Radiographic:		
Length of acute myelitis lesion (T2) *	0.000	0.075, 0.216
Location of longest myelitis lesion (cervical & cervicothoracic versus thoracic & thoracolumbar)	0.730	-0.892, 0.626
Presence of hypointense lesion (T1) *	0.000	0.623, 2.068
Total additive # of cord segments affected (T2, remission) *	0.004	0.041, 0.205
Total # of cord lesions (remission)	0.330	-0.143, 0.422
Brain/brainstem lesions *		
• Normal (constant)		
• Asymptomatic	0.06	-0.033, 1.650
• Symptomatic	0.076	-0.083, 1.692

* Variables with p<0.10, included in multivariable regression model

[†]Site and race were collinear and could not be independently evaluated but were controlled for in the multivariable regression model

Table 2.Demographic and clinical characteristics of the cohort ($n=182$).

Sex – female (%)	161 (88)
Race (%)	
Caucasian descent	63 (35)
Asian descent	57 (31)
African descent	48 (26)
Latin descent	14(8)
Anti-aquaporin-4 seropositivity (%)	182 (100)
Age at onset	
■ mean years (SD)	39.2 (16.6)
■ median years (IQR)	37.0 (23.8)
Duration of disease	
■ mean years (SD)	9.7 (5.9)
■ median years (IQR)	9.0 (7.9)
Delay in diagnosis/preventive treatment	
■ mean years (SD)	3.6 (5.0)
■ median years (IQR)	1.3 (4.9)
Time on MS therapy	
■ mean years (SD)	0.7 (1.9)
■ median years (IQR)	0.0 (0.0)
EDSS	
■ mean (SD)	4.0 (2.5)
■ median (IQR)	4.0 (4.0)

Table 3.

Contributors to disability per multiple regression modeling.

Variable	<i>p</i> -value	Coefficient	95% Confidence interval
Age at Onset	0.000	0.06	0.04, 0.08
Delay in diagnosis	0.006	0.09	0.02, 0.15
Length of acute myelitis lesion (T2)	0.000	0.16	0.08, 0.23
Brain/brainstem lesions			
Normal versus symptomatic	0.023	0.91	0.12, 1.71