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Factors Associated With Disability Improvement and Worsening Independent of Attacks in Patients With AQP4-IgG+ NMOSD and MOGAD

A Multicenter Cohort Study

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Abstract

Background and Objectives

Disability trajectories in aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) are primarily driven by attack-related damage. Confirmed disability worsening (CDW) independent of attacks has been described but occurs infrequently in AQP4-IgG+ NMOSD and MOGAD. Confirmed disability improvement (CDI) has not been evaluated in large cohorts. We determined the frequency of CDI and CDW independent of attacks and identified clinical factors associated with these outcomes in AQP4-IgG+ NMOSD and MOGAD.

Methods

This retrospective, multicenter cohort study analyzed data from the German Neuromyelitis Optica Study Group (NEMOS) registry. Adult patients with AQP4-IgG+ NMOSD or MOGAD and longitudinal Expanded Disability Status Scale (EDSS) assessments were included. EDSS episodes were defined as periods with ≥3 EDSS assessments without attacks, obtained ≥90 days after attack. CDW and CDI were defined as sustained EDSS increase or decrease (≥1.5 for baseline EDSS 0; ≥1.0 for EDSS 1.0–5.5; ≥0.5 for EDSS ≥6.0) confirmed after at least 6 months. The primary outcomes were annualized CDI and CDW rates. Risk factors were assessed using multivariable Anderson-Gill regression models.

Results

A total of 338 EDSS episodes of 307 patients (n: 202/105, median age at EDSS change: 56/41 years, 88/49% female, both $p < 0.001$; AQP4-IgG+ NMOSD/MOGAD) were included. Adjusted annualized CDI and CDW rates did not differ between AQP4-IgG+ NMOSD (CDI: 0.083, 95% CI 0.029–0.233; CDW: 0.025, 95% CI 0.007–0.092) and MOGAD (CDI: 0.057, 95% CI 0.012–0.277; CDW: 0.036, 95% CI 0.002–0.513). In AQP4-IgG+ NMOSD, a lower number of prior attacks was associated with higher CDI rates (hazard ratio [HR] 0.89, 95% CI 0.82–0.97). Younger age was associated with increased CDI rates in both AQP4-IgG+ NMOSD and MOGAD (HR 0.96, 95% CI 0.94–0.99, for both).

Discussion

CDI and CDW independent of attacks, although rare, occur in AQP4-IgG+ NMOSD and MOGAD. The association between fewer prior attacks and higher CDI rates in AQP4-IgG+ NMOSD underscores the importance of early attack prevention. Limitations include the retrospective design, and the limited number of CDI and CDW events.

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Glossary

AAR = annualized attack rate; **AQP4–IgG+NMOSD** = aquaporin-4 immunoglobulin G-seropositive neuromyelitis optica spectrim disorder; **CDI** = confirmed disability improvement; **CDW** = confirmed disability worsening; **EDSS** = Expanded Disability Status Scale; **FSS** = functional system score; **HR** = hazard ratio; **MOGAD** = myelin-oligodendrocyte glycoprotein-associated disease; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **PIRA** = progression independent of relapse activity.

Introduction

Aquaporin-4 immunoglobulin G-seropositive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD) and myelin-oligodendrocyte glycoprotein-associated disease (MOGAD) are rare but distinct immune-mediated disorders of the CNS characterized by attacks predominantly affecting the optic nerves and spinal cord.[1-5] Disability outcomes in AQP4-IgG+ NMOSD and MOGAD are highly variable, driven by the frequency, severity, and management of acute attacks, as well as the extent of recovery following each episode.[6,7] For individuals with AQP4-IgG+ NMOSD, the cumulative effects of attacks often result in irreversible neurologic deficits, emphasizing the importance of early and effective intervention.[6,8,9] By contrast, a significant proportion of individuals with MOGAD may be attack-free for a long period of time and hence experience less severe long-term disability.[10]

A progressive disease course in NMOSD has been considered to be rare.[11] However, subclinical retinal atrophy and prolonged neuroaxonal retinal damage could be shown for both AQP4-IgG+ NMOSD and MOGAD.[12,13] Recent studies have reported on confirmed disability worsening (CDW) and progression independent of relapse activity (PIRA), which occurred rarely in AQP4-IgG+ NMOSD and MOGAD, especially compared with multiple sclerosis (MS).[14-16] In addition to the concept of CDW/PIRA, confirmed disability improvement (CDI) has been identified as an outcome, especially in MS.[17,18]

Using the Neuromyelitis Optica Study Group (NEMOS) registry, we evaluated changes in the Expanded Disability Status Scale (EDSS) and determined the rate of CDI and CDW independent of attacks in individuals with AQP4-IgG+ NMOSD and MOGAD. We hypothesized that (1) annualized rates of CDI and CDW independent of attacks differ between individuals with AQP4-IgG+ NMOSD and those with MOGAD and that (2) clinical and/or demographic variables are associated with the occurrence of CDI and CDW independent of attacks.

Methods

Study Population and Inclusion Criteria

This retrospective and observational study included patients with AQP4-IgG+ NMOSD as well as patients diagnosed with MOGAD based on the published diagnostic criteria.[2,3,19] We screened EDSS scores of 646 patients. Only patients with AQP4-IgG+ NMOSD and MOGAD who had at least 3 recorded EDSS scores between attacks (measured within at least 6 months) or after their last attack (≥90 days postattack) were included in the study.

Data Acquisition and Variables

EDSS scores and, if available, functional system scores (FSS) and ambulation index scores, as well as data on attacks (date and anatomic site) were reviewed from regular follow-up visits. Further demographic and disease-related data were extracted from the German Neuromyelitis Optica Study Group (NEMOS) registry.

Outcome Measures

The primary outcomes were the proportion of EDSS episodes with CDI or CDW independent of attacks and the annualized rates of CDI and CDW independent of attacks. We extracted EDSS scores from each patient that were recorded either between 2 clinical attacks or following the last attack (≥90 days postattack). All EDSS scores obtained between 2 attacks or after the final attack were grouped into a single EDSS episode (Figure 1). EDSS episodes containing fewer than 3 EDSS scores were excluded from analysis. The first EDSS score within each episode was defined as the baseline EDSS score. CDI and CDW were defined according to previously published criteria: If the baseline EDSS score was 0, the cutoff for worsening (defined by a following EDSS score) was 1.5. If the baseline EDSS score was between 1.0 and 5.5, the cutoff for both improvement and worsening was 1.0. If the baseline EDSS score was 6.0 or higher, the cutoff (for improvement and worsening) was 0.5. Confirmation of improvement or worsening required an independent EDSS score determined at least 6 months after the initial EDSS change, which had to be equal to or exceed the first change in the respective direction.[14] The confirmation EDSS score was set as a new baseline EDSS score to allow for multiple EDSS episodes and for recurring events per patient. If an EDSS episode did not meet the criteria for either CDI or CDW, it was classified as without EDSS change. CDI and CDW proportions were calculated as the number of patients (or EDSS episodes) that exhibited CDI or CDW divided by the total number of cases.

Statistical Analyses

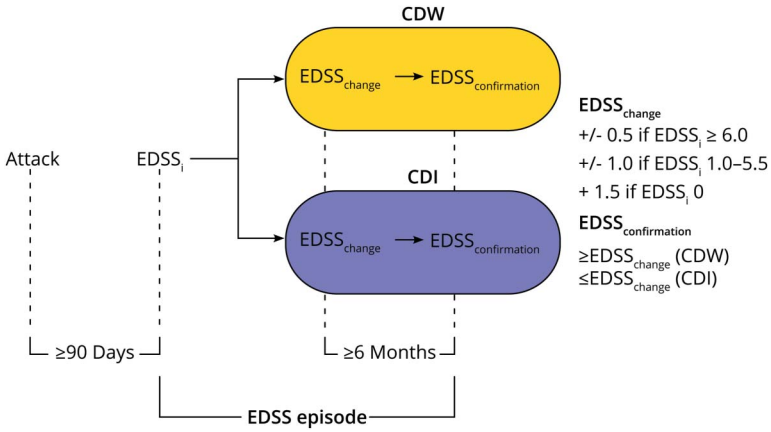
Central tendencies and dispersion of continuous variables were expressed as median with interquartile range ([IQR],

spanning from the 25th to the 75th percentile). Categorical variables were expressed as percentages. Differences between cohorts were tested using the Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Annualized CDI and CDW rates were estimated using a Poisson regression model adjusted for the time interval between the baseline EDSS score and the EDSS change. A second (adjusted) model was fitted to control for the number of EDSS scores within an EDSS episode, baseline EDSS score, and age at EDSS change or last EDSS score within an EDSS episode. To assess potential bias through prolonged attack recovery, we estimated annualized CDI and CDW rates based on EDSS scores that were recorded either between 2 clinical attacks or ≥180 days postattack (compared with ≥90 days postattack). Annualized attack rates (AARs) for the time between disease manifestation and EDSS change or last EDSS were calculated using negative binomial regression models, which were chosen to accommodate overdispersion in the number of attacks per patient. Person-time was included as an offset to yield rates per person-year. To assess factors associated with CDI and CDW and to account for differences in the time between the baseline EDSS score and CDI/CDW, we applied Andersen-Gill models, an extension of the Cox proportional hazards model that accommodates recurrent events. All models incorporated patient-level clustering using the patient identification as a clustering variable, ensuring valid inference in the presence of multiple events per individual. Nevertheless, residual intraindividual correlation cannot be fully excluded and may have resulted in some underestimation of variance, potentially affecting the precision of hazard ratio (HR) estimates. HRs, 95% CI, and *p* values (for H_0: HR = 1) for covariates were estimated. The primary covariates were the number of prior attacks, sex, and age at the time of EDSS change or last EDSS within an EDSS episode. Furthermore, as both a higher number of measured EDSS scores and a higher baseline EDSS score (which lowers the threshold for defining CDI or CDW) could theoretically increase the probability of detecting these outcomes, the model was adjusted for the number of EDSS assessments per episode and the baseline EDSS score. Separate models were constructed for CDI and CDW outcomes, as well as for patients with AQP4-IgG+ NMOSD and MOGAD. In models targeting CDI, only episodes with CDI or without EDSS change were included (and vice versa for CDW models). To assess the relationship between the number of EDSS scores within an EDSS episode and the time between the baseline EDSS score and the changed EDSS score that led to CDI/CDW, we calculated the Spearman rank correlation coefficient ρ and corresponding *p* value (for H_0: ρ = 0). We additionally calculated AAR for myelitis (AAR-myelitis) and optic neuritis (AAR-optic neuritis) events (AAR for other phenotypes were not calculated because of the low number of events). For the calculation of the AAR, the interval between the first symptom and the EDSS change was used, and estimates were obtained using negative binomial regression models. To analyze FS and ambulation index score changes within EDSS episodes, we calculated the difference between the FS/ambulation index score at baseline and at CDI, CDW, or at the last available EDSS assessment in episodes without EDSS change. We determined the proportion of EDSS episodes showing FS/ambulation index score improvement among CDI episodes and worsening among CDW episodes, and among those episodes without EDSS change. All analyses were performed using a script written in Python and R.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants were enrolled in the NEMOS registry and provided written informed consent for data collection and analysis. Ethical approval was granted by each local ethics committee.

Figure 1 Schematic Definition of an EDSS Episode With Confirmed Disability Improvement (CDI) and Worsening (CDW)



Each EDSS episode consisted of at least 3 EDSS scores. The index EDSS score ($EDSS_i$) was defined as an EDSS score at least 90 days postattack, followed by a second changed EDSS score ($EDSS_{change}$) ± 0.5 EDSS steps if $EDSS_i$ score was ≥6.0, ± 1.0 EDSS steps if $EDSS_i$ score was 1.0–5.5, and +1.5 if $EDSS_i$ score was 0, and a subsequent confirmatory EDSS score ($EDSS_{confirmation}$) obtained at least 6 months after the $EDSS_{change}$ score. EDSS = Expanded Disability Status Scale.

Data Availability

Deidentified data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Demography

A total of 307 patients from 24 centers met the inclusion criteria (AQP4-IgG+ NMOSD: n = 202, MOGAD: n = 105, Table 1). Across all patients, 338 EDSS episodes were recorded, with 229 episodes in patients with AQP4-IgG+ NMOSD and 109 in patients with MOGAD. EDSS scores documented from 05/2000 to 12/2023 were analyzed for this study. Of the 307 patients, 284 contributed a single EDSS episode, while 23 (19 patients with AQP4-IgG+ NMOSD) contributed 2 or more episodes. The overall cohort was predominantly female (75%), with a significantly higher proportion in AQP4-IgG+ NMOSD (88%) than in MOGAD (49%). The median age at disease manifestation was slightly higher in patients with AQP4-IgG+ NMOSD than in patients with MOGAD. Similarly, the age at the time of EDSS change (in individuals with CDI/CDW episodes) or at the last EDSS assessment (in individuals without EDSS change) was significantly higher in AQP4-IgG+ NMOSD. The median first recorded EDSS score was higher in patients with AQP4-IgG+ NMOSD compared with patients with MOGAD.

Confirmed Disability Improvement and Confirmed Disability Worsening Independent of Attacks in Patients With AQP4-IgG+ NMOSD and MOGAD

Overall, we observed CDI in 88/338 (26%) and CDW in 51/338 (15%) EDSS episodes (from 307 patients, Table 1). The proportion of EDSS episodes with CDI did not differ between patients with AQP4-IgG+ NMOSD (55/202 patients, 27%; 61/229 episodes, 27%) and MOGAD (26/105 patients, 25%; 27/109 episodes, 25%). The proportion of episodes with CDW was slightly higher in patients with AQP4-IgG+ NMOSD (37/202 patients, 18%; 41/229 episodes, 18%) compared with patients with MOGAD (10/105 patients, 10%; 10/109 episodes, 9%). Adjusted annualized CDI and CDW rates were comparable between patients with AQP4-IgG+ NMOSD and MOGAD. Likewise, adjusted annualized CDI (AQP4-IgG+ NMOSD: 0.059, 95% CI 0.019–0.186; MOGAD: 0.047, 95% CI 0.008–0.268) and CDW rates (AQP4-IgG+ NMOSD: 0.030, 95% CI 0.008–0.104; MOGAD: 0.010, 95% CI 0.000–0.252) estimated using a longer postattack threshold (180 days) did not differ significantly from those estimated using the shorter threshold (90 days). In patients with AQP4-IgG+ NMOSD and MOGAD, there were no differences in the proportion of female patients, age at disease manifestation, or age at EDSS change among those with CDI, CDW, or no EDSS change (Tables 2 and 3). Patients with AQP4-IgG+ NMOSD with CDI showed shorter intervals from disease manifestation to EDSS change compared with those with CDW or no EDSS change. Similarly, patients with MOGAD with CDI had a shorter time to EDSS change than those without EDSS change. Among patients with AQP4-IgG+ NMOSD, the median EDSS episode length was shorter in those with CDI compared with those with CDW or no EDSS change. In contrast, no significant differences in EDSS episode length were observed among the 3 subgroups in MOGAD. In patients with AQP4-IgG+ NMOSD, EDSS episodes with CDI or CDW had a higher median number of recorded EDSS scores compared with episodes without EDSS change. In MOGAD, EDSS episodes with CDI had a higher median number of recorded EDSS scores compared with those without EDSS change. In patients with AQP4-IgG+ NMOSD and MOGAD, the median EDSS score difference (last minus first EDSS within an EDSS episode) was −1.0 in episodes with CDI and 1.0 in those with CDW. There were no significant differences in the AAR, AAR-myelitis, or AAR-optic neuritis across CDI, CDW, and no EDSS change groups in either AQP4-IgG+ NMOSD or MOGAD.

Changes in FSS and Ambulation Index Score in Patients With AQP4-IgG+ NMOSD and MOGAD

We assessed the proportion of EDSS episodes with FSS improvement or worsening within each EDSS outcome category (Table 4). In AQP4-IgG+ NMOSD, CDI episodes more frequently showed improvement in bowel and bladder function and ambulation index scores compared with episodes without EDSS change. Conversely, CDW episodes more often demonstrated worsening in pyramidal and visual function, as well as ambulation index scores relative to episodes without EDSS change. In MOGAD, CDI episodes were associated with more frequent visual function improvement compared with episodes without EDSS change, whereas CDW episodes showed a higher proportion of bowel and bladder worsening.

Clinical Variables Associated With CDI and CDW Independent of Attacks

A lower number of prior attacks was significantly associated with a higher CDI rate in AQP4-IgG+ NMOSD (Table 5). The time to CDI in 25% of EDSS episodes was approximately 2.6-fold longer in the subgroup with more than 1 prior attack (2.85 years) compared with those with only 1 prior attack (1.09 years, $p = 0.02$, log-rank test, Figure 2). Younger age at EDSS change was associated with an increased CDI rate in both AQP4-IgG+ NMOSD and MOGAD. Notably, both a higher number of documented EDSS scores and a higher baseline EDSS score were associated with an increased CDI rate in individuals with AQP4-IgG+ NMOSD and MOGAD. However, the number of documented EDSS scores did not correlate with the time between the baseline EDSS score and the EDSS score change that led to CDI or CDW, respectively (AQP4-IgG+ NMOSD: $\rho = 0.01$, $p = 0.89$, n = 229; MOGAD: $\rho = 0.18$, $p = 0.07$, n = 109; Spearman correlation, H_0: $\rho = 0$). A lower number of prior attacks was associated with a higher CDW rate in individuals with MOGAD, whereas no association was found in individuals with AQP4-IgG+ NMOSD.

Table 1 Demographic and Clinical Characteristics and Confirmed Disability Improvement and Worsening in Patients With AQP4-IgG+ NMOSD and MOGAD

	All	AQP4-IgG+ NMOSD	MOGAD	*p* Value
Number of patients	307	202	105	—
Number of female patients, (%)	229 (75)	178 (88)	51 (49)	<0.001‡
Median (IQR) age at manifestation, y	41 (30 to 52)	43 (32 to 55)	35 (26 to 45)	<0.001#
Median (IQR) first EDSS score	3.0 (1.5 to 4.0)	3.5 (2.0 to 5.0)	2.0 (1.0 to 3.0)	<0.001#
Median (IQR) age at EDSS change/last EDSS, y	53 (39 to 62)	56 (45 to 64)	41 (35 to 55)	<0.001#
Number of patients with CDI, (%)	81 (26)	55 (27)	26 (25)	0.89‡
Number of patients with CDW, (%)	47 (15)	37 (18)	10 (10)	0.09‡
Number of patients with CDW and CDI, (%)	11 (4)	10 (5)	1 (1)	—
Number of EDSS episodes	338	229	109	—
Median (IQR) EDSS episode length, y	3.2 (2.0 to 4.7)	3.3 (2.0 to 5.0)	3.0 (2.0 to 4.3)	0.06#
Number of episodes with CDI, (%)	88 (26)	61 (27)	27 (25)	0.82‡
Number of episodes with CDW, (%)	51 (15)	41 (18)	10 (9)	0.05‡
Annualized CDI rate (95% CI)	0.084 (0.068 to 0.103)	0.083 (0.065 to 0.107)	0.086 (0.059 to 0.125)	—
Adjusted annualized CDI rate (95% CI)	0.100 (0.047 to 0.213)	0.083 (0.029 to 0.233)	0.057 (0.012 to 0.277)	—
Annualized CDW rate (95% CI)	0.049 (0.037 to 0.064)	0.056 (0.041 to 0.076)	0.032 (0.017 to 0.059)	—
Adjusted annualized CDW rate (95% CI)	0.019 (0.007 to 0.054)	0.025 (0.007 to 0.092)	0.036 (0.002 to 0.513)	—

Abbreviations: AQP4-IgG+ NMOSD = aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder; CDI = confirmed disability improvement; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.
p values result from χ^2 (‡) or Mann-Whitney *U* test (#, AQP4-IgG+ NMOSD vs MOGAD). Annualized rates were adjusted for the number of EDSS scores obtained during an EDSS episode, baseline EDSS score, and age at EDSS change or last EDSS score.

Discussion

In this longitudinal, multicenter cohort study using the German NEMOS registry, we report for the first time on CDI in a large cohort of patients with AQP4-IgG+ NMOSD and MOGAD. We estimated the proportion of CDI and CDW in these cohorts and identified factors contributing to CDI and CDW.

Overall, 27% of all EDSS episodes showed CDI in AQP4-IgG+ NMOSD and 25% in MOGAD. A lower number of attacks (in individuals with AQP4-IgG+ NMOSD) and a younger age (in individuals with AQP4-IgG+ NMOSD and those with MOGAD) were associated with a higher CDI rate.

In recent studies on CDI in MS it has been emphasized that CDI might be an interesting and complementary outcome measure for clinical studies.[17] CDI has not been reported so far in AQP4-IgG+ NMOSD and MOGAD, and the general concept of irreversible clinical deterioration after attacks, especially for AQP4-IgG+ NMOSD, should be scrutinized. Factors which may contribute to CDI include reversible damage after attacks, potential repair mechanisms, and reserve capacity within the CNS. We found that a lower number of preceding attacks was associated with CDI in individuals with AQP4-IgG+ NMOSD. This reflects that each attack and lesion influences the extent of neuronal injury and thus determines clinical improvement and reduces the chance of recovery from subsequent attacks. In addition, prolonged effects of prompt and intensive attack treatments (e.g., high-dose glucocorticoids with/without oral tapering or apheresis) and also intensive and ongoing physical therapy, as well as optimizing symptomatic therapy, may lead to CDI.[20-22] We also identified younger age being associated with CDI in AQP4-IgG+ NMOSD and MOGAD. In line with this, a previous NEMOS study (from the same underlying cohort, but including patients with NMOSD without AQP4-IgG) showed that patients with late-onset NMOSD (≥50 years) had a higher rate of incomplete attack recovery and a higher frequency of relapse-associated worsening compared with younger individuals, indicating a more pronounced irreversible deficit. In addition, this older patient group reached an EDSS score of 4 earlier.[23] Particularly in older patients, treatment de-escalation or even treatment interruption is more frequently discussed, potentially because of side effects such as infections and age-related changes of the immune system related to immunosenescence. These considerations should therefore be carefully weighed against the increased risk of poorer attack recovery and a reduced chance of disability improvement.[24]

Table 2 Clinical Characteristics of EDSS Episodes With Confirmed Disability Improvement, Confirmed Disability Worsening, and No EDSS Change Independent of Attacks in Patients With AQP4-IgG+ NMOSD

				p Value		
	CDI	CDW	No EDSS change	CDI vs CDW	CDI vs no EDSS change	CDW vs no EDSS change
Number of EDSS episodes	61	41	127	—	—	—
Number of patients	55	37	123	—	—	—
Number of female patients (%)	47 (85)	33 (89)	110 (89)	0.94‡	0.51‡	0.95‡
Median (IQR) age at manifestation, y	45 (37 to 56)	43 (36 to 55)	43 (30 to 54)	0.56#	0.18#	0.59#
Median (IQR) age at EDSS change, y	55 (48 to 61)	59 (46 to 66)	55 (43 to 64)	0.22#	0.94#	0.28#
Median (IQR) time from manifestation to EDSS change, y	6.1 (2.9 to 12.5)	12.2 (6.4 to 17.1)	9.3 (5.6 to 14.8)	<0.01#	<0.01#	0.31#
Median (IQR) EDSS episode length, y	2.6 (1.6 to 3.8)	3.5 (2.0 to 5.6)	4.0 (2.2 to 5.2)	0.04#	<0.001#	0.56#
Median (IQR) number of EDSS scores	6 (5 to 11)	8 (5 to 12)	4 (3 to 5)	0.38#	<0.001#	<0.001#
Median (IQR) EDSS score difference	−1.0 (−1.5 to −1.0)	1.0 (1.0 to 2.0)	0.0 (0.0 to 0.5)	<0.001#	<0.001#	<0.001#
AAR (95% CI)	0.490 (0.363 to 0.662)	0.390 (0.276 to 0.553)	0.417 (0.342 to 0.508)	—	—	—
AAR-myelitis (95% CI)	0.308 (0.223 to 0.424)	0.250 (0.173 to 0.361)	0.244 (0.198 to 0.302)	—	—	—
AAR-optic neuritis (95% CI)	0.099 (0.066 to 0.149)	0.077 (0.048 to 0.121)	0.108 (0.085 to 0.139)	—	—	—

Abbreviations: AAR = annualized attack rate; AQP4-IgG+ NMOSD = aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder; CDI = confirmed disability improvement; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; IQR = interquartile range.
p values result from χ^2 (‡) or Mann-Whitney *U* test (#). AAR was calculated from disease manifestation to EDSS change/last EDSS score.

The proportion of EDSS episodes with CDW was 18% in AQP4-IgG+ NMOSD, which was approximately twice as high as the 9% observed in MOGAD.

In recent years, the concept of PIRA has emerged and was initially described in MS.[25-28] Usually, patients with AQP4-IgG+ NMOSD acquire disability through incomplete recovery from attacks rather than PIRA.[29] However, in 2 placebo-controlled phase III studies, 1 evaluating ravulizumab and the other inebilizumab for AQP4-IgG+ NMOSD, a small fraction of patients (up to 10%) experienced EDSS worsening without an associated attack.[30,31] Further studies on CDW could confirm that a small fraction of patients with NMOSD and also—to a minor proportion—with MOGAD experience PIRA, but detailed analysis of associated risk factors were not performed.[14-16] Our study confirmed the occurrence of CDW independent of attacks in patients with AQP4-IgG+ NMOSD and MOGAD. The proportion of EDSS episodes with CDW in patients with AQP4-IgG+ NMOSD in our study was lower (18%) than that reported in a previous study (24.5%, 12 out of 49 patients).[14] However, the annualized PIRA rate (0.08, 95% CI 0.05–0.14) was comparable with the (unadjusted) annualized CDW rate in our study (0.056, 95% CI 0.041–0.076). Two other multicentric studies reported a lower PIRA prevalence in AQP4-IgG+ NMOSD of around 2.5%,[15,16] similar to those (around 3.0%) of a smaller cohort study with 33 individuals from Japan.[32] In the Korean study, the authors excluded 9 PIRA events because of confounding factors such as comorbidities, which were not captured in our cohort.[16]

In MOGAD, a previous study identified no PIRA based on 3 visits/EDSS assessments with a median period of 16 months between the baseline EDSS assessment and follow-up and a median period of 11 months between follow-up and confirmation.[33] In our study, the median duration of EDSS episodes (from baseline to the confirmatory EDSS score) associated with CDW was 2.1, with a median of 4 EDSS assessments. The slightly higher number of EDSS assessments in our study may partly explain (the higher likelihood of detecting) CDW in individuals with MOGAD. In a previous study the proportion of CDW in MOGAD was reported at 11.1%, with an annualized PIRA rate of 0.04 (95% CI 0.01–0.11), closely aligning with our findings: a proportion of EDSS episodes with CDW of 9% and an (unadjusted) annualized rate of 0.032 (95% CI 0.017–0.059).[14]

The differences in the proportion of EDSS episodes with CDW may be due to methodologic aspects: For example, the above mentioned previous study used a 3- to 6-month confirmation period for EDSS progression, whereas our analysis applied a 6-month confirmation period.[14] In addition, their study followed

Table 3 Clinical Characteristics of EDSS Episodes With Confirmed Disability Improvement, Confirmed Disability Worsening, and No EDSS Change Independent of Attacks in Patients With MOGAD

				p Value		
	CDI	CDW	No EDSS change	CDI vs CDW	CDI vs no EDSS change	CDW vs no EDSS change
Number of EDSS episodes	27	10	72	—	—	—
Number of patients	26	10	70	—	—	—
Number of female patients (%)	12 (46)	2 (20)	38 (54)	0.24‡	0.76‡	0.09‡
Median (IQR) age at manifestation, y	37 (28 to 44)	35 (23 to 44)	34 (22 to 46)	0.66#	0.52#	0.84#
Median (IQR) age at EDSS change, y	40 (32 to 52)	43 (37 to 52)	42 (36 to 58)	0.57#	0.19#	0.80#
Median (IQR) time from manifestation to EDSS change, y	3.6 (2.2 to 6.3)	4.0 (2.9 to 15.2)	6.3 (3.9 to 15.0)	0.31#	<0.01#	0.39#
Median (IQR) EDSS episode length, y	2.5 (1.8 to 3.8)	2.1 (1.6 to 3.3)	3.2 (2.0 to 4.5)	0.67#	0.23#	0.31#
Median (IQR) number of EDSS scores	5 (4 to 8)	4 (3 to 6)	4 (3 to 5)	0.06#	<0.001#	0.37#
Median (IQR) EDSS score difference	−1.0 (−1.0 to −1.0)	1.0 (1.0 to 1.5)	0.0 (0.0 to 0.0)	<0.001#	<0.001#	<0.001#
AAR (95% CI)	0.636 (0.402 to 1.007)	0.306 (0.138 to 0.676)	0.422 (0.322 to 0.554)	—	—	—
AAR-myelitis (95% CI)	0.077 (0.036 to 0.163)	0.099 (0.037 to 0.268)	0.116 (0.083 to 0.163)	—	—	—
AAR-optic neuritis (95% CI)	0.377 (0.229 to 0.621)	0.134 (0.053 to 0.339)	0.174 (0.128 to 0.238)	—	—	—

Abbreviations: AAR = annualized attack rate; CDI = confirmed disability improvement; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.
p values result from Mann-Whitney U (#), χ^2 test (‡). AAR was calculated from disease manifestation to EDSS change/last EDSS score.

a monocentric design, in contrast to the multicentric approach in our work. Such discrepancies may also arise from differences in registry structures and, potentially, from variations in the average frequency of visits and EDSS assessment intervals. Furthermore, national differences in access to high-efficacy immunotherapies could influence long-term outcomes and should be addressed in future studies.[34] In AQP4-IgG+ NMOSD, EDSS episodes associated with CDI were significantly shorter in duration, and episodes associated with CDI or CDW included significantly more EDSS assessments compared with episodes without EDSS change. Based on these findings and given the fact that previous studies with shorter observation time revealed a lower proportion of EDSS episodes with CDW, reporting only proportions—especially when comparing subgroups or disease entities—without accounting for these confounders should be approached with caution. We therefore suggest focusing on (annualized) rates instead. These can—as demonstrated in this study—be adjusted for covariates such as the number of EDSS assessments, the time from baseline EDSS to the EDSS change leading to CDI or CDW, and age, thereby correcting for intrinsically varying observation times.

We found that a lower number of attacks was associated with a higher CDW rate in patients with MOGAD, which appears contradictory. However, the overall number of patients and EDSS episodes with CDW was low. Consequently, the corresponding confidence intervals were relatively wide in some MOGAD CDW models, indicating limited precision of the estimates. These findings should therefore be interpreted with caution. It is possible that individuals with MOGAD with lower disease activity (i.e., fewer relapses over time) are associated with more severe attacks (e.g., with longitudinally extensive transverse myelitis). This interpretation is supported by an increase in the AAR of optic neuritis in EDSS episodes with CDI and a slightly elevated AAR of myelitis in EDSS episodes with CDW among individuals with MOGAD. These observations may suggest that CDI and CDW are driven by distinct clinical phenotypes as also reflected by FSS (see below). Only recent studies demonstrated better outcomes after early plasma exchange for acute MOGAD attacks, but apheresis therapy is used as first-line treatment in a minority of patients.[7,35] Whether prompt and rigorous attack treatment has an influence on CDI and CDW needs to be determined.

The presence of both CDI and CDW within the same cohort indicates that disability trajectories in AQP4-IgG+ NMOSD and MOGAD are heterogeneous and dynamic. At the cohort level, opposing directions of change may balance each other, resulting in an overall stable distribution of disability despite substantial individual-level improvement or worsening. Thus,

Table 4 Proportion of EDSS Episodes With Functional System and Ambulation Index Score Improvement or Worsening According to EDSS Outcome Category

	Number of episodes with FS score improvement/total number of CDI episodes (number of patients)			Number of episodes with FS score worsening/total number of CDW episodes (number of patients)		
	CDI	No EDSS change	*p* Value	CDW	No EDSS change	*p* Value
AQP4-IgG+ NMOSD						
Pyramidal function	17/45 (39)	20/84 (84)	0.11	15/28 (26)	18/84 (84)	<0.01
Cerebellar function	10/44 (39)	17/82 (82)	0.82	4/27 (25)	18/82 (82)	0.58
Brainstem function	5/44 (38)	13/84 (84)	0.60	8/28 (26)	17/84 (84)	0.43
Sensory function	18/45 (39)	24/85 (85)	0.24	10/28 (26)	16/85 (85)	0.08
Bowel and bladder function	16/45 (39)	9/85 (85)	<0.001	8/28 (26)	24/85 (85)	1.00
Visual function	11/43 (38)	20/84 (84)	0.83	11/28 (26)	16/84 (84)	0.04
Mental function	4/44 (39)	11/81 (81)	0.57	8/28 (26)	24/81 (81)	1.00
Ambulation index	15/38 (33)	9/68 (67)	<0.01	10/20 (20)	9/68 (67)	<0.01
MOGAD						
Pyramidal function	8/23 (22)	10/62 (60)	0.08	0/7 (7)	9/62 (60)	0.58
Cerebellar function	5/23 (22)	7/61 (59)	0.30	2/8 (8)	12/61 (59)	0.66
Brainstem function	2/23 (22)	4/62 (60)	0.66	2/8 (8)	10/62 (60)	0.62
Sensory function	8/23 (22)	12/63 (61)	0.15	2/8 (8)	9/63 (61)	0.60
Bowel and bladder function	2/23 (22)	6/62 (60)	1.00	5/8 (8)	5/62 (60)	<0.001
Visual function	12/23 (22)	8/62 (60)	<0.001	2/7 (7)	9/62 (60)	0.31
Mental function	3/23 (22)	3/62 (60)	0.34	2/7 (7)	11/62 (60)	0.61
Ambulation index	3/20 (19)	5/55 (53)	0.43	1/3 (3)	4/55 (53)	0.24

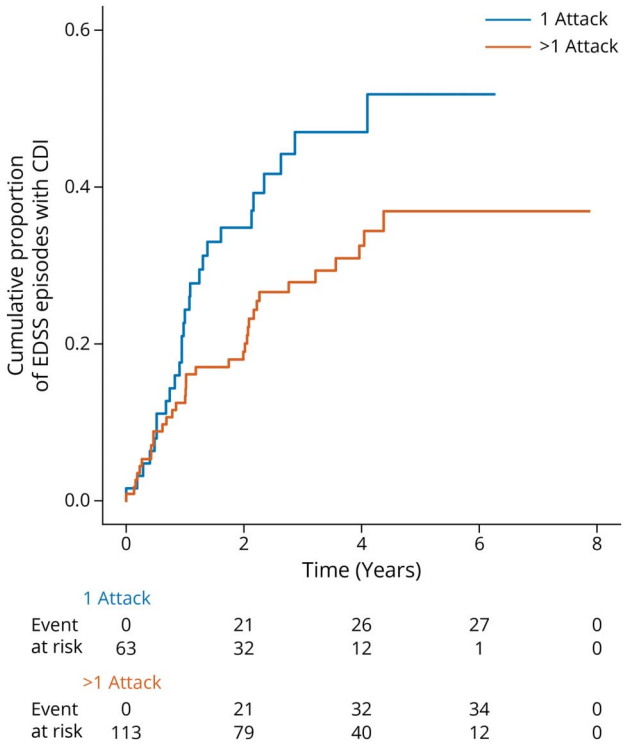
Abbreviations: AQP4-IgG+ NMOSD = aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder; CDI = confirmed disability improvement; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.
Values represent the number of EDSS episodes with functional system (FS) score improvement (for CDI comparisons, numerator) or worsening (for CDW comparisons, numerator) and the total number of EDSS episodes within the respective EDSS outcome group (CDI, CDW, or no EDSS change) for which the corresponding FS scores were available (denominator). The number of patients included in this analysis based on available data is shown in parentheses. Overall numbers of EDSS episodes were n = 229 for AQP4-IgG+ NMOSD (CDI: n = 61, CDW: n = 41, no EDSS change: n = 127) and n = 109 for MOGAD (CDI: n = 27, CDW: n = 10, no EDSS change: n = 72). Denominators vary across functional systems because of missing scores. *p* values result from Fisher exact test.

Table 5 Andersen-Gill Cox Proportional Hazards Model With Robust Standard Errors Clustered by Patient to Account for Recurring Events

	AQP4-IgG+ NMOSD				MOGAD			
	CDI		CDW		CDI		CDW	
	HR (95% CI), n	*p* Value	HR (95% CI), n	*p* Value	HR (95% CI), n	*p* Value	HR (95% CI), n	*p* Value
Number of prior attacks	0.89 (0.82–0.97), 188	<0.01	1.00 (0.94–1.07), 168	0.92	0.91 (0.79–1.05), 99	0.19	0.73 (0.55–0.97), 82	0.03
Age	0.96 (0.94–0.99), 188	<0.01	1.00 (0.98–1.03), 168	0.85	0.96 (0.94–0.99), 99	<0.01	0.98 (0.93–1.03), 82	0.37
Sex (male)	1.32 (0.64–2.70), 188	0.45	0.53 (0.18–1.56), 168	0.25	1.43 (0.62–3.26), 99	0.40	5.29 (0.75–37.54), 82	0.10
Number of EDSS scores	1.15 (1.09–1.22), 188	<0.001	1.23 (1.13–1.34), 168	<0.001	1.25 (1.08–1.44), 99	<0.01	1.03 (0.71–1.51), 82	0.87
Baseline EDSS score	1.29 (1.13–1.48), 188	<0.001	0.91 (0.76–1.08), 168	0.26	1.43 (1.21–1.69), 99	<0.001	1.73 (0.97–3.11), 82	0.07

Abbreviations: AQP4-IgG+ NMOSD = aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder; CDI = confirmed disability improvement; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.

Figure 2 Cumulative Proportion of EDSS Episodes With Confirmed Disability Improvement (CDI) in Individuals With AQP4-IgG+ NMOSD, Stratified by the Number of (Prior) Attacks



Analyses allowed for recurrent CDI events within individuals. AQP4-IgG+ NMOSD = aquaporin-4 immunoglobulin G–seropositive neuromyelitis optica spectrum disorder; EDSS = Expanded Disability Status Scale.

group-level stability should not be interpreted as the absence of clinically meaningful disability change. It must be acknowledged that small EDSS changes at the individual level may indeed indicate true disability improvement or worsening; however, it may also reflect biologic fluctuation, measurement variability, or interrater differences rather than true structural disease modification. Thus, in a cohort with overall stable disability distribution, opposing random variations may mimic dynamic individual trajectories without indicating genuine progression or recovery. Our findings argue against a uniformly progressive disease model and support the use of analytic approaches that capture both improvement and worsening to more accurately characterize disease evolution and treatment effects.

Clinical assessment of disease-related disability in NMOSD, MOGAD, and MS is typically performed using the EDSS. So far, a detailed analysis of FS and ambulation index scores in the context of CDI and CDW have not been reported. We demonstrated that certain subscales (pyramidal, visual, bowel and bladder, ambulation index) contribute more strongly to CDI or CDW, in line with typical disease manifestations in NMOSD and MOGAD. In AQP4-IgG+ NMOSD and MOGAD, adult disease phenotypes are largely confined to optic neuritis and myelitis. Myelitis-related disability is primarily reflected in pyramidal, sensory, and, specifically for MOGAD, in sphincter FS scores. However, sphincter function is captured by relatively coarse EDSS categories and may be influenced by subjective reporting, nonstandardized or missing diagnostic examinations (e.g., for neurogenic bladder dysfunction). Overall, interrater variability or transient factors such as infections or medication effects may affect the detection of CDI or CDW events. Thus, although multidimensional, EDSS scores may not fully capture disability dynamics in these conditions. Subtle numerical changes in FS scores may nevertheless reflect clinically meaningful improvements or deteriorations that are insufficiently reflected in the total EDSS score. Consequently, the proportion of EDSS episodes with CDI or CDW may be underestimated when relying solely on EDSS.

A limitation of this study is the temporally non-standardized assessment of EDSS scores in this real-world setting. The frequency of EDSS evaluations may have varied between patients, potentially reflecting individualized disease-monitoring practices influenced by differences in disease activity. To at least partially address this limitation computationally, we adjusted for observation time in our statistical models, as this variable was also associated with the number of recorded EDSS scores. Nevertheless, it remains possible that stable disease courses are underrepresented in this study because of less frequent visits. Furthermore, sociodemographic factors such as limited access to specialized care bias the visit frequency and comorbidities are important confounders. Notably, owing to the retrospective design of our study, factors associated with CDI should be interpreted as hypothesis-generating rather than predictive and should be verified in future prospective studies. Although this study included 338 EDSS assessments from 307 patients, the low incidence of CDW and CDI warrants caution, as it increases the risk of type II errors when comparing the rates and incidences of CDW and CDI between AQP4-IgG+ NMOSD and MOGAD. Regarding further variables associated with CDW and CDI, we could not account for effects such as physical therapy and socioeconomic factors which could significantly contribute to alterations in body functions, reflected by EDSS changes. Moreover, it remains unclear how the type and duration of long-term immunotherapy and concomitant steroid therapy influence the risk of CDI or CDW. This aspect may also be a reason why, especially when considering differences in approval status and feasibility of immunotherapies, the results reported here may not be fully generalizable to populations with different healthcare systems, genetic backgrounds, or disease phenotypes. Information on treatment of acute attacks was not available and could therefore not be controlled for. The comparable adjusted annualized CDI and CDW rates observed when applying different postattack thresholds (including 180 days) argue against a major influence of prolonged treatment-related effects on the results. However, the number of events was limited, reducing statistical power and a modest prolonged treatment-related effect

cannot be entirely excluded. Another limitation is the potential interrater variability across and within the participating centers, although EDSS assessments are performed by experienced raters at regular visits in NEMOS centers. Although this reflects real-world clinical practice, it could have affected measurement reliability. Even in clinically stable disease, EDSS scores may vary because of day-to-day functional fluctuations, rater-dependent differences, or subtle changes in functional system scoring, which may lead to apparent CDI or CDW events independent of true biologic change. Taken together, these potential sources of bias in EDSS acquisition highlight that, even in routine clinical practice, optimal disease monitoring would benefit from standardized EDSS assessments and additional patient-reported outcome measures with a clear protocol specifying when EDSS scores should be obtained (in remission-, attack-, and attack-remission–related). Moreover, we were not able to evaluate the association of MRI parameters (e.g., lesion size and distribution and number of lesions) and paraclinical disease activity (new silent lesions) with CDW and CDI. Nevertheless, the occurrence of silent lesions outside of attacks in NMOSD and MOGAD seems to be rare.[36] Moreover, it would be of interest to longitudinally investigate biomarkers such as neurofilament light chains and glial fibrillary acidic protein in context with CDW and CDI, which we were not able to include in this study.[37-39] Recent studies have identified cardiovascular comorbidities and risk factors as being potentially associated with worse disability outcomes, as measured by static EDSS scores or recovery from attacks.[40,41] However, the extent to which these factors—along with other comorbidities and infections—contribute to CDI or CDW remains unclear.

Measuring EDSS changes and detecting CDI and CDW are key aspects of disease monitoring of patients with NMOSD and MOGAD. Our data suggest that effective attack prevention can not only reduce the risk of attack-related disability accumulation in AQP4-IgG+ NMOSD but may also facilitate conditions under which functional improvement (CDI) is more likely to occur. The lower CDI rate in older individuals with AQP4-IgG+ NMOSD and MOGAD underscores the importance of stringent disease control in the elderly to prevent further disability accumulation. As the number of EDSS assessments per episode influenced the probability of detecting CDI and CDW, these variables should be carefully considered when interpreting EDSS dynamics, both in clinical practice and future studies. Besides the role of immunotherapies, further aspects such as comorbidities as well as biomarkers should be addressed in future studies to enable a multimodal monitoring of disease progression or improvement.

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