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Updated diagnostic criteria for neuromyelitis optica spectrum disorder: Similar outcomes of previously separate cohorts

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Abstract

Background: The specificity of the aquaporin-4 antibody to predict recurrent inflammatory central nervous system disease has led to the design of the 2015 neuromyelitis optica spectrum disorder criteria which capture all aquaporin-4 antibody seropositive patients.

Objective: The purpose of this study was to compare treatment outcomes in aquaporin-4 antibody seropositive patients who met the previous 2006 clinical criteria for neuromyelitis optica with patients who meet the 2015 neuromyelitis optica spectrum disorder criteria.

Methods: The study involved a three-center retrospective chart review of clinical outcomes among aquaporin-4 patients diagnosed with neuromyelitis optica and neuromyelitis optica spectrum disorder.

Results: Hazard ratios of relapse during immunosuppressive therapy, relative to pre-therapy, were not significantly different for patients who met the 2006 criteria of neuromyelitis optica versus the 2015 neuromyelitis optica spectrum disorder criteria among those treated with azathioprine ($p = 0.24$), mycophenolate mofetil ($p = 0.63$), or rituximab ($p = 0.97$).

Conclusion: Reductions in the hazard of relapse during treatment with immunosuppressive therapies, relative to average pre-treatment, were not different for aquaporin-4 antibody seropositive patients categorized using the 2006 criteria of neuromyelitis optica and the 2015 neuromyelitis optica spectrum disorder criteria. These therapeutic findings support the design of the 2015 neuromyelitis optica spectrum disorder criteria which capture all aquaporin-4 antibody seropositive patients.

Keywords: Neuromyelitis optica, neuromyelitis optica spectrum disorder, annual relapse rate, diagnostic criteria, treatment response

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Introduction

Neuromyelitis optica (NMO) is a rare inflammatory disease that preferentially affects the optic nerves and spinal cord and is distinct from multiple sclerosis (MS).[1,2] Until recently, NMO diagnosis has been based on application of 1999 or 2006 clinical criteria that each require a history of both optic neuritis (ON) and transverse myelitis (TM).[1,3] The discovery of the aquaporin-4 antibody (AQP4-IgG), which is highly specific for NMO,[4] facilitated recognition of a wider array of clinical and neuroimaging manifestations that were described by the term neuromyelitis optica spectrum disorder (NMOSD).[3] These findings led to revision of the diagnostic criteria in 2015; the new criteria unify the terms NMO and NMOSD and confer the diagnosis of NMOSD in AQP4-IgG seropositive patients with a wider range of central nervous system (CNS) localization, including the brain and brainstem, even after a single attack.[5]

Based on the specificity of AQP4-IgG for prediction of recurrent inflammatory CNS disease,[6,7] many clinicians have treated seropositive patients with limited diseases (e.g., a single attack) similarly to those who fulfill 2006 NMO criteria. If limited

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seropositive NMOSD and historically defined seropositive NMO are indeed the same disease at different clinical stages (i.e., limited NMOSD patients are destined to fulfill 2006 NMO criteria via future clinical attacks) then it would be expected that both NMO and NMOSD seropositive patients, as previously defined, would have similar responses to preventive therapy. There are no approved disease-modifying therapies (DMTs) for NMO or NMOSD, but observational data suggest a positive effect of immunosuppressive treatments, including azathioprine, mycophenolate mofetil, prednisone, and rituximab.[8,9] The goal of the current study was to validate the clinical relevance of the new diagnostic criteria by comparing the treatment response of historically defined seropositive NMO and limited seropositive NMOSD patients, as defined by the 2015 International Panel for NMO Diagnosis (IPND) criteria.[5]

Patients and methods

This was an Institutional Review Board (IRB) approved, multicenter retrospective review of NMO and NMOSD patients treated at the University of Texas Southwestern Medical Center in Dallas, Texas, Johns Hopkins Hospital in Baltimore, Maryland, and Mayo Clinic in Scottsdale, Arizona, USA.

Restrictions

In our analysis of relapse reduction during NMO preventive therapies, we define NMO preventive therapies to be azathioprine, mycophenolate mofetil, and rituximab. When analyzing relapse rate reduction during NMO preventive therapy, only the first treatment a patient received using one of the three NMO preventive therapies was included in the analysis. Patients were required to have been treated with azathioprine, mycophenolate mofetil, or rituximab for at least six months. Patients were required to have pre-treatment data, but no minimum pre-treatment duration restriction was implemented. Patients who received cyclophosphamide, methotrexate, or mitoxantrone prior to treatment with an NMO preventive therapy were excluded from analysis. Patients who were treated with an MS DMT (interferon β-1a, glatiramer acetate, or natalizumab) prior to treatment with an NMO preventive therapy remained in the analysis. Patients receiving more than one therapy were excluded from analysis, with the exception of concurrent therapy of prednisone with azathioprine or mycophenolate mofetil.

Relapse

A relapse was defined as an acute clinical event resulting in a change in neurological examination persisting for more than 24 h localizing to the spinal cord, brain, brainstem, and/or optic nerve not attributable to a pseudoflare of previous relapse. The annualized relapse rate (ARR) was calculated by dividing the number of relapses experienced by the duration of follow-up (in years).

Serological status

The serological status of each patient was determined by each center using commercially available AQP4-IgG tests, including indirect immunofluorescence, enzyme-linked immunosorbent assay (ELISA) and cell-based assays. Patients who tested positive at any time in their disease course were considered seropositive for the purposes of this study.

Analysis

Analysis was performed using SAS software, Version 9.4. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA.

Preliminary Cox proportional hazards models were used to investigate differences in the time to first relapse after the initiation of NMO preventative therapy between the NMO and NMOSD cohorts. A Cox proportional hazards model was fitted with categorical variables corresponding to treatment with azathioprine, mycophenolate mofetil, and rituximab, stratified by diagnosis, while controlling for the squared log time (in years) to the start of treatment after onset, the squared centered and scaled age, and the center at which each patient was seen.

In accordance with our primary objective, an Anderson and Gill (AG) model for recurrent event survival data was fitted to examine reductions in the hazard of relapse during treatment, relative to pre-treatment, stratified by the center at which each patient was seen.[10] An additional frailty effect for each patient was incorporated into the model to account for additional within-subject dependence. Time-dependent covariates corresponding to treatment with azathioprine, mycophenolate mofetil, or rituximab were included in the model to examine the effect of each treatment on the hazard of relapse relative to pre-treatment. Two additional time-dependent treatment effects were included in the model to capture the additional effect of concurrent

treatment with prednisone and azathioprine or mycophenolate mofetil on the hazard ratio of relapse relative to pretreatment. Initially, the time-dependent covariates for each treatment (i.e. azathioprine, mycophenolate mofetil, rituximab, prednisone in addition to azathioprine, and prednisone in addition to mycophenolate mofetil) were stratified by diagnosis and the effect estimates were compared via contrasts based on the asymptotic chi-squared distribution. If the treatment effect estimates were not found to be significantly different between the two diagnoses, the model was refit with common time-dependent treatment effects for the two diagnoses. Additional covariates included in the model were the squared centered and scaled age of patients, a time-dependent covariate which is zero during the pretreatment period and one during treatment, and the squared log of years to treatment during the treatment period. The functional forms of age and years to treatment were chosen because they provided superior fit to the observed data.

Secondary exploratory analyses were performed to investigate demographic, clinical, radiological, and disease history differences between seropositive NMO and limited seropositive NMOSD patients. Categorical characteristics were compared between seropositive NMO and limited seropositive NMOSD patient cohorts using Fisher's exact test. Continuous variables were compared between seropositive NMO and limited seropositive NMOSD patient cohorts using a two-sample *t*-test when necessary assumptions were verified and the Mann-Whitney test otherwise. To compare time to first relapse (in years) between seropositive NMO and limited seropositive NMOSD patient cohorts, survival curves stratified by diagnosis were estimated and compared using the log-rank test. Similarly, survival curves corresponding to time to the initiation of an NMO preventive therapy (in years) stratified by diagnosis were estimated and compared using the Wilcoxon test due to evidence of violations of the proportional hazards assumption. The odds ratio (OR) was calculated to determine the risk of AQP4-IgG seropositive NMOSD to final diagnosis of NMO based on the initiation of an NMO preventive therapy. Due to the exploratory nature of these secondary analyses, *p*-values were not adjusted for multiple testing.

The significance level was set as $\alpha = 0.05$ and significance was defined as a *p*-value $<\alpha$. The value of P_{25} denotes the 25th percentile and P_{75} denotes the 75th percentile.

Results

A cohort of 152 aquaporin-4 antibody seropositive patients were initially selected based on their final diagnosis of NMO or NMOSD, representing all patients between 1999–2012 who met inclusion criteria. Diagnosis was reassessed using the 2006 NMO diagnostic criteria and the 2015 IPND NMOSD criteria.[3,5] Twenty-three additional patients were excluded from further analysis due to incomplete treatment, clinical event, or disease history data. A final total of 129 patients were included in the study, 77 (59.7%) ultimately diagnosed as NMO and 52 (40.3%) ultimately diagnosed as limited seropositive NMOSD. The median follow-up time was six years with a range from seven months to 35 years. Eight patients initially tested AQP4-IgG seronegative but were later confirmed to be seropositive.

Table 1. Demographic characteristics of study patients.

Final diagnosis	NMO	NMOSD	*p*-Value
No. of patients (*n*)	77	52	
Mean age of onset (years ±std. dev.)	39.27±15.82	45.74±15.94	0.02
Female (%)	68 (88.31)	48 (92.31)	0.56
Ethnicity (%)			0.66
African American	34 (44.16)	16 (30.77)	
Caucasian	32 (41.56)	28 (53.85)	
Asian	4 (5.19)	3 (5.77)	
Hispanic	6 (7.79)	4 (7.69)	
Unknown	1 (1.30)	1 (1.92)	
Initial diagnosis (%)			NA
NMOSD	70 (90.91)	52 (100.0)	
NMO	7 (9.09)	0 (0.0)	

NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; y: years; std. dev.: standard deviation.

Demographics and patient characteristics of NMO and NMOSD patients

Table 1 describes the mean age of onset, gender distribution, ethnicity distribution, AQP4-IgG serostatus, and initial diagnosis distribution of the historically defined seropositive NMO and limited seropositive NMOSD patients in the current dataset. We found historical NMO and limited seropositive NMOSD patient populations to be similar in their ethnicity and the percentage of female patients in each group. The mean age of onset for NMO patients was 39.27±15.82 years, which was lower than that of NMOSD patients (45.74±15.94 years; $p = 0.02$).

Table 2 describes the clinical characteristics and history of patients stratified by final diagnosis of historically defined seropositive NMO or limited seropositive NMOSD. At onset, the historically-defined seropositive NMO patient group had similar

Table 2. Clinical characteristics of study patients by cohort.

Final diagnosis	NMO	NMOSD	*p*-Value
No. of patients	77	52	
Presentation at onset (%)			
TM	39 (50.65)	42 (80.77)	0.0005
ON	42 (54.55)	6 (11.54)	<0.0001
Cerebral	0 (0.0)	1 (1.92)	0.40
N/V	7 (9.09)	2 (3.85)	0.31
Hiccups	4 (5.19)	1 (1.92)	0.41
Other brainstem	1 (1.30)	2 (3.85)	0.56
LETM	35 (45.45)	37 (71.15)	0.004
Median number of demyelinating events (p_{25}, p_{75})			
No. of ON episodes	1 (1, 2)	0 (0, 0)	<0.0001
No. of TM episodes	2 (1, 3)	2 (1, 3.5)	0.95
Clinical event history (%)			
TM	77 (100.00)	45 (86.54)	0.0009
ON	77 (100.00)	6 (11.54)	<0.0001
Cerebral	2 (2.60)	3 (5.77)	0.65
N/V	10 (12.99)	6 (11.54)	1.00
Hiccups	5 (6.49)	1 (1.92)	0.40
Other brainstem	7 (9.09)	2 (3.85)	0.31
Radiologic history (%)			
Brain normal	37 (48.05)	16 (30.77)	0.05
Brain MS	9 (11.69)	4 (7.69)	0.56
Brain NSWML	31 (40.26)	19 (36.54)	0.67
ADEM/PRES	0 (0.0)	1 (1.92)	0.40
LETM	74 (96.10)	46 (88.46)	0.09
PTM	3 (3.90)	1 (1.92)	0.65
Median years to first relapse after onset (p_{25}, p_{75})	0.87 (0.28, 2.46)	0.95 (0.49, 3.33)	0.10
Median number of relapses (p_{25}, p_{75})	3 (2, 4)	2 (1, 3)	0.001
Median annual relapse rate (p_{25}, p_{75})	0.50 (0.29, 0.78)	0.43 (0.17, 0.71)	0.13
Median disease duration in years (p_{25}, p_{75})	6.44 (3.80, 11.31)	5.39 (2.57, 8.36)	0.04
Median years to NMO treatment (p_{25}, p_{75})	3.17 (0.67, 6.26)	1.07 (0.27, 3.15)	0.009
Median number of relapses prior to NMO treatment (p_{25}, p_{75}), *n*	2 (1, 3)	1 (0, 1.5)	0.0004

ADEM: acute disseminated encephalomyelitis; LETM: longitudinally extensive transverse myelitis; MS: multiple sclerosis; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorder; NSWML: non-specific white matter lesions; N/V: nausea/vomiting; ON: optic neuritis; p_{25}: 25th percentile; p_{75}: 75th percentile; PRES: posterior reversible encephalopathy syndrome; PTM: partial transverse myelitis; TM: transverse myelitis.

proportions of patients presenting with TM (50.65%) and ON (54.55%), while the limited seropositive NMOSD patient group had a greater proportion of patients who presented with TM (80.77%; $p = 0.0005$) and a lesser proportion who presented with ON (11.54%; $p < 0.0001$). Additionally, the median time to initiation of an NMO preventive therapy after onset was greater for the historically-defined seropositive NMO patient group (3.17 years) relative to the limited seropositive NMOSD patient group (1.07 years; $p = 0.009$). Similarly, seropositive NMO patients experienced greater median number of relapses prior to the initiation of therapy (two relapses) than the NMOSD patients (one relapse; $p = 0.0004$).

Patient characteristics based on diagnosis on initial presentation

Of the 129 patients included in the study, seven met the diagnostic criteria for NMO with simultaneous ON and TM on initial presentation; the other 122 were recognized as limited seropositive NMOSD. After a median time of two years (range: one month to 28 years), 70 (57.4%) of these patients with initially limited seropositive NMOSD ultimately met criteria for historically-defined NMO with both ON and TM.

Treatment decreases the odds of conversion to a final diagnosis of NMO

Of the 122 AQP4-IgG seropositive patients who initially did not meet NMO diagnostic criteria, 62 were treated with an NMO preventive therapy prior to definitive NMO diagnosis, while the remaining 60 were not treated until after additional attacks confirmed the diagnosis of NMO or were never treated. Of the 62 patients treated prior to satisfying diagnostic criteria for NMO, 19 (30.6%) finally fulfilled NMO diagnostic criteria via additional attacks despite therapy, compared to 51 of the 60 (85%) in the untreated cohort who met NMO diagnostic criteria with subsequent relapses. Thus, the odds of treated seropositive patients converting to NMO was very low (OR = 0.08, 95% confidence interval (CI): 0.03–0.19, $p < 0.0001$) and the odds of untreated patients relapsing and confirming the diagnosis of historically defined NMO was high (OR = 12.8, 95% CI: 5.26–31.26, $p < 0.0001$).

Similar time to first relapse after initiation of preventative therapy

We hypothesized that after the start of an NMO preventative therapy, the survival times to first relapse would not be different between historically defined seropositive NMO and limited seropositive NMOSD patient groups. Figure 1 displays the Kaplan-Meier curves corresponding to the time to first relapse after the initiation of therapy for azathioprine, mycophenolate mofetil, and rituximab, stratified by diagnosis. Figure 2 depicts the occurrence of relapses after the initiation of therapy for historically defined seropositive NMO and limited seropositive NMOSD patients receiving azathioprine, mycophenolate mofetil, and rituximab. For those patients whose first NMO preventative therapy was azathioprine, it was found that the difference in the survivorship function between the two patient groups was not statistically significant ($p = 0.24$). Additionally, it was found that the difference in the survivorship function for those patients concurrently treated with azathioprine and prednisone was not significantly different between the historically defined seropositive NMO group and the NMOSD group ($p = 0.71$). For those patients whose first NMO preventative therapy was mycophenolate mofetil, it was again found that the difference in the survivorship function between the two patient groups was not statistically significant ($p = 0.63$). We were unable to analyze the effect of concurrent treatment of mycophenolate mofetil with prednisone stratified by diagnosis due to the fact that only a single NMO patient received mycophenolate mofetil and prednisone simultaneously. Lastly, for those patients whose first NMO preventative therapy was rituximab, it was again found that the difference in the survivorship function between the two patient groups was not statistically significant ($p = 0.97$).

Similar reductions in ARR in historical NMO and limited seropositive NMOSD patients on preventive treatment

We hypothesized that historically defined seropositive NMO and limited seropositive NMOSD patient groups would experience similar reductions in the hazard of relapse during NMO preventive therapy relative to pretherapy. A total of 24 patients (13 NMO, 11 NMOSD) received azathioprine as their initial NMO preventive therapy. Of the 24 patients, 10 patients (six NMO, four NMOSD) received both prednisone and azathioprine simultaneously. A total of 21 patients (11 NMO, 10 NMOSD) received mycophenolate mofetil as their initial NMO preventive therapy. Of the 21 patients, four patients (three NMO, one NMOSD) received both prednisone and mycophenolate mofetil simultaneously. A total of 26 patients (16 NMO, 10 NMOSD) received rituximab as their initial NMO preventive therapy.

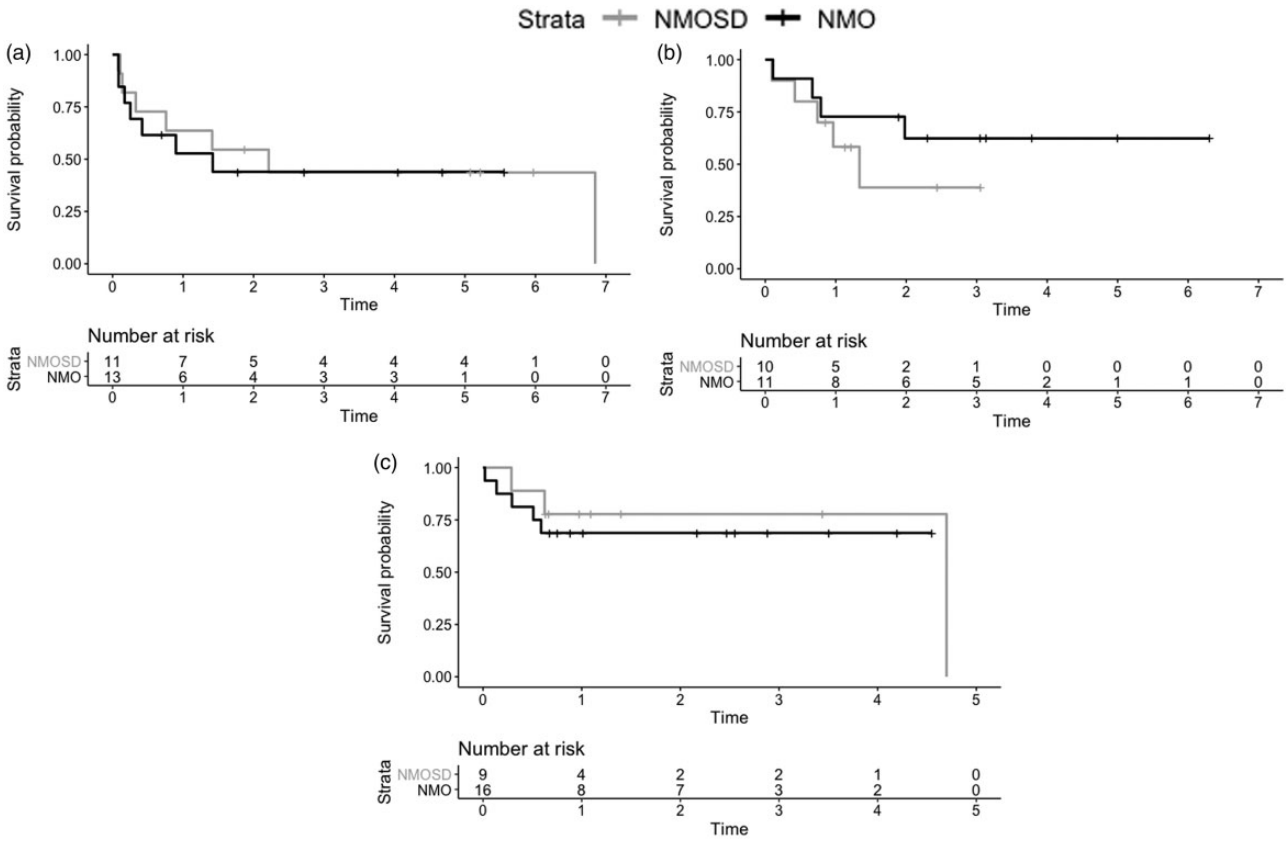

Figure 1. Kaplan-Meier curves for time to first relapse after the initiation of (a) azathioprine, (b) cellcept, and (c) rituximab, stratified by final diagnosis of seropositive neuromyelitis optica (NMO) versus limited seropositive neuromyelitis optica spectrum disorder (NMOSD).

Initial analysis was performed to test differences in the effect of the three NMO preventive therapies and the addition of prednisone with azathioprine and mycophenolate mofetil on the reduction of the hazard of relapse during treatment, relative to pre-treatment, for seropositive NMO patients versus seropositive NMOSD patients. Reductions in hazard of relapse were found to not be different between seropositive patients diagnosed as NMO versus NMOSD during treatment with azathioprine ($p = 0.23$), mycophenolate mofetil ($p = 0.24$), or rituximab ($p = 0.71$), relative to average pre-treatment ARR. The additional effect of the addition of prednisone on the hazard ratio of relapse relative to pretreatment was not statistically different between diagnoses for azathioprine ($p = 0.25$) or mycophenolate mofetil ($p = 0.94$). Similarly, the combined effect of prednisone and azathioprine or mycophenolate was found to not be significantly different between the two diagnoses ($p = 0.66$ and $p = 0.94$, respectively). Models were then refit with common time-dependent treatment covariates for the two diagnoses. The hazard ratio of relapse during azathioprine treatment relative to pretreatment was found to be 0.60 (95% CI: 0.30–1.22, $p = 0.16$). The hazard ratio of relapse during mycophenolate treatment relative to pretreatment was found to be 0.67 (95% CI: 0.28–1.60, $p = 0.37$). The hazard ratio of relapse during rituximab treatment relative to pre-treatment was found to be 0.26 (95% CI: 0.12–0.57, $p = 0.0008$). The additional reduction of the hazard ratio of relapse due to prednisone during treatment with azathioprine was 0.67 (95% CI: 0.26–1.70, $p = 0.40$). The additional reduction of the hazard ratio of relapse due to prednisone during treatment with mycophenolate mofetil was 0.29 (95% CI: 0.05–1.52, $p = 0.14$). However, the hazard ratio of relapse during combination therapy with azathioprine and prednisone relative to pretreatment was found to be 0.40 (95% CI: (0.18–0.91), $p = 0.03$). Lastly, the hazard ratio of relapse during combination therapy with mycophenolate mofetil and prednisone relative to pretreatment was found to be 0.19 (95% CI: 0.04–1.01, $p = 0.05$).

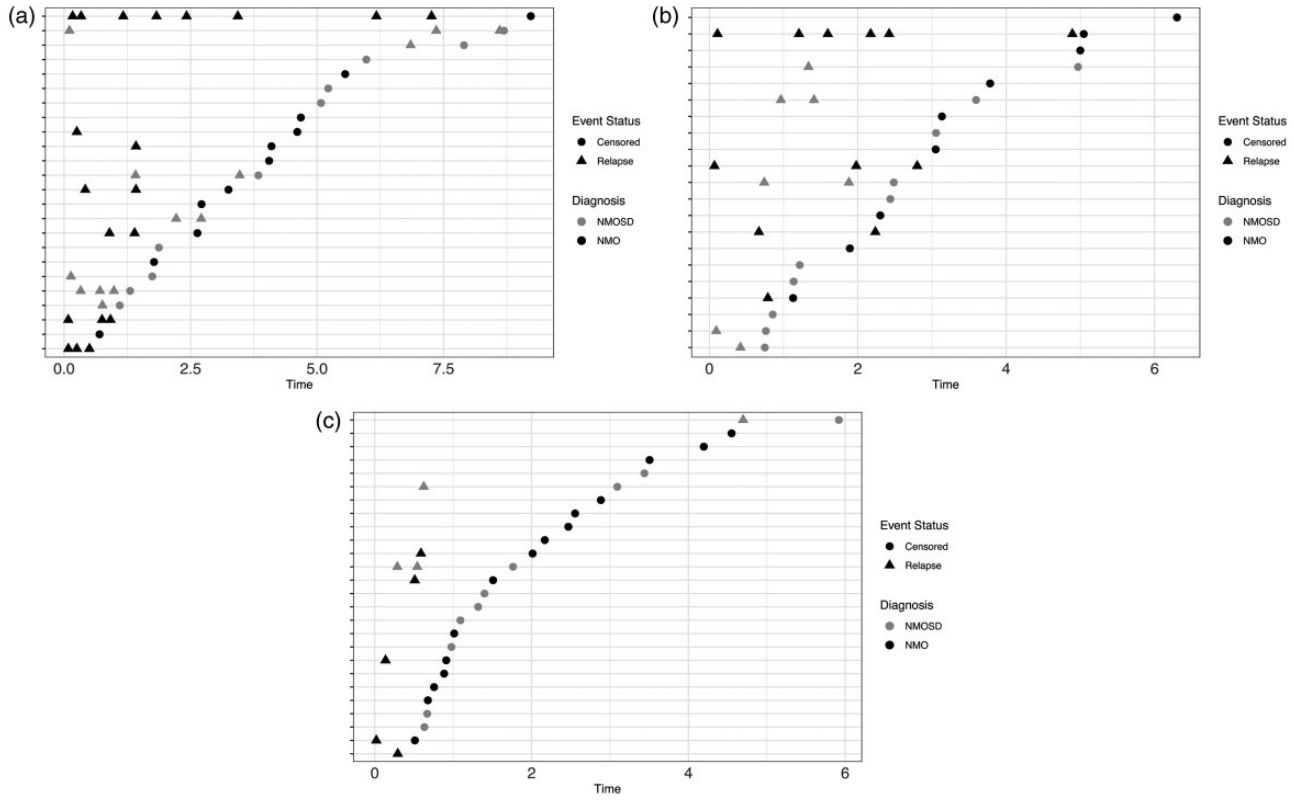

Figure 2. Relapse occurrence for patients receiving (a) azathioprine, (b) cellcept, and (c) rituximab as their initial neuromyelitis optica (NMO) preventative therapy, stratified by final diagnosis of seropositive NMO versus limited seropositive neuromyelitis optica spectrum disorder (NMOSD).

Discussion

With the identification of the AQP4-IgG as a specific biomarker of NMO came the realization that NMO included a broader phenotypic spectrum than previously appreciated.[6] Thus, many clinicians have treated patients with limited seropositive NMOSD in the same way as they would have treated historically defined NMO patients, with immunosuppressants, such as azathioprine, mycophenolate mofetil, prednisone, and rituximab.[8,9] Simplification of patient classification and the diagnostic process with the updated 2015 clinical criteria allows for patients with a single clinical event and positive AQP4-IgG antibody test to be diagnosed with NMOSD and therefore begin treatment to try to prevent a second attack. Our multi-center, retrospective review of historically defined seropositive NMO versus limited seropositive NMOSD patients and their treatment history found similar responses with preventive immunotherapy. Specifically, the hazard ratio of the addition of preventive immunotherapy, relative to average pre-treatment ARR, was found to not be significantly different for the two groups. This finding lends evidence to the hypothesis that limited seropositive NMO is the same disease as historically defined NMO but detected at an earlier time point. It also suggests that immunosuppressive treatment at any time point is effective in reducing the odds of conversion to 2006 NMO. These findings also support the unification of the terms NMO and NMOSD within the 2015 IPND revised diagnostic criteria.[5] In this study we found the statistically significant benefit of rituximab and concurrent treatment of azathioprine and prednisone while controlling for a function of the time to the initiation of treatment after onset and a function of age at onset. Additionally, we found a near statistically significant benefit of concurrent treatment of mycophenolate mofetil and prednisone while controlling for a function of the time to the initiation of treatment after onset and a function of age at onset.

Limitations of the current study result from the analysis of retrospective data. Specifically, the patients in each cohort do not represent random samples. Additionally, initiation of a particular treatment was at the discretion of the treating physician and not randomized. Lastly, the sample sizes of patients

analyzed for the effect of treatment was limited due to the availability of complete treatment data satisfying the designated inclusion/exclusion criteria.

Authors' Note

A DeSena is now affiliated to Department of Neurology, Cincinnati Children's Hospital Medical Center, USA.

Conflict of Interests

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