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Short and Long-Term Effects of Intravenous Methylprednisolone and Plasma Exchange Combination in NMOSD Attacks

Duygu ÖZKAN YAŞARGÜN[1], Ayça Simay ERSÖZ[1], Recai TÜRKOĞLU[1], Erdem TÜZÜN[2]

[1]University of Health Sciences, Haydarpaşa Numune Training and Research Hospital, Department of Neurology, Istanbul, Türkiye
[2]Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, Istanbul, Türkiye

ABSTRACT

Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a debilitating autoimmune condition that, without timely intervention, can lead to severe disability or even death. Neuromyelitis optica spectrum disorder is an inflammatory disease of the central nervous system characterized by severe attacks such as optic neuritis and transverse myelitis. This study compared the short- and long-term effects of high-dose intravenous methylprednisolone (IVMP) and IVMP+plasma exchange (PLEX) treatment regimens.

Methods: The study evaluated changes in patients' Expanded Disability Status Scale (EDSS) scores over a six-month follow-up period by using different ANOVA and linear regression methods.

Results: Both IVMP and IVMP+PLEX treatments resulted in clinical improvement, with the addition of PLEX showing a more significant reduction in EDSS scores, particularly during the long follow-up period. Moreover, seropositive patients (AQP4/MOG-IgG positive) demonstrated a better response to treatment. Age and baseline EDSS scores were identified as key factors influencing post-treatment improvement.

Conclusion: Our results suggest that the addition of PLEX to IVMP treatment might be suitable especially for severe NMOSD attacks.

Keywords: Intravenous methylprednisolone, NMOSD, NMOSD attacks, plasma exchange

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INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a debilitating autoimmune condition that, without timely intervention, can lead to severe disability or even death. Neuromyelitis optica spectrum disorder is an inflammatory disease of the central nervous system (CNS) characterized by severe attacks of optic neuritis and transverse myelitis. In most cases, NMOSD is associated with pathogenic immunoglobulin G (IgG) antibodies against aquaporin-4 (AQP4) (1). The Aquaporin-4 (AQP-4) IgG antibody identified in seropositive patients targets the AQP-4 water channels located on the feet of astrocytes in the CNS.

Neuromyelitis optica spectrum disorder attacks are one of the neurological emergencies which can result in respiratory failure that may lead to death, especially during severe attacks. Patients can present with different variations of six clinical core characteristics defined as acute optic neuritis, acute myelitis, area postrema syndrome, brainstem syndrome, diencephalic syndrome, and cerebral syndrome.

Unlike multiple sclerosis; NMOSD rarely follows a progressive course, however, inflammatory changes due to attacks lead to disability accumulation. Neuromyelitis optica spectrum disorder attacks drive disability progression, highlighting the urgency of effective treatment.

Highlights

- **Early diagnosis and personalized treatment strategies are important in NMOSD.**
- **AQP4-IgG positive patients demonstrated a better response to PLEX and IVMP treatment.**
- **Despite its high cost, adding PLEX to IVMP is recommended for severe NMOSD attacks.**

High-dose intravenous methylprednisolone (IVMP) (1 gram/day for 3–7 days) forms the initial treatment protocol during attacks to prevent disease-related disability. While IVMP remains the first-line treatment for NMOSD attacks, its limitations necessitate adjunct therapies like plasma exchange (PLEX). Despite its cost, PLEX therapy appears to be highly effective due to its targeting of specific antibodies, complement cascade and various pro-inflammatory proteins. Studies reveal a

Correspondence Address: Duygu Özkan Yaşargün, Department of Neurology, University of Health Sciences, Haydarpaşa Numune Training and Research Hospital, Istanbul, Türkiye •
E-mail: duyzkan01@gmail.com
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significant improvement in around 44–75 % of NMOSD patients treated with PLEX (2–4).

Although there is no evidence-based data on the optimal timing for initiating PLEX therapy according to the severity of the attacks; according to the American Society for Apheresis guidelines, plasma exchange has taken its place as the second-line treatment in acute refractory NMOSD patients.

While there are publications on the effectiveness of PLEX therapy on NMOSD attacks, the number of studies comparing it with IVMP is quite limited. Some studies have shown that delaying PLEX therapy does not affect attack sequelae; however, in three studies involving all patients with CNS demyelination except NMOSD patients, early PLEX therapy was shown to significantly reduce disability scores in patients after 6 months (5–7).

We aimed to retrospectively analyze the short-term (during relapse and discharge) and long-term (1, 3, and 6 months after treatment) prognoses of patients admitted to our neurology clinic with NMOSD attacks, who received IVMP or IVMP + PLEX therapy, investigate types of attacks more frequently associated with PLEX therapy and evaluate the variability of treatment response to PLEX between seropositive (AQP-4-IgG or MOG-IgG positive) and seronegative patients.

METHODS

Study design

All consecutive patients with NMOSD were admitted between January 2012 and January 2024 to Haydarpaşa Numune Training and Research Hospital. Patient records were retrospectively collected from our MS center database. All patients fulfilled the NMOSD criteria and were treated with either only high dose steroids (1000 mg/day) or high dose steroid + PLEX therapy.

Patients who met the seropositive or seronegative NMOSD diagnostic criteria according to the criteria published by the NMO study group (NEMOS) were enrolled in the study. The types of attacks in patients were categorized into six categories: acute optic neuritis, acute myelitis, area postrema syndrome, brainstem syndrome, diencephalic syndrome, and cerebral syndrome.

The patients' files were retrospectively reviewed, and the recorded neurological examination data were used. Expanded Disability Status Scale (EDSS) scores recorded at baseline (before the attack), during the relapse, at discharge, at the 1st month, 3rd month and 6th month of follow-up were also utilized.

The magnetic resonance imaging (MRI) records in the picture archiving and communication system (PACS), the treatment protocol taken before the attack, the time when the treatment started, and the AQP-4/MOG IgG antibody results, as well as the visual acuity examination data, were utilized in the study.

The differences between the baseline clinical scores (EDSS) and succeeding clinical scores (EDSS) of the patients were also considered. Thus, as an additional parameter, clinical score improvement ratio (clinical score during acute attack – final clinical score) / (clinical score during acute attack – baseline clinical score) was determined.

Statistical Analysis

The statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows program version 24.0 (IBM Corp., Armonk, NY). Two main statistical methods were employed: repeated measures ANOVA and linear regression analysis.

Repeated measures ANOVA were conducted to assess the impact of treatment type (IVMP vs. IVMP+PLEX) on the change in Expanded Disability Status Scale (EDSS) scores over different times. Results with p less than 0.05 were considered statistically significant. A linear regression analysis was conducted to examine the factors influencing the recovery score. The assumptions of linear regression, such as linearity, independence, homoscedasticity, and normality of residuals, were checked. The regression model included all predictors to assess their individual contributions to the cure rate. The significance of the predictors was evaluated using t-tests, and the overall fit of the model was assessed using R-squared and adjusted R-squared values.

RESULTS

Demographic and Clinical Variables

Twenty-seven patients with NMOSD (22 women) were included in the study. The ages of these patients ranged from 26 to 65. Additionally, the disease duration of the patients was 2 to 27 years. Clinical data collected from patients specifically for the study are shown in Table 1.

Effect of Relapse Treatment and Other Clinical Variables on EDSS Change

The post-treatment recovery effects of 27 patients with NMOSD included in the study were evaluated by repeated measures ANOVA, which revealed that the EDSS changes after IVMP or IVMP+PLEX treatment were significant [F (3,75)=4.758; p=0.011)]. However, when the between-subject effect on this change was evaluated, the result was not significant.

In the study, ordinal (antibody positivity, attack type, immunotherapy, baseline EDSS levels, OCB type) and numerical (age, disease duration) factors affecting the change in EDSS observed after treatment (discharge, month 1–3 and 6) were also evaluated with Mixed-Design ANCOVA. The results presented in Table 2 demonstrate that no clinical variable had a significant effect on EDSS levels. Age [F (6,21)=2.333; p=0.089] and baseline EDSS level [F (6,54)=2.367; p=0.086] were considered to exert an influence on this change at the trend level. Since the age variable was numeric and some of the groups had less than two variables in baseline EDSS values, post-hoc tests were not applied.

The Effect of the Method Used in Relapse Treatment on Individual EDSS Change

The study included 27 participants, divided into two groups: those receiving IVMP treatment (N=15) and those receiving IVMP+PLEX (N=12) following relapse. The EDSS scores of the participants, measured at various time points (baseline, relapse, discharge, and at 1, 3, and 6 months), were analyzed using a repeated measures ANOVA test. A mixed-design ANOVA test was performed to determine whether the treatment options (IVMP or IVMP+PLEX) had an effect on the change in EDSS values. The analysis revealed that while there was a significant change in EDSS scores from baseline to discharge [F (1,25)=69.948, p<0.001], and at months 1 [F (1,25)=71.337, p<0.001], month 3 [F (1,25)=30.488, p<0.001], and month 6 [F (1,25)=31.143, p<0.001], this change was not influenced by the type of treatment [$F_{basal*discharge*treatment}$ (1,25)=1.796, p=0.192, η^2=0.067; $F_{basal*month1*treatment}$ (1,25)=0.151, p=0.701, η^2=0.006; $F_{basal*month3*treatment}$ (1,25)=0.36, p=0.851, η^2=0.001; $F_{basal*month6*treatment}$ (1,25)=1.219, p=0.280, η^2=0.047].

Nevertheless, when EDSS scores recorded at individual time points were considered, IVMP+PLEX treatment proved to be significantly more effective than IVMP treatment. Figure 1 illustrates the time intervals in

Table 1. Clinical variables of patients with NMOSD

			N	%
Anti-Aqp4/MOG Antibody		Both Negative	15	55.6
		Aqp4 Positive	10	37.0
		MOG Positive	2	7.4
Immunotherapy before relapse		Azathioprine	13	48.1
		Rituximab	5	18.5
		Both	9	33.3
Location of the attack	**Optic nerve**	No	8	29.6
		Yes	19	70.4
	Cerebral	No	25	92.6
		Yes	2	7.4
	Brainstem	No	20	74.1
		Yes	7	25.9
	Spinal Cord	No	14	51.9
		Yes	13	48.1
Relapse Treatment		IVMP	15	55.6
		IVMP+PLEX	12	44.4
Baseline EDSS		1.0	7	25.9
		1.5	10	37.0
		2.0	4	14.8
		2.5	3	11.1
		3.0	2	7.4
		4.0	1	3.7
OCB Type		Type 1	21	77.8
		Type 2	6	22.2

Anti MOG: anti myelin oligodendrocyte glycoprotein; Anti Aqp4: anti aquaporin4 antibody; EDSS: expanded disability status scale; OCB: oligoclonal bands.

Table 2. Summary of mixed-design ANCOVA results for EDSS change from discharge to sixth month

Within-subjects effect			**df**	**F**	**Sig.**	η^2
EDSS x Relapse treatment x	**Age**		4.844	2.333	0.089	0.400
	Disease duration		7.704	0.557	0.788	0.285
	Anti-Aqp4/MOG antibody		4.570	1.490	0.215	0.124
	Immunotherapy		4.268	1.860	0.130	0.150
	Location of the attack	**Optic**	2.047	0.204	0.425	0.037
		Cerebral	2.118	0.286	0.765	0.012
		Brainstem	2.131	0.870	0.461	0.036
		Spinal cord	2.141	1.502	0.222	0.061
	Baseline EDSS		3.301	2.367	0.086	0.208
	OCB Type		2.031	0.845	0.437	0.035

Anti MOG: anti myelin oligodendrocyte glycoprotein; Anti Aqp4: anti aquaporin4 antibody; EDSS: expanded disability status scale; OCB: oligoclonal bands.

which treatment impacts changes in EDSS scores. The treatment type was shown to influence the EDSS changes observed in the period between relapse and 1 month after attack treatment [F (1,25)=10.354, p=0.004)] and also between relapse and 6 months after treatment [F (1,25)=12.605, p=0.002)]. Additionally, the treatment type also significantly affected EDSS score changes measured from the discharge period to month 1 [F (1,25)=6.633, p=0.016)], month 3 [F (1,25)=6.313, p=0.019)], and month 6 [F (1,25)=10.556, p=0.003)].

As shown in Table 3, patients treated with IVMP experienced an average decrease of 0.4 points in EDSS scores from relapse to month 1, whereas those receiving IVMP+PLEX showed a greater reduction of 1.1 points. Moreover, the mean EDSS score difference between relapse and month 6 was 0.7 for IVMP patients, compared to 1.6 for those treated with IVMP+PLEX.

The differences between the EDSS scores measured at discharge and those at months 1, 3, and 6 were found to be influenced by the treatment administered. Specifically, patients who received IVMP treatment experienced a decrease in EDSS scores during months 1 and 3, but this reduction plateaued by month 6. In contrast, patients treated with IVMP+PLEX showed a continued decline in EDSS scores across months 1,

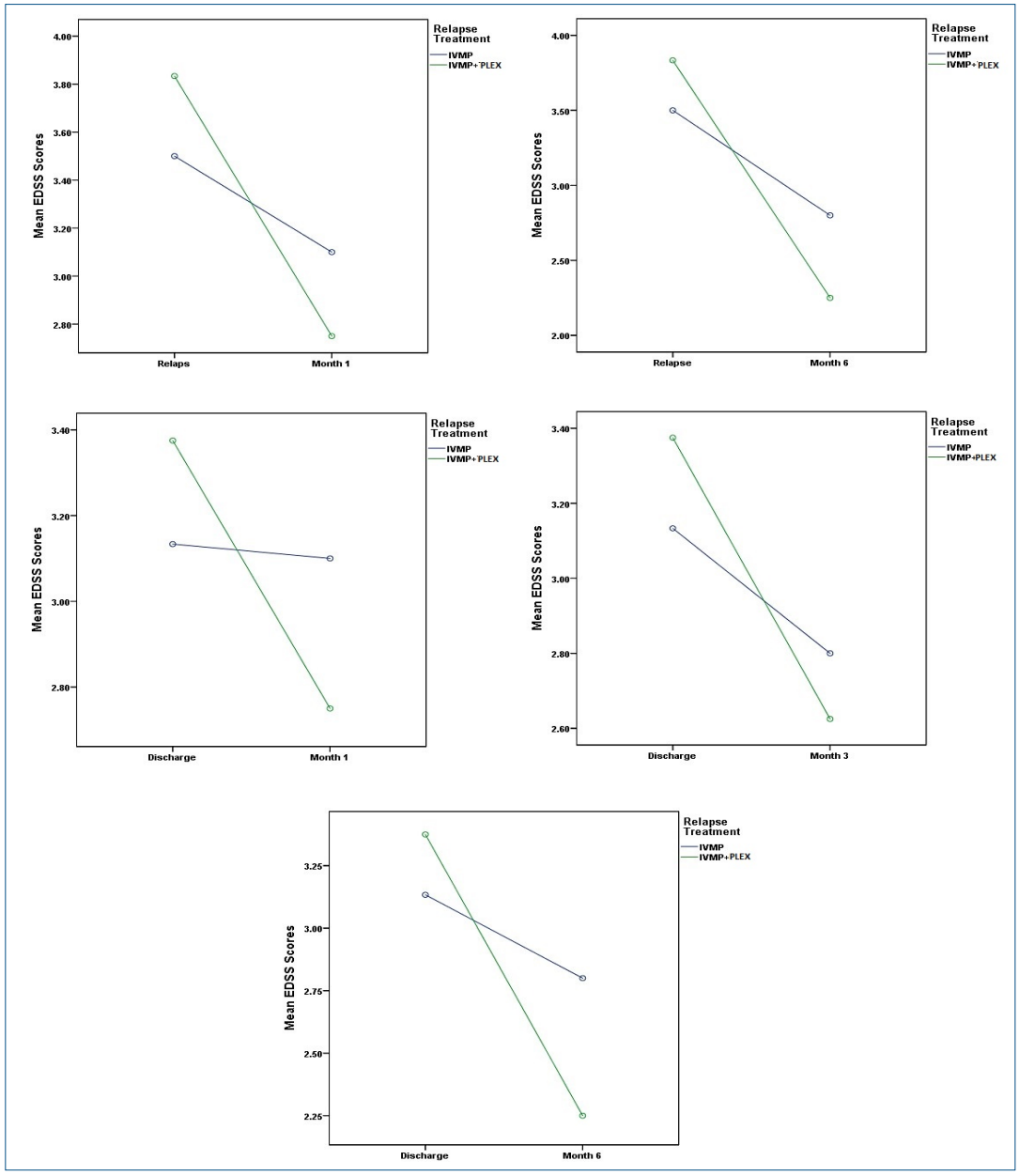

Figure 1. Periods of EDSS change affected by relapse treatment methods.

Table 3. Repeated measures ANOVA results of EDSS means in the evaluated periods

	Relapse											
		Discharge	**F**	**p**	**Month 1**	**F**	**p**	**Month 3**	**F**	**p**	**Month 6**	**F**	**p**
IVMP	3.50±1.05	3.13±1.23	0.256	0.617	3.10±1.07	10.354	0.004	2.80±1.19	13.703	0.066	2.80±1.19	12.605	0.002
IVMP+PLEX	3.83±1.37	3.37±1.41			2.75±1.25			2.62±1.35			2.25±1.23		
		Discharge											
					Month 1	**F**	**p**	**Month 3**	**F**	**p**	**Month 6**	**F**	**p**
IVMP		3.13±1.23			3.10±1.07	6.633	0.016	2.80±1.19	6.313	0.019	2.80±1.19	10.556	0.003
IVMP+PLEX		3.37±1.41			2.75±1.25			2.62±1.35			2.25±1.23		
					Month 1								
								Month 3	**F**	**p**	**Month 6**	**F**	**p**
IVMP					3.10±1.07			2.80±1.19	0.466	0.501	2.80±1.19	1.515	0.230
IVMP+PLEX					2.75±1.25			2.62±1.35			2.25±1.23		
								Month 3					
											Month 6	**F**	**p**
					IVMP			2.80±1.19			2.80±1.19	2.586	0.120
					IVMP+PLEX			2.62±1.35			2.25±1.23		

EDSS: expanded disability status scale; IVMP: intravenous methylprednisolone; PLEX: Plasma exchange.

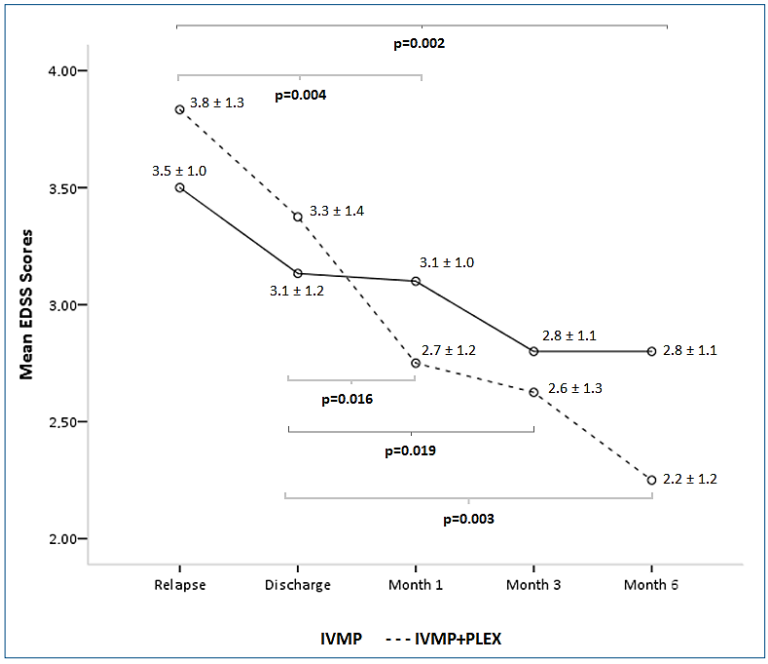

Figure 2. EDSS change due to relapse treatment.

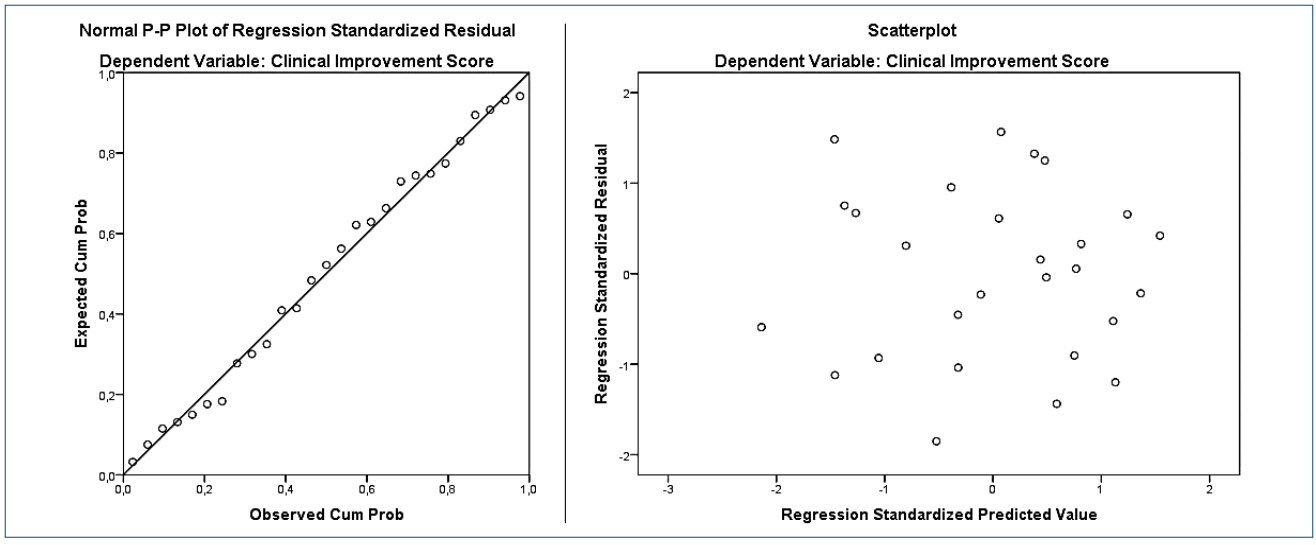

Figure 3. Clinical improvement score.

3, and 6 (Fig. 2). The effect of treatment on EDSS changes seen at other time intervals was not significant.

A Preliminary Linear Regression Model for Prediction of Clinical Improvement Score

The impact of various predictors, including treatment types, on the Clinical Recovery Score was also investigated using a multivariate linear regression model (Fig. 3). Although treatment options did not significantly influence the score, key factors such as age at diagnosis, disease duration, and the presence of Aqp4/MOG antibodies were identified as significant predictors (Formula 1, Table 4).

Formula 1:

Clinical improvement score=1.129 + (-0.01× Age of diagnosis onset) + (-0,034× Duration of disease) + (Aqp4, MOG IgG presence)

A higher proportion of clinical score improvement indicated better response to the treatment. An increase in the baseline EDSS score results in a change of -0.82 units in the proportion of clinical score improvement. Conversely, an increase in disease duration leads to a change of 0.06 units, while the presence of anti-Aqp4/MOG antibodies alters the proportion of clinical score improvement by 0.66 units. Thus, seropositive patients had a better response to treatment.

Table 4. Linear regression results for proportion of clinical score improvement

Predictor	B	SE	Beta	t	p Value
Baseline EDSS	-0.827	0.246	-0.457	-3.363	0.003
Duration of disease	0.063	0.023	-0.292	-2.804	0.010
Anti-Aqp4/MOG antibody	0.660	0.207	0.302	3.193	0.004

Anti MOG: anti myelin oligodendrocyte glycoprotein; Anti-Aqp4: anti aquaporin4 antibody; EDSS: expanded disability status scale; OCB: oligoclonal bands.

DISCUSSION

Plasma exchange has taken its place as the second-line therapy for acute NMOSD attacks when high dose IVMP is not effective enough. The guidelines from the American Academy of Neurology and from the American Society for Apheresis recommend the use of PLEX for the treatment of acute refractory NMOSD patients (8,9).

The rationale for PLEX use in NMOSD is based on the fact that a significant proportion of NMOSD patients are AQP4-antibody seropositive and pathological studies of NMOSD patients show immunoglobulin and activated complement deposition in active brain lesions (10). Plasma exchange reduces pathogenic antibodies, complement components and pro-inflammatory cytokines and the removal of these components can help interrupt the progression of tissue damage (11).

Our study comparing two treatment regimens (high dose IVMP vs high dose IVMP+ PLEX) demonstrates that each treatment resulted in clinical improvement measured by EDSS. In our study, a significant change in EDSS scores was observed from baseline to months 1, 3, and 6. This change was more prominent with the IVMP + PLEX regimen.

Different studies suggest a mean decline of 0.8–1.8 in EDSS after PLEX treatment (12). Some studies have demonstrated an improved outcome in patients receiving the PLEX+steroids regimen in comparison with steroids alone or receiving PLEX alone compared with steroids. In 2009, Bonnan et al. reported 43 patients with acute longitudinally extensive transverse myelitis patients, receiving either PLEX+IVMP or IVMP alone. The ΔEDSS, difference from residual to baseline EDSS was evaluated. Similar to our study, PLEX+IVMP treatment established a more substantial EDSS reduction. In another study by Bonnan et al., PLEX + IVMP was significantly more effective in lowering EDSS on discharge and at follow-up (13). In another study by Bhatia et al. Plasma exchange therapy was done with a median delay of 7 days (0–54). The clinical improvement was complete in 50% of the attacks when PLEX therapy was started on day 0, whereas it was 1–5% when PLEX was started on day 20 (14).

In our study patients treated with IVMP experienced an average decrease of 0.4 points in EDSS scores from relapse to month 1, whereas those receiving IVMP+PLEX showed a greater reduction of 1.1 points. Moreover, the mean EDSS score difference between relapse and month 6 was 0.7 for IVMP patients, compared to 1.6 for those treated with IVMP+PLEX. Thus, the EDSS change in time intervals between relapse to month 1 and relapse to month 6 seems to be influenced by the treatment type.

Overall, our results have shown that seropositive patients have a better response to treatment, whereas age and baseline EDSS score exert a marginal influence on the EDSS level change after treatment. By contrast, gender, antibody type, OCB type, disease duration, immunosuppresive treatment and attack type do not seem to influence the outcomes of treatment response with both treatment regimens. Our findings also suggest that in addition to the treatment type, patient-specific characteristics also play a substantial role in recovery outcomes. This finding highlights the importance of early diagnosis and personalized treatment strategies in optimizing patient recovery. Further research could explore how these predictors interact and disclose their long-term impact on recovery from NMOSD attacks.

Ethics Committee Approval: This study was approved by the Haydarpaşa Numune Science Research Ethics Committee with the Approval No: 2024-13/20.

Informed Consent: The written informed consents were obtained from all participations.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept– DÖY, ASE, RT; Design– DÖ, ASE, RT; Supervision RT, ET; Resource– DÖY, ASE, RT; Materials– DÖY, ASE; Data Collection and/or Processing– DÖY, ASE, RT; Analysis and/or Interpretation– DÖY, ASE, RT, ET; Literature Search DÖY, ASE; Writing– DÖY, ASE, RT, ET; Critical Reviews-RT, ET.

Conflict of Interest: The authors declared that there is no conflict of interest.

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