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Neuromyelitis optica: Clinical course and potential prognostic indicators

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune neurological disorder associated with antibodies to aquaporin-4 (AQP4). NMOSD has been thought to follow a progressive disease course, with step-wise accumulation of disability over time, even in patients undergoing immunosuppressive/immunomodulatory therapy. The influence of factors such as AQP4 seropositivity, AQP4 serum titer levels, and administration of plasmapheresis on NMOSD prognosis is, as yet, unclear.

Methods: We performed a retrospective chart review of 53 persons with NMOSD at Duke University Hospital—collecting data on longitudinal disease course, imaging, demographics, and serum AQP4 titers (measured using the ELISA or FACS method). Most patients in our cohort were treated with high-dose corticosteroids and, following diagnosis, received maintenance immunosuppressive/immunomodulatory therapies. Longitudinal data on EDSS scores were used to calculate the slope of disability over time for each participant. We additionally investigated the correlation between initial AQP4 seropositivity, initial AQP4 serum titer levels, and treatment with plasmapheresis on disability progression for each participant.

Results: Contrary to current views on NMOSD disease course, the majority of our participants showed either no change (31.9%) or improvement (27.1%) in disability over time. Our results additionally revealed no significant association between clinical prognosis and initial AQP4 seropositivity ($p = 0.830$), initial AQP4 serum titer levels ($p = 0.338$), or administration of plasmapheresis ($p = 0.1149$).

Conclusions: Our study presents a contemporary view of the clinical course of NMOSD and shows a more favorable view of its disease course than prior studies (performed before high-efficacy disease modifying therapies became widely-used for this patient population). Most patients in this study received treatment with high-dose corticosteroids following NMOSD flares, as well as a variety of maintenance immunosuppressive therapies. The results of this study cannot shed light on the disease course of untreated NMOSD. Our findings additionally challenge the theory that AQP4 seropositivity or serum titer levels at time of diagnosis may be used to effectively predict NMOSD prognosis. While we were unable to find evidence supporting a favorable effect of plasmapheresis administration on disease outcomes, further research is needed to determine the role plasmapheresis ought to play in the treatment of NMOSD.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disorder affecting the central nervous system. Clinical manifestations range from optic neuritis (ON) and transverse myelitis (TM) to the less common area postrema syndrome (Wingerchuk et al., 2015). Due to the rarity of this condition and the historical difficulty in performing large studies on NMOSD, our understanding of its course and prognosis is still evolving. Previous studies on the disease course of NMOSD reflect poor neurologic outcomes even in cohorts treated with corticosteroids and immunosuppressive therapies. Such studies reported that up to 50% of NMOSD patients reach a Kurtzke Extended Disability Status Scale (EDSS) score of 6 or more (Kurtzke, 1983) within the first 10 years of their diagnosis (Ghezzi et al., 2004,

Abbreviations: NMOSD, Neuromyelitis optica spectrum disorder; ON, Optic neuritis; TM, Transverse myelitis; EDDS, extended disability status scale, AQP4, aquaporin-4.

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Collongues et al., 2010, Drulovic et al., 2019) and another found that 52% of patients become legally blind in at least one eye within three years of diagnosis (Vanikieti et al., 2017).

NMOSD is associated with serum positivity of aquaporin-4 (AQP4) antibodies and the titer level may correlate with severity of NMOSD symptomatology (Takahashi et al., 2007). Conflicting evidence exists on whether serum levels of AQP4 antibodies can be used to predict risk of relapse and long-term outcomes. Though some found an increase in serum AQP4 antibody levels prior to relapses and a decrease in serum AQP4 antibody levels during periods of remission and following treatment (Jarius et al., 2008, Jarius et al., 2010, Jarius and Wildemann, 2013, Akaishi et al., 2020a), others failed to replicate this finding (Jitprapaikulsan et al., 2020, Isobe et al., 2013). Even if serum AQP4 antibodies are proven to reliably increase prior to relapses (exhibiting good sensitivity for relapse risk), their value as a predictor for relapse risk may be limited by a lack of specificity; in one series, elevations in AQP4 antibody levels led to clinical symptoms in only 50% of cases (Akaishi et al., 2020a). No reliable predictors of acute NMOSD exacerbation have been identified. Isolating such a predictor would allow clinicians to escalate therapy in patients with greater risk of relapse.

Plasmapheresis' effectiveness (Bonnan and Cabre, 2012) in treating NMOSD attacks is gaining recognition with studies finding that patients who do not undergo plasmapheresis within 3 weeks of an NMOSD flare are far less likely to regain their former baseline (Bonnan et al., 2018, Abboud et al., 2016). High-dose intravenous (IV) glucocorticoids are the current first-line treatment option for acute NMOSD. While plasmapheresis is seen as an important early therapy for acute attacks, the extent of the impact early administration of plasmapheresis has in acute NMOSD (Bonnan et al., 2018) needs to be further explored. While used as an early adjunct when available at the site of care, plasmapheresis serves as delayed rescue therapy (Sellner et al., 2010, Trebst et al., 2014) in facilities without ready access to this intervention.

This study reports disease course in a cohort of NMOSD patients from a single academic medical center in the United States. As it is unclear whether AQP4 serostatus and serum titers can predict disability accumulation in NMOSD, we explore the relationship between these two measures and neurologic outcomes in NMOSD. We also explore the relationship between timing of administration of plasmapheresis and clinical disease course.

2. Methods

We completed a retrospective review of all patients diagnosed with NMOSD at Duke University Hospital (DUH) between January 1, 2000, and January 1, 2021. Accuracy of NMOSD diagnosis was determined for each patient using the international consensus diagnostic criteria (Wingerchuk et al., 2015). All patients meeting these criteria within the studied timeframe were included in analyses.

Demographic, clinical, serologic and cerebrospinal fluid test results, and imaging findings were collected in all patients from year of diagnosis to January 1, 2022, or until time of last encounter within the DUH system. Disability was scored using motor function (EDSS) for patients with a TM-predominant course and scored based on visual acuity for patients with an ON-predominant course. When patients experienced both TM and ON symptoms, their disability was scored based on a 0-7 scale weighted to the modality (visual ability vs motor function) associated with the highest level of disability (See supplemental material). Visual ability was calculated using the most affected eye. AQP4 seropositivity was reported using the ELISA method until 2017 at which point the FACS method was used to report serum antibody findings.

All patients with positive AQP4 serum titers (>1:5 titer) were assigned to the positive titer group, in keeping with the guidelines set by Mayo Clinic Laboratories where these serum titers were performed. A study performed by this laboratory showed that this methodology of AQP4-IgG titration resulted in 100% specificity for NMOSD (Redenbaugh et al., 2021). All patients with negative AQP4 serum titers were assigned to the negative titer group. Of the patients with positive titers for whom exact titer levels were available, those with a titer level greater than or equal to 1:100,000 were assigned to the high titer group. Those with a positive titer level below 1:100,000 were assigned to the low titer group. Our laboratory began reporting titer levels from 2017 onwards. As a result, data on titer positivity but not titer value was available for patients who were tested for the presence of antibodies prior to this year.

To control for a wide variation in duration of time followed, we used the slope of disability over time as a proxy for disease course in each individual patient.

2.1. Statistical analysis

Statistical analyses were conducted in R Studio version 1.4. Descriptive statistics are displayed as mean ± SD. Each patient was followed from the year they were diagnosed with NMOSD to the year they were lost to follow-up. A two-sample t-test with unequal variances was used to compare the slope of disability over time for patients in the 3 paired groups. Slope was calculated using Excel's built in Slope function derived from the following formula: $slope = \frac{\Sigma(x-\bar{x})(y-\bar{y})}{\Sigma(x-\bar{x})^{\wedge}2}$. Disability values within 3 months of initial flare were excluded from slope analysis to ensure that slopes reflected chronic rather than acute phase disease course. *A p* value < 0.05 was defined as statistically significant. A Wilcoxon rank sum test was used to compare disability in first year from onset in the 3 paired groups.

3. Results

3.1. Demographics

Of 68 patients identified through the outlined search strategy, 53 fulfilled the inclusion criteria and were confirmed to have NMOSD. Demographic and disease-related data for these 53 NMOSD patients are summarized in Table 1. Of note, two patients' initial presentation occurred prior to 2004 when AQP4 titer testing first became available. Both were originally misdiagnosed with multiple sclerosis and received their first AQP4 titer and diagnosis of NMOSD several years following their initial presentation.

3.2. Imaging

Initial MRI findings were available for 45 out of 53 patients and are summarized in Table 2.

3.3. Disease course and outcomes

While all 53 patients were included in descriptive statistics, 6 patients were excluded from outcome analysis due to insufficiency of longitudinal data (less than 2 years). Eight patients died during the follow-up period—at a median age of 63.6 years, and duration of NMOSD at death 1.1 years; 1 patient died from lung cancer, 2 from failure to thrive, 1 from infection, and cause of death was not available for the remaining 4 patients. Patients were followed for an average of 5.2 ± 3.9 years (range: 0.05 to 15.8 years).

3.3.1. All patients

The majority of patients did not experience worsening disability over time (median = 0, range = -2.5 to 3.0). Nineteen (40.43%) out of 47 patients showed worsening disability over time, 15 (31.91%) showed no change in disability over time, and 13 (27.7%) showed improvement in disability over time. A figure showing progression of disability over time for individual patients can be found in supplemental materials.

3.3.2. TM- predominant patients

Of our 29 patients for whom TM was a predominant symptom, EDSS

Table 1
This table illustrates the demographic and disease related characteristics of our subject pool.

Demographic and disease-related characteristics (n = 53) except as otherwise indicated	No. (%)/mean +/- SD [range]
Sex	
Female	41 (77.4)
Age	42.79 +/- 18.34 [12.0-81.7]
Race	
Black	37 (69.8)
White	12 (22.6)
Latinx	4 (7.5)
Associated conditions	37 (69.8)
Depression	7 (13.2)
Anxiety	7 (13.2)
Hypertension	21 (39.6)
Diabetes	12 (22.6)
Osteoporosis	3 (5.7)
Associated autoimmune conditions	11 (20.8)
Hypothyroidism	7 (13.2)
Lupus	4 (7.5)
Raynaud's disease	2 (3.8)
Myasthenia gravis	2 (3.8)
Sjogren's syndrome	1 (1.9)
Associated comorbidities	
History of malignancy	6 (11.3)
History of smoking	24 (45.3)
History of prior immunosuppressive uses	1 (1.9)
Symptom(s) at initial presentation ($n = 51$)	
Acute myelitis	35 (68.6)
Optic neuritis	17 (33.3)
Area Postrema Syndrome	8 (15.7)
Acute Brainstem Syndrome	1 (2.0)
Symptomatic Cerebral Syndrome	0 (0.0)
Symptomatic Narcolepsy Syndrome	0 (0.0)
Predominant symptom ($n = 50$)	
Transverse Myelitis	29 (58.0)
Optic Neuritis	13 (26.0)
Both	8 (16.0)
AQP4 Titer (High vs Low) ($n = 19$)	
High	9 (47.4)
Low	10 (52.6)
AQP4 Titer (Positive vs Negative) ($n = 51$)	
Positive	42 (82.4)
Negative	9 (17.6)
Average follow-up period (years)	5.2± 3.9 [0.05-15.8]

Table 2
This table illustrates the imaging characteristics of our subject pool.

Characteristics of initial MRI findings in NMOSD patients ($n = 45$)	No. (%)/mean +/- SD [range]
Optic nerve/Chiasm	9 (20.0)
Brain	16 (35.6)
Brainstem	10 (22.2)
Spinal Cord	38 (84.4)
Length of longest lesion (vertebral bodies) ($n = 17$)	7.11 +/- 5.31 [1 – 20]

during first year of presentation was available for 25 patients (mean = 4.6 ± 2.69). Ten of 25 patients were wheelchair bound at the end of their first year. Two of 29 patients were excluded from slope analyses due to lack of longitudinal data. There was no significant association between disability and time (mean slope of disability = -0.09 ± 0.84). 10 (39.2%) out of 27 patients showed worsening disability over time, 7 (25%) showed no change in disability over time, and 10 (35.7%) showed improvement in disability over time. Ten (34.5%) out of 29 patients were wheelchair bound at last follow-up.

3.3.3. ON-predominant patients

Twelve of our 13 patients for whom ON was the predominant symptom experienced asymmetric vision loss—with a "worse" eye that experienced more severe NMOSD related vision loss than their "better" eye. We reported visual disability based on the visual ability of their worst eye, and, separately, reported visual disability based of the visual ability of their better eye.

Worse eye reporting. Of our 13 patients for whom ON was the predominant symptom, data on worse eye visual acuity during first year of presentation was available for 8 patients (mean = 5, median = 5, SD = 1.07). All 8 patients were legally blind at the end of their first year. One out of our 13 patients were excluded from slope analyses due to lack of longitudinal data. There was no significant association between disability and time (mean slope of disability = 0.32 ± 0.87). Six (50%) out of 12 patients showed worsening disability over time, 4 (33.3%) showed no change in disability over time, and 2 (16.7%) showed improvement in disability over time. 9 (69.2%) out of 13 patients were legally blind at last follow-up. (Definition of legally blind: Snellen equivalent 20/200 or worse).

Better eye reporting. Of our 13 patients for whom ON was the predominant symptom, data on better eye visual acuity during first year of presentation was available for 9 patients (mean = 1.778, median = 2, SD = 1.56). One out of 9 patients was legally blind at the end of their first year. One out of our 13 patients were excluded from slope analyses due to lack of longitudinal data. There was no significant association between disability and time (mean slope of disability over time = 0.34 ± 0.47). Nine (75%) out of 12 patients showed worsening disability over time, 1 (8.3%) showed no change in disability over time, and 2 (16.7%) showed improvement in disability over time. Three (23.1%) out of 13 patients were legally blind at last follow-up.

3.4. Quantitative analysis

We found no significant association between progression of disability and high initial AQP4 serum titer (mean = 0.24 ± 0.44) versus low initial AQP4 serum titer (mean = 0.53 ± 1.16); t(7.72) = -0.610, p = 0.559. (power = 15%) (Fig. 2), nor association between progression of disability and positive initial AQP4 serum titer (mean = 0.10 ± 0.77) versus negative initial AQP4 titer (mean = 0.06 ± 1.00); t(10.51) = -0.117, p = 0.901. (power = 6%) (Fig. 3). We found no significant association between progression of disability and plasmapheresis treatment (mean = -0.09 ± 0.75) versus no treatment (mean = 0.20 ± 0.99)); t(33.08) = 1.17, p = 0.249. (power = 21%) (Fig. 4). Neither did we find a significant association between disability during first year of diagnosis and serum titer level high (mean = 4.86 ± 3.08) versus low (mean = 4.14 ± 2.27); (Z = -0.648, p = 0.517), serostatus positive (mean = 4.48 ± 2.54) versus negative (mean = 4.75 ± 2.43); (Z = -0.193, p = 0.847), nor plasmapheresis received (mean = 4.07 ± 2.76) versus not (mean = 4.64 ± 2.46); (Z = -0.635, p = 0.525).

4. Discussion

4.1. Demographics

Our study population consisted predominantly of Black/African American individuals (69.8%), with White/Caucasian individuals constituting the second largest race group (22.6%), in contrast with the majority of prior studies performed in a predominantly White/Caucasian population (Redenbaugh et al., 2021; Papp et al., 2021; Mealy et al., 2012). Our data showed a female to male ratio of 3:1 and seropositive to seronegative ratio of 5:1, consistent with ratios reported by past studies (Redenbaugh et al., 2021).

4.2. Disease course

Current understanding of the disease course of NMOSD suggests that, even when appropriately treated with immunosuppressive agents, this

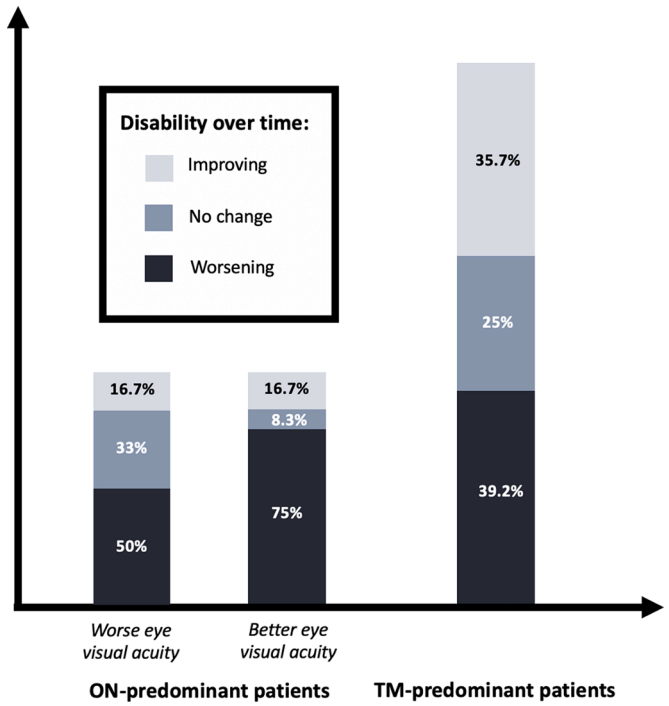

Fig. 1. Disability over time by patient symptomology. This figure illustrates that most patients in the TM-predominant group did not show worsening disability over time, and that half the patients in the ON-predominant group did not show worsening disability over time when disability was measured using their worse eye. Most patients in the ON-predominant group did show worsening disability over time when disability was measured using their better eye.

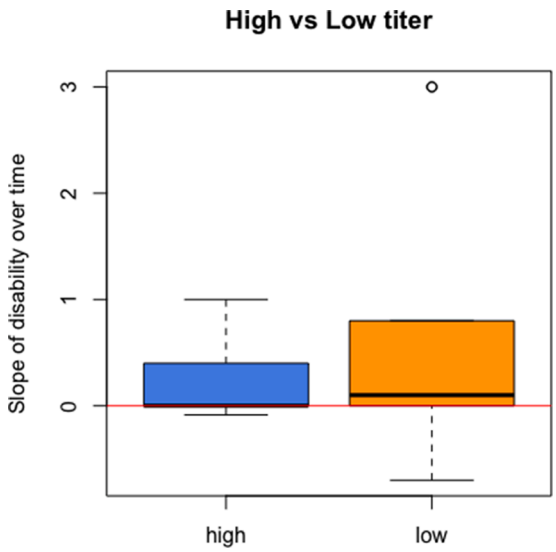

Fig. 2. Slope of disability over time by AQP4 serum titer level. This figure illustrates that the effect of AQP4 serum titer level on slope of disability over time was not significant. ($p = 0.559$).

condition manifests with consistently increasing, stepwise progression of disability—without remission of residual disability between relapses. Our results suggest that patients with NMOSD may not necessarily accumulate disability and may exhibit remission of residual disability between relapses when diagnosed early in the course and started on high efficacy therapy. Our patients did not consistently exhibit increasing disability over time—their median slope of disability over time was 0. Fewer than half of our patients showed a positive slope (indicating

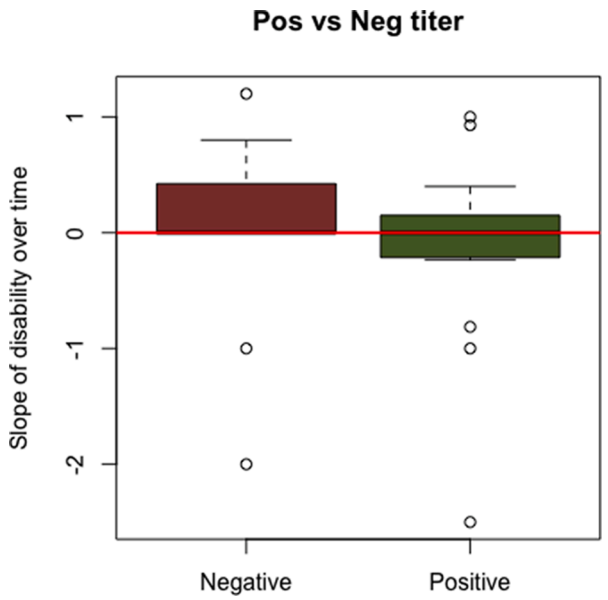

Fig. 3. Slope of disability over time by AQP4 serostatus. This figure illustrates that the effect of AQP4 serostatus on slope of disability over time was not significant. ($p = 0.901$).

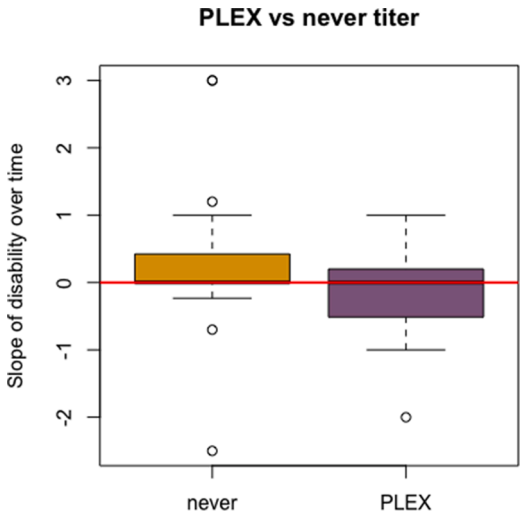

Fig. 4. Slope of disability over time by plasmapheresis administration. This figure illustrates that the effect of plasmapheresis administration on slope of disability over time was not significant. ($p = 0.249$).

worsening disability over time), and 27.7% showed improvement in disability over time. Most patients in our cohort were treated with high-dose corticosteroids during acute flares and received a variety of maintenance immunosuppressive therapies. It should be noted that the remission of residual disability seen in some patients was not in the absence of treatment and that these results shed no light on the prognosis or course of untreated NMO. Prior studies on disease course in NMOSD mostly followed one of two methodologies: reporting the percentage of patients who achieved a specified EDSS at increasing disease durations, or reporting the time taken to reach a specified EDSS. These methodologies rely on the assumption that patients with even treated NMOSD accumulate disability without remission. Studies on visual disability in NMOSD made the same assumptions and used visual acuity at time of final follow-up as their main outcome measure.

A difference between our study and prior works on NMOSD disease course is the creation of a compound disability variable that

incorporates both visual acuity and EDSS as input and allows us to include patients with an ON-predominant course and a TM-predominant course in the same cohort. Most prior studies analyzed disease course in ON and TM predominant patients separately.

To allow our results to be more easily compared to prior works, we performed additional analyses that evaluated our ON-predominant and TM-predominant cohort separately. We saw no evidence supporting a consistently worsening functional baseline in either cohort. Only half of ON-predominant patients, and fewer than half of TM patients showed worsening disability over time.

Prior studies on visual acuity in NMOSD used three main metrics to report visual outcomes: scoring the visual acuity of patient's most affected eye (Mealy et al., 2018), scoring visual outcomes based on findings from both eyes (Lin et al., 2019), or reporting visual acuity by individual eye rather than by patient (Vanikieti et al., 2017). Several studies also used optical coherence tomography to precisely quantify retinal neural loss and thus lesion severity (Brody et al., 2016, Balcer and Galetta, 2013). While these methods effectively describe visual outcomes from a clinician's perspective—identifying the amount of biological damage NMOSD can do—they may not accurately reflect functional visual ability and vision related quality of life, the metrics of most concern for patients. Ophthalmological studies have shown that better eye visual acuity is at least as good or a better predictor of vision related quality of life (Monteiro et al., 2012) and vision related disability (Musch et al., 2017) than even binocular assessments of visual acuity. While analyses of worse eye visual acuity are useful for tracking the clinical effects of NMOSD, the current lack of better eye visual acuity reporting, highlights the need for patient centered outcome initiatives.

Our findings comparing worse eye and better eye visual acuity imply that the functional visual ability of NMOSD patients might be more favorable than described in prior studies, which almost exclusively used worse eye or binocular measures of visual acuity. When we scored visual disability based on worse eye visual acuity, we found 9 out of 13 (69.2%) patients were legally blind at time of final follow-up—a less favorable estimate of visual outcome than reported in prior studies (Vanikieti et al., 2017, Mealy et al., 2018). When we scored visual disability based on better eye visual acuity, our results showed a more favorable prognosis than reported in prior studies—with only 3 out of 13 (23.1%) patients being legally blind at time of final follow-up.

As most of our participants first presented with NMOSD symptoms on or after 2016, our study presents a contemporary analysis of NMOSD prognosis. Improvements in awareness of NMOSD leading to earlier diagnosis and earlier treatment initiation in recent years may contribute to the more favorable view of disease course shown in our study versus prior studies on NMOSD prognosis. Nevertheless, while these results may show a more favorable view of disease course, they do not dispute the perception of NMOSD as a severe condition justifying high-efficacy therapy in qualifying patients. A high proportion of patients studied still experienced grave disability: 69.2% of our patients with optic neuritis as a primary symptom were legally blind at last follow-up, and 20.9% of patients with acute myelitis were wheelchair bound at time of last follow-up. These findings highlight the value of early diagnosis of NMOSD and the importance of early aggressive therapy in managing this condition.

4.3. AQP4 serum titer levels as a predictor of prognosis

We found no evidence that either AQP4 seropositivity or AQP4 serum titer levels predict disease course of NMOSD. There was no significant difference in slope of disability over time, or in initial disability levels between patients of different serostatus or between patients of high vs low titer levels. We acknowledge that our sample size is small and our study was not powered to detect such an association. Past studies on the subject found mixed results. Some found that seronegative patients have a higher level of disability than seropositive patients (Rubin et al., 2000), others found that seropositive patients have a higher level of disability than seronegative patients (Sepulveda et al., 2019, Shosha et al., 2020), and still others found, as we did, no difference in disease course or disability between seropositive and seronegative patients (Cabrera-Gómez et al., 2009, Jiao et al., 2013).

Studies looking into effects of serum titer level in seropositive patients found similarly mixed results—with some finding a positive correlation between titer levels and disability (Takahashi et al., 2007) and others finding no correlation between these two variables (Jitprapaikulsan et al., 2020, Fragoso et al., 2019, Kessler et al., 2017).

4.4. Effect of plasmapheresis administration on prognosis

While we found no significant association between progression of disability and plasmapheresis treatment, we found a trend towards better outcomes (slower progression of disability) in patients who received plasmapheresis within 30 days of initial presentation, though this analysis was limited by a small sample size. Our standard treatment approach is to combine high dose glucocorticoids and plasmapheresis with early initiation of chronic disease-modifying therapy at time of NMOSD diagnosis; however, delays in diagnosis prevented some patients from receiving plasmapheresis within 30 days of their initial presentation. Prior studies found that treatment with plasmapheresis decreases AQP4 titer levels (Akaishi et al., 2020b) and leads to better outcomes (Bonnan et al., 2018, Abboud et al., 2016). Plasmapheresis is still often used as an adjunctive rather than a first-line therapy for NMOSD attacks (Bonnan and Cabre, 2012), though its efficacy has been gaining recognition and in well-resourced tertiary care centers, it is now often a first-line therapy.

There is a need for further research into the effects of plasmapheresis treatment on clinical outcomes in NMOSD. It is yet to be determined whether plasmapheresis ought to be more widely considered (in combination with high-dose steroids) a first-line therapy for NMOSD exacerbations.

4.5. Limitations

There are several limitations to our study. The first is its retrospective design—several participants, particularly those whose symptom onset occurred prior to 2013, had gaps in their medical record—data on disability level was not consistently available for each year of follow-up. To circumvent these gaps in disability reporting and to allow patients with many years of follow-up to be compared to patients with more recent diagnosis, we adopted the strategy of using the slope of disability over time as a proxy for disability progression. The abovementioned gaps in disability reporting prevented us from being able to apply more advanced modeling methods to adjust for this difference in follow-up time. While this methodology allows us to determine broadly whether patients show increasing, steady, or improving disability over time—it does not allow us to analyze on the trajectory of disease progression over time. Prior studies have suggested that relapses and disability accumulation in NMOSD may be concentrated in the first two-years following diagnosis, with patients reaching a plateau in functional ability (Collongues et al., 2010, Drulovic et al., 2019).

The second limitation of this study is our small sample size reducing the statistical power of our outcome analyses. While we did not find statistically-significant associations between clinical prognosis and AQP4 seropositivity, AQP4 serum titer level, or plasmapheresis administration, the study lacked the power needed to detect these associations for all but the largest effect sizes. Given the rarity of NMOSD, sample size has been a common limitation in both our study and prior studies on this condition—highlighting the ongoing need for multi-center studies on NMOSD and the development of multi-center databases of NMOSD data.

5. Conclusion

Neuromyelitis optica spectrum disorder may not follow a steadily

progressive course with inevitable accumulation of disability over time. Our study suggests that disability accumulation primarily occurs at the time of diagnosis, supporting the argument for early recognition and treatment to improve long-term neurologic outcomes. Our results also failed to support an association between clinical prognosis and AQP4 seropositivity or AQP4 serum titer levels, highlighting the importance of exploring and identifying other possible clinical/paraclinical predictors of disease progression.

We were unable to find evidence supporting a favorable effect of plasmapheresis administration on disease outcomes but our study may have lacked the power needed to pick up on such an association. More research on the effects of plasmapheresis administration on clinical outcomes in NMOSD is needed to determine the role plasmapheresis should play in treating acute flares.

This study also highlights a need for patient-centered outcome measures in the study of NMOSD. This is particularly true for evaluating visual prognosis in NMOSD. Doing so would allow NMOSD patients a more accurate understanding of how their functional visual ability and vision-related quality of life may progress.

Given the rarity of this condition, sample size has been a common limitation in both our study and prior studies on NMOSD—highlighting the ongoing need for multi-center studies on this condition and the development of multi-center databases of NMOSD data.

CRediT authorship contribution statement

Nidhila Masha: Writing – original draft. **Dorlan J. Kimbrough:** Writing – review & editing. **Christopher P. Eckstein:** Writing – review & editing. **Nicholas M. Hudak:** Writing – review & editing. **Mark B Skeen:** Writing – review & editing. **F. Lee Hartsell:** Writing – review & editing. **Michael W. Lutz:** Writing – review & editing. **Suma Shah:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Suma Shah receives research support from Verasci and Biogen. She has received honaria from EMD Serono.

Dorlan Kimbrough serves as a consultant for CVS Health

Christopher P. Eckstein receives research funding from Sanofi, Genzyme, and EMD Serono—as well as honoraria from Viela Bio.

Mark B. Skeen serves as a consultant for Biogen, Novartis, Alexion, and Brixtol Myers Squibb, and works part-time at WCG.

Michael W. Lutz receives funding for his research from NIA/NIH. Dr. Lutx received consulting fees and travel expenses to attend scientific conferences from Zinfandel Pharmaceuticals.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104414.

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