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Apheresis therapies for NMOSD attacks

A retrospective study of 207 therapeutic interventions

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Neurol Neuroimmunol Neuroinflamm 2018;5:e504. doi:10.1212/NXI.0000000000000504

Abstract

Objective

To analyze whether 1 of the 2 apheresis techniques, therapeutic plasma exchange (PE) or immunoadsorption (IA), is superior in treating neuromyelitis optica spectrum disorder (NMOSD) attacks and to identify predictive factors for complete remission (CR).

Methods

This retrospective cohort study was based on the registry of the German Neuromyelitis Optica Study Group, a nationwide network established in 2008. It recruited patients with neuromyelitis optica diagnosed according to the 2006 Wingerchuk criteria or with aquaporin-4 (AQP4-ab)-antibody–seropositive NMOSD treated at 6 regional hospitals and 16 tertiary referral centers until March 2013. Besides descriptive data analysis of patient and attack characteristics, generalized estimation equation (GEE) analyses were applied to compare the effectiveness of the 2 apheresis techniques. A GEE model was generated to assess predictors of outcome.

Results

Two hundred and seven attacks in 105 patients (87% AQP4-ab-antibody seropositive) were treated with at least 1 apheresis therapy. Neither PE nor IA was proven superior in the therapy of NMOSD attacks. CR was only achieved with early apheresis therapy. Strong predictors for CR were the use of apheresis therapy as first-line therapy (OR 12.27, 95% CI: 1.04–144.91, p = 0.047), time from onset of attack to start of therapy in days (OR 0.94, 95% CI: 0.89–0.99, p = 0.014), the presence of AQP4-ab-antibodies (OR 33.34, 95% CI: 1.76–631.17, p = 0.019), and monofocal attack manifestation (OR 4.71, 95% CI: 1.03–21.62, p = 0.046).

Conclusions

Our findings suggest early use of an apheresis therapy in NMOSD attacks, particularly in AQP4-ab-seropositive patients. No superiority was shown for one of the 2 apheresis techniques.

Classification of evidence

This study provides Class IV evidence that for patients with NMOSD, neither PE nor IA is superior in the treatment of attacks.

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

NEMOS (Neuromyelitis Optica Study Group) coinvestigators are listed in the appendix at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

AQP4-ab = aquaporin-4; **CR** = complete remission; **EDSS** = Expanded Disability Status Scale; **GEE** = generalized estimating equation; **IA** = immunoadsorption; **IQR** = interquartile range; **NEMOS** = Neuromyelitis Optica Study Group; **NMOSD** = neuromyelitis optica spectrum disorder; **NR** = no remission; **ON** = optic neuritis; **PE** = plasma exchange; **PR** = partial remission.

Adequate treatment of attacks in neuromyelitis optica spectrum disorders (NMOSDs) is crucial as long-term disability in these patients is accumulated by poor recovery from attacks.[1,2] We have previously shown in a retrospective analysis that aggressive treatment of attacks, particularly escalation of attack therapy, can improve the attack outcome with the sequence of treatments being crucial.[3] In particular, our study suggested that first-line therapy with apheresis therapies may be superior to high-dose steroid pulse therapy in attacks involving the spinal cord.

Apheresis therapies aim to eliminate pathogenic antibodies and other proinflammatory factors from the patient's circulation. Two major techniques are used. Therapeutic plasma exchange (PE) separates patient's plasma from the whole blood.[4] Centrifugation devices or highly permeable filters are used to separate the plasma filtrate with molecules up to 1,000 kD, including immunoglobulins, complement factors, and albumin from blood cells. The plasma filtrate is discarded, and either 5% albumin solution or fresh-frozen plasma is added to the filtered blood before reinfusion. For immunoadsorption (IA), plasma separation is equally needed as the first step.[5] The plasma fraction is then passed through an IA device. Single-pass devices use tryptophan as an adsorber, whereas reusable devices use in most cases the *Staphylococcus aureus* cell wall–derived protein A. Several plasma constituents, including immunoglobulins and complement, are removed from the plasma, whereas albumin and clotting factors are mostly spared and reinfused. Besides the immediate intravasal reduction of autoantibodies, e.g., those targeting aquaporin-4 (AQP4-ab),[6] PE and IA also show effects on immunoglobulin redistribution and subsequent immunomodulatory changes.[7–10]

It remains to be elucidated whether one of the apheresis therapies might be superior in the treatment of NMOSD attacks. We therefore conducted a retrospective analysis of 207 NMOSD attacks in 105 patients who were treated either with PE or IA and aimed to identify predictive factors for a favorable therapeutic response.

Methods

Study design

This retrospective cohort study is based on data of the registry of the German Neuromyelitis Optica Study Group (NEMOS, nemos-net.de). Final data entry varied across centers and was performed between January 2012 and March 2013. At this time, the registry contained 215 patients with both NMO diagnosed according to the 2006 Wingerchuk criteria[11] and AQP4-ab-seropositive NMOSD.[12]

Previously, we identified and characterized 1,124 attacks in 186 patients with NMO and NMOSD, treated at 6 regional hospitals and 16 tertiary referral centres.[3] Of these, all attacks treated with an apheresis therapy, PE or IA, were included in this subgroup analysis. Twelve centers used both PE and IA, 9 centers used only PE, and 1 center used only IA. Further details on data collection, quality, and processing can be found in the original characterization of the cohort.[3]

For each patient, demographic and diagnostic data, as well as the number and dates of acute attacks from disease onset to last follow-up, were included in the analysis. Moreover, attack-related clinical features (Expanded Disability Status Scale [EDSS] and visual acuity were available) and information on attack treatment and outcome were assessed from the patient records. The definition of an attack followed the definition used for MS relapses: an objective neurologic worsening lasting for at least 24 hours in the absence of fever or infections and occurring more than 30 days after the previous attack. All attacks were confirmed by neurologic examination.

PE and IA were conducted according to local standard procedures. IA was performed using tryptophan (TR-350; Diamed Medizintechnik GmbH) or protein A (Immunosorba; Fresenius Medical Care) as an adsorber. One apheresis treatment course was defined as at least 3 therapeutic PEs or at least 3 IAs.

Short-term remission status of attack-related neurologic deficits was chosen as the primary outcome parameter and rated as complete remission (CR) when there was full recovery, partial remission (PR) when there was incomplete recovery, and no remission (NR) when there was no improvement at all of the attack-related neurologic deficits in relation to the therapy cycle. The remission status was evaluated immediately after the end of the apheresis therapy.

The primary research question was to evaluate whether PE or IA was more beneficial for NMOSD attack therapy. Given its retrospective nature, this study was expected to provide Class IV evidence.

Standard protocol approvals, registrations, and patient consents

Ethics approval was obtained from the Institutional Review Board of the Ruhr University Bochum (#4573-13) and of the participating centers. Patients provided written informed

consent. The study was performed according to ICH/GCP and current German legal requirements; it was not registered because registration was neither required nor available for retrospective, noninterventional studies at the time of data collection.

Statistical analysis

Patient characteristics were descriptively analyzed. Comparison of the use as first-line or consecutive treatment of PE and IA, as well as distribution among treatment courses and clinical attack manifestation, was performed using the exact χ^2 test. Generalized estimating equations (GEEs)[13] with remission status (CR vs PR or NR) of attacks as the dependent variable were used for the analysis of direct comparisons of the effectiveness of PE vs IA in the first- or second-line use. ORs with 95% CIs and corresponding p values were given. GEE analyses with the same dependent variable were also used to identify predictors of outcome. The following variables were analyzed: sex, age at attack, time from onset of disease to attack, AQP4-status, NMO vs NMOSD, clinical manifestation (absence or presence of myelitis, isolated manifestation of optic neuritis [ON] or myelitis vs simultaneous), disease-modifying immunotherapy, time from onset of attack to initiation of therapy, apheresis as first- vs second-line therapy, technique of therapy (PE vs IA), and center (to control for a center effect). We indicated missing data in the figure legends; the corresponding observations were dropped in the multivariate statistical analyses as usual. p Values < 0.05 were considered statistically significant. All tests were performed as exploratory data analysis, therefore, no adjustments for multiple testing were made. IBM SPSS Statistics, Version 24, STATA (Data Analysis and Statistical Software; StataCorp LP) and StatXact 6 (CYTEL Software Corp) were used for computations and GraphPad Prism version 6.0f (GraphPad Software) for visualization.

Data availability

As far as permitted, according to data protection requirements and consent provided by the participants, original data are available from the corresponding author on request from any qualified investigator within 5 years after publication.

Results

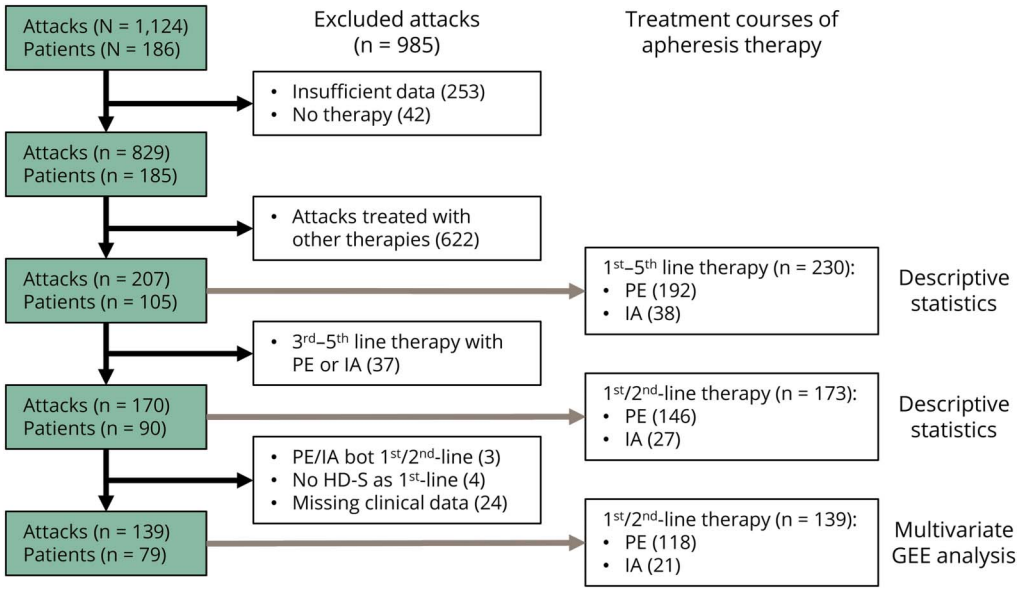
Demographic and clinical characteristics

Among the initial 1,124 attacks in 186 patients, 253 attacks were excluded due to insufficient data, 42 were not treated, and 622 attacks did not receive an apheresis therapy (figure 1).

Two hundred and seven attacks in 105 patients were treated with apheresis therapies, of these 189 with a single apheresis therapy and 18 with multiple apheresis therapies. A total of 192 PE (in 99 patients) and 38 IA procedures (in 23 patients), each with at least 3 exchanges, were examined. Patient and attack characteristics are given in table 1.

Apheresis therapies were applied as first-line choice in 72 attacks, as second-line (another attack therapy was given before the start of apheresis therapy) in 98 attacks, and as third-line or later (2 or more previous attack therapies were given) in 37 attacks. Time from onset of attack to start of therapy was

Figure 1 Study flow chart



HD-S = high-dose IV steroids; IA = immunoadsorption; PE = plasma exchange.

Table 1 Patient characteristics

	Patients (n = 105)
NMO[a] (n, %)	84 (80%)
AQP4-ab positive NMOSD[b] (n, %)	21 (20%)
Female sex (n, %)	82 (78%)
Age at onset (y; mean, SD)	43.4 (14.7)
Disease onset to last visit (y; median, IQR)	5.9 (3.0–10.1)
AQP4-ab positive[c] (n, %)	91 (87%)
≥1 optic neuritis ever (n, %)	87 (83%)
≥1 myelitis ever (n, %)	102 (97%)
Relapsing disease course[d] (n, %)	99 (94%)
Attacks/patient (n, IQR)	5 (3–8)
ARR (n = 97; median, IQR)[e]	0.91 (0.63–1.46)

Abbreviations: AQP4-ab = anti-aquaporin-4 antibody; ARR = annualized relapse rate; IQR = interquartile range; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder.
[a] According to 2006 Wingerchuk criteria.[11]
[b] According to Wingerchuk et al. 2007.[12]
[c] AQP4-ab result not available in 1 NMO patient.
[d] Two or more attacks.
[e] Only patients with follow-up >1 year.

median 1 day (interquartile range [IQR] 0–4, n = 58) in first-line therapy, 11.5 days (IQR 5.0–22.75, n = 92) in second-line therapy, and 15.5 days (IQR 10–45.75, n = 32) in third-line or later therapy. No difference between PE and IA usage was found in terms of distribution among lines of therapy (p = 0.303, exact χ^2 test) and clinical attack manifestation (p = 0.055, exact χ^2 test, figure 2).

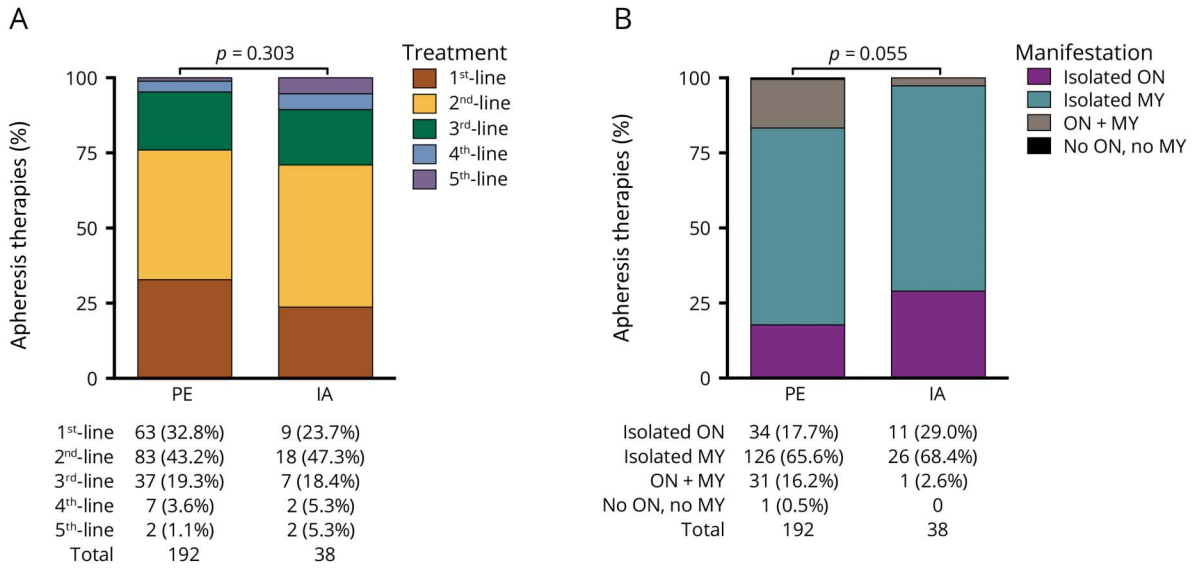
PE and IA are both effective in the therapy of NMOSD attacks

Both PE and IA were effective and induced at least PR in most attacks when used as first- to fifth-line therapy (figure 3, A and B). Although attacks treated with IA always showed a clinical response as nonresponders were not found in this treatment group, we could not show a difference in efficacy between PE and IA (p = 0.264, GEE analysis, CR as the dependent variable) (figure 3C). There was also no difference for the change in EDSS between PE and IA (figure 3D). Because of overlapping effects of preceding attack therapies, we excluded third- to fifth-line apheresis therapies from this statistical analysis. Clinical characteristics of first- and second-line apheresis therapies are given in table 2.

The use of apheresis therapies as first-line and early therapy is associated with the highest remission rate

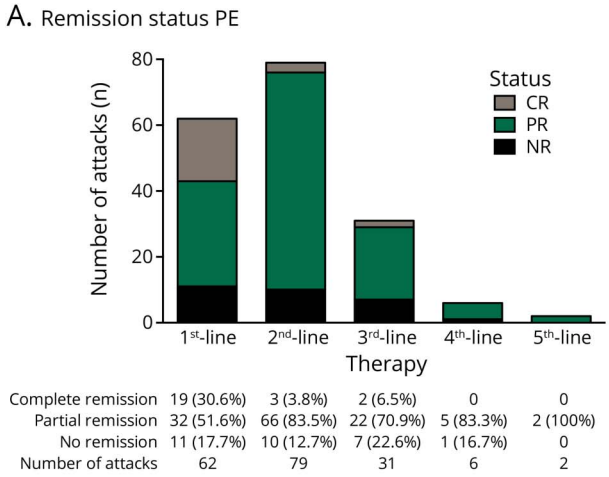
CR was only reached with apheresis therapy initiated early (first- and second-line therapy in IA, first- to third-line therapy in PE). Forty percent of patients had CR when apheresis therapy was started without delay, i.e., day 0–2 after onset of symptoms, but improvement declined stepwise with later treatment start (figure 3E). No patient completely recovered when apheresis therapy was commenced later than 20 days after symptom onset. CR was reached more often with early PE (start after symptom onset day 0–6: 29%; day ≥7: 3.7%, n = 144 attacks) than with early IA treatment (start after symptom onset day 0–6: 6.7%; day ≥7: 0%, n = 28 attacks).

Figure 2 Overview of apheresis therapies

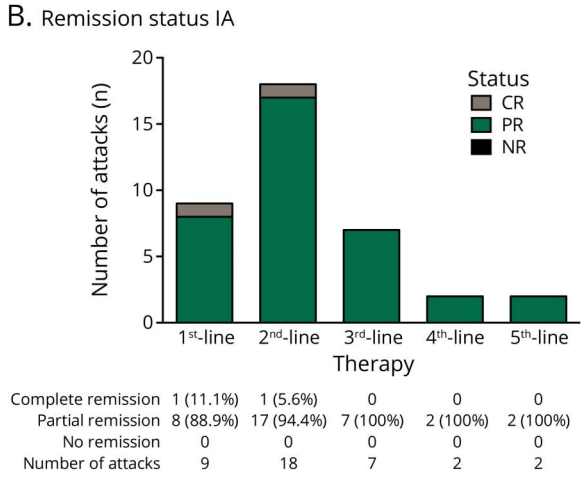


Plasma exchange and immunoadsorption were applied at similar frequencies for escalation from first- to fifth-line treatment (A) and for various clinical manifestations (B) of NMOSD attacks. The chi-square test was used for statistical analysis. IA = immunoadsorption; MY = myelitis; ON = optic neuritis; PE = plasma exchange.

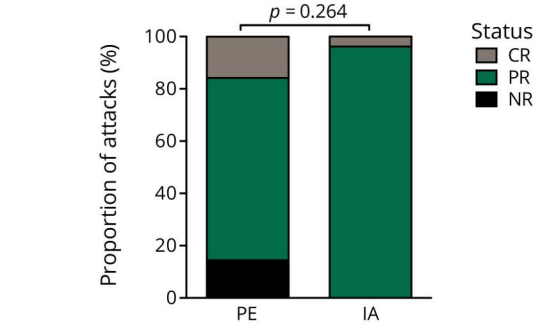
Figure 3 Clinical outcome of apheresis therapies for NMOSD attacks



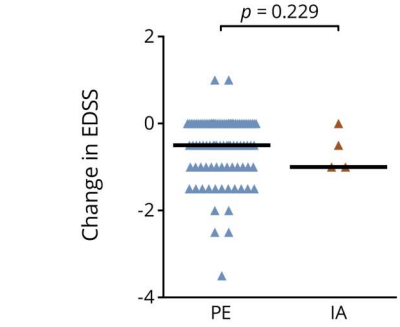
	1st-line	2nd-line	3rd-line	4th-line	5th-line
Complete remission	19 (30.6%)	3 (3.8%)	2 (6.5%)	0	0
Partial remission	32 (51.6%)	66 (83.5%)	22 (70.9%)	5 (83.3%)	2 (100%)
No remission	11 (17.7%)	10 (12.7%)	7 (22.6%)	1 (16.7%)	0
Number of attacks	62	79	31	6	2



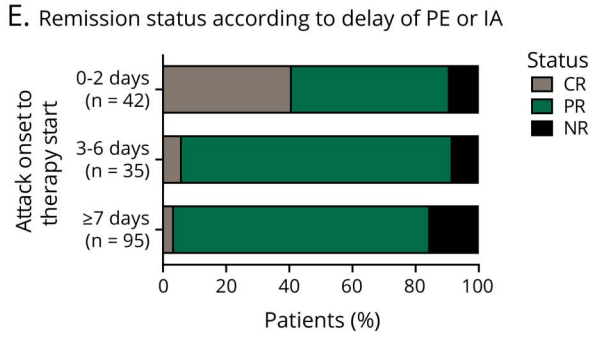
	1st-line	2nd-line	3rd-line	4th-line	5th-line
Complete remission	1 (11.1%)	1 (5.6%)	0	0	0
Partial remission	8 (88.9%)	17 (94.4%)	7 (100%)	2 (100%)	2 (100%)
No remission	0	0	0	0	0
Number of attacks	9	18	7	2	2



	PE	IA
Complete remission	22 (15.8%)	1 (3.8%)
Partial remission	97 (69.8%)	25 (96.2%)
No remission	20 (14.4%)	0
Number of attacks	139	26



	PE	IA
Median	-0.5	-1.0
Mean	-0.526	-1.700
SD	0.730	2.439
Number of attacks	97	5



Remission status of all attacks (total n = 207) treated with plasma exchange (A) or immunoadsorption (B). Missing data plasma exchange: 1st line, n = 1; 2nd line, n = 4; 3rd line, n = 6; and 4th line, n = 1. (C) Short-term remission status after first- or second-line therapy with plasma exchange or immunoadsorption. Treatment courses with PE/IA as first- and second-line therapy were excluded (n = 2). Missing data plasma exchange: 1st line, n = 1 and 2nd line, n = 4. Generalized estimation equations with complete remission as the dependent variable were used for statistical analysis. (D) Change in EDSS after first or second-line therapy with plasma exchange (gray triangles) or immunoadsorption (red triangles). Missing data plasma exchange: 1st line, n = 19; 2nd line, n = 30; missing data immunoadsorption: 1st line, n = 7 and 2nd line, n = 15. One out of range value (immunoadsorption, −6.0) is not shown. Generalized estimation equations were used for statistical analysis. The Median is highlighted as black line. (E) Short-term remission status after apheresis therapy according to time intervals of attack onset to start of therapy. CR = complete remission; IA = immunoadsorption; NR = no remission; PE = plasma exchange; PR = partial remission.

For multivariate GEE analyses of predictors of CR, we further excluded attacks that were treated with an apheresis therapy in both first and second line of treatment (n = 3), attacks where a second-line apheresis therapy was not preceded by high-dose steroids (n = 4), and attacks with missing clinical information (n = 24). Therefore, multivariate analyses were possible in 139 attacks in 79 patients (see flow chart figure 1).

Strong predictors for CR were the use of apheresis therapy as first-line therapy (OR 12.271; 95% CI: 1.04–144.91, $p = 0.047$), time from onset of attack to start of therapy in days (OR 0.937;

Table 2 First- and second-line use of apheresis therapies for NMOSD attacks

	First line (n = 72)			Second line (n = 101)		
	PE (n = 63)	IA (n = 9)	*p* Value	PE (n = 83)	IA (n = 18)	*p* Value
Characteristics of attacks and therapies						
Isolated optic neuritis (n, %)	10 (15.9%)	2 (22.2%)	0.879[a]	14 (16.9%)	6 (33.3%)	0.167[a]
Isolated myelitis (n, %)	44 (69.8%)	6 (66.7%)		55 (66.3%)	12 (66.7%)	
MY + ON (n, %)	9 (14.3%)	1 (11.1%)		13 (15.7%)	0	
Age at attack (y; mean, SD)	44.9 (16.3)	38.2 (7.7)	0.192[b]	49.6 (14.4)	39.0 (9.4)	**0.002**[b]
Disease duration (y; median, IQR)	3.3 (0.8–9.0)	4.6 (2.8–8.8)	0.216[b]	2.7 (0.2–6.1)	2.5 (0.8–4.8)	0.845[b]
Attack number (median, IQR)	6 (3–12)	4 (3–8)	0.411[b]	4 (2–7)	4 (3–7)	0.524[b]
EDSS at start of therapy (median, IQR)	6.0 (3.5–7.5) (n = 50)	8.5 (4.5–9.5) (n = 3)	0.116[b]	7.0 (4.1–8.0) (n = 56)	5.8 (3.9–7.1) (n = 6)	0.281[b]
HD-S as first-line therapy (n, %)	NA	NA	NA	77 (92.8%)	17 (94.4%)	0.800[a]
Time from attack onset to start of therapy (d; median, IQR)	1 (0–4) (n = 52)	1.5 (0–18) (n = 6)	0.548[b]	13 (6–23) (n = 74)	6 (5–24) (n = 18)	0.321[b]
No. of exchanges (median, IQR)	5 (5–8) (n = 55)	8 (5.75–9) (n = 6)	**0.020**[b]	5 (5–7) (n = 75)	5 (5–6) (n = 17)	0.552[b]
Plasma exchange volume per session (l; median, IQR)	3 (2.5–3.5) (n = 15)	2 (n = 1)	NA	2.5 (2.35–3.5) (n = 28)	2 (1.5–2.55) (n = 9)	0.063[b]
Characteristics of patients						
Treated patients (n)	28	7		70	15	
NMO (n, %)	22 (78.6%)	6 (85.7%)	0.673[a]	55 (78.6%)	12 (80%)	0.902[a]
AQP4-ab positive NMOSD (n, %)	6 (21.4%)	1 (14.3%)		15 (21.4%)	3 (20%)	
Female sex (n, %)	23 (82.1%)	6 (85.7%)	0.823[a]	54 (77.1%)	13 (86.7%)	0.413[a]
AQP4-ab positive (n, %)	26 (92.9%)	5 (71.4%)	0.111[a]	60 (87%)	15 (100%)	0.139[a]

Abbreviations: AQP4-ab = anti-aquaporin-4 antibody; EDSS = Expanded Disability Status Scale; HD-S = high-dose IV steroids; IA = immunoadsorption; IQR = interquartile range; MY = myelitis; NA = not applicable; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; PE = plasma exchange.
Characteristics of attacks and therapies and below characteristics of treated patients (total, n = 90). Missing data second line: MY + ON (n = 1), AQP4-ab status (n = 1). Significant values ($p < 0.05$) are shown in bold.
[a] χ^2 test.
[b] Mann-Whitney test was used for statistical analysis.

95% CI: 0.89–0.99, $p = 0.014$), and the presence of AQP4-abs (OR 33.338; 95% CI: 1.76–631.17, $p = 0.019$) (table 3). Monofocal attack manifestations were more likely to show CR than multifocal attacks (OR 4.709; 95% CI: 1.03–21.62, $p = 0.046$). Age (per year) was an intermediate predictor (OR 0.925; 95% CI: 0.85–1.01, $p = 0.081$): the chance to have a CR of attack symptoms decreased with age by approximately 8% per year. Other factors such as apheresis technique, sex, center, diagnosis of NMO vs NMOSD, disease duration, or presence of disease-modifying immunotherapy did not predict CR.

Discussion

Two hundred and seven NMOSD attacks in 105 patients were identified in the NEMOS registry, which were all treated with an apheresis therapy (PE or IA). Confirming previous reports from smaller patient cohorts,[14–22] both PE and IA were effective in the therapy of NMOSD attacks. We could not detect differences between the 2 apheresis techniques with regard to clinical outcome. Although techniques are different, both therapies aim at eliminating circulating antibodies from the patient's circulation. This is of particular importance in patients with NMOSD. Accordingly, our analysis revealed that the presence of serum AQP4-abs was a strong predictor for CR after apheresis therapies. This is in contrast to observations from other case series, where effectiveness of apheresis therapy was independent of the AQP4-ab serostatus[16,17,23] and supports the notion that AQP4-abs have direct pathogenic effects. Nevertheless, these differences have to be interpreted with caution as endpoints in these case series were different. Moreover, the analyzed number of seropositive patients in our GEE analysis was more than 10

Table 3 Factors associated with complete remission from NMOSD attacks after apheresis therapy

	Multivariate analysis	
	***p* Value**	**OR (95% CI)**
Female sex (vs. male)	0.456	3.447 (0.13–89.40)
Age at attack (per 1 y)	0.081	0.925 (0.85–1.01)
Time from onset of disease to attack (per 1 y)	0.247	0.926 (0.81–1.06)
AQP4-ab positive (vs negative)	**0.019**	**33.338 (1.76–631.17)**
NMO (vs NMOSD)	0.316	2.951 (0.36–24.41)
MY present (vs absent)	0.726	1.350 (0.25–7.2)
Isolated ON or MY (vs simultaneous ON + MY)	**0.046**	**4.709 (1.03–21.62)**
Prophylactic immunotherapy present (vs absent)	0.532	1.683 (0.33–8.63)
Time from onset of attack to start of therapy (per 1 d)	**0.014**	**0.937 (0.89–0.99)**
First-line apheresis therapy (vs second-line)	**0.047**	**12.271 (1.04–144.91)**
PE (vs IA)	0.107	4.946 (0.71–34.59)
Center number	0.247	1.080 (0.95–1.23)

Abbreviations: AQP4-ab = anti-aquaporin-4 antibody; IA = immunoadsorption; MY = myelitis; NMO = neuromyelitis optica; NMOSD = NMO spectrum disorder; ON = optic neuritis; PE = plasma exchange.
Multivariate generalized estimating equation (GEE) analyses with remission status (complete remission vs partial remission and no remission) of attacks as the dependent variable (working correlation matrix autoregressive of the 1st order; n = 79 patients).
Significant values ($p < 0.05$) are shown in bold.

times as high as the seronegatives, resulting in considerable statistical uncertainty. Therefore, apheresis therapies should also be considered in antibody-negative NMOSD patients.

In NMOSD attacks, escalation and sequence of therapy is decisive, and we have previously observed an advantage for patients treated with apheresis therapies as a first choice when the spinal cord was affected.[3] Here, we could not show a superiority for one of the 2 different apheresis techniques in the use as first-line therapy. Because of the small numbers of patients with IA therapy included in our study, our data could be biased. A definite comparison between the 2 techniques should be conducted in a prospective randomized clinical trial with appropriate patient numbers. In the absence of further evidence, the decision to use one of both techniques should be made taking availability, side effects, economic factors, and patient preferences into account.[24]

The time between attack onset and start of therapy is decisive, and early initiation of PE was shown to be a predictor of good outcome in studies of CNS demyelination.[25,26] In a recent study, early initiation of PE within 5 days was identified as a strong predictor for CR of severe attacks in patients with NMOSD.[27] Most of our patients received apheresis after a remarkably short period, usually because they had experienced insufficient remission of earlier relapses on steroid treatment and were being treated at tertiary care centers with immediate availability of apheresis therapies. Indeed, time from onset of attack to start of therapy was also a strong predictor in our current study, and an immediate start (within 2 days of symptom onset) was associated with a 40% rate of CR as compared to 3.2% when started later as 6 days after symptom onset. Whether high-dose steroids should be given shortly before or concomitant with apheresis therapy is, however, an open question. In our previous study, first-line exclusive apheresis therapy without high-dose steroid pulse therapy was superior to first-line high-dose steroids in cases of isolated myelitis, but not in ON.[3] The concomitant application of high-dose steroids started on the day of admission, and PE initiated "as early as possible" is a procedure reported to be highly efficient in patients with severe NMOSD attacks.[16,27]

Monofocal vs multifocal attack manifestation was also a predictor of CR with apheresis therapies. However, it has to be noted that monofocal attacks principally have a better chance to recover completely compared with multiregional involvement independent of the chosen attack therapy.[3]

Because of its retrospective nature, our study has limitations. Nevertheless, the analysis comprises one of the largest data sets assembled so far for the analysis of apheresis therapies in NMOSD attacks. Data quality was highly ensured by the "flying doctor" approach as previously described; briefly, 2 neurologists visited the contributing centers and used a predefined standardized evaluation form to assess clinical data.[3] However, bias cannot be excluded. Particularly the decision on therapy modality, IA or PE, and on the time point when apheresis therapy was started was an individual decision of the treating physician. A center effect could be excluded in our data set, reflecting a high standard and good availability of apheresis therapies in the participating centers. Unfortunately, data of attack severity or tolerability of therapy were not systematically registered and could therefore not be included in our analysis. In addition, delayed improvement may have been missed because remission status was assessed at the conclusion of apheresis, and no prespecified follow-up visits were performed; because this applied to both PE and IA groups, however, it is unlikely to have compromised our main finding. Of interest, concomitant long-term immunotherapy had influence neither on the use of apheresis therapy nor on its effectiveness.

This study has immediate implications for clinical management of NMOSD attacks. The early start of apheresis therapies is strongly recommended. Whether IA or PE is used can be decided individually.

Author contributions

I. Kleiter and C. Trebst designed the study, analyzed the data, created the figures, conducted literature research, and wrote the manuscript. K-D. Wernecke performed statistical analysis.

A. Gahlen, N. Borisow and K. Fischer collected ("flying doctor approach") and analyzed the data. K. Hellwig, F. Pache, K. Ruprecht, J. Havla, T. Kümpfel, O. Aktas, H-P. Hartung, M. Ringelstein, C. Geis, C. Kleinschnitz, A. Berthele, B. Hemmer, K. Angstwurm, J-P. Stellmann, S. Schuster, M. Stangel, F. Lauda, H. Tumani, C. Mayer, M. Krumbholz, L. Zeltner, U. Ziemann, R. Linker, M. Schwab, M. Marziniak, F. Then Bergh, U. Hofstadt-van Oy, O. Neuhaus, U. Zettl, J. Faiss, B. Wildemann, F. Paul and S. Jarius collected and analyzed the data. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

Acknowledgment

IK and CT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank all the patients for participating in the study. The NEMOS cohort/NationNMO is supported by the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS; for NEMOS NationNMO-DAB FKZ 01GI1602C to J.S., NationNMO-PAT FKZ 01GI1602B to O.A., and NationNMO-LAB FKZ 01GI1602A to B.W.).

Study funding

There was no specific funding for the study.

Disclosure

I. Kleiter received travel funding and/or speaker honoraria from Biogen, Merck, Novartis, Sanofi, and Roche; served as an associate editor for *BMC Neurology*; consulted for Bayer HealthCare, Chugai, Roche, and Shire; and received research support from Chugai and DiaMed. A. Gahlen received travel funding from Sanofi Genzyme. N. Borisow, K. Fischer, and K-D Wernecke report no disclosures. K. Hellwig served on the scientific advisory boards of Novartis, Genzyme, Teva, Merck, and Roche; received travel funding and/or speaker honoraria from Bayer, Biogen, Merck Serono, Novartis, Teva, Sanofi Genzyme, and Roche; received speaker honoraria from Biogen, Bayer, Teva, Sanofi, Merck, and Novartis; and received research support from Biogen, Bayer, Teva, Merck, and Novartis. F. Pache received travel funding from Genzyme, Bayer, Biogen, ECTRIMS and received research support from Charite-Universitatsmedizin Berlin, Berlin Institute of Health, KKNMS-Bundesministerium für Bildung und Forschung, Ministry in Germany, and Novartis. K. Ruprecht served on the scientific advisory boards of Sanofi-Aventis/Genzyme, Novartis, and Roche; received travel funding and/or speaker honoraria from Bayer, Biogen, Merck Serono, Sanofi-Aventis/Genzyme, Teva, Novartis, and the Guthy Jackson Charitable Foundation; served as an academic editor for *PLoS One*; received publishing royalties from Elsevier; and received research support from Novartis, Merck Serono, and German Ministry of Education and Research. J. Havla served on the scientific advisory boards of and received speaker honoraria from Novartis, Merck, Roche, Sanofi Genzyme, and Santhera Pharmaceuticals; received travel funding and/or personal compensation from Novartis and Merck Serono; and received research support from Friedrich-Baur Stiftung. T. Kumpfel received travel funding and/or speaker honoraria from Bayer, Teva, Merck, Novartis, Sanofi-Aventis/Genzyme, CLB Behring, Roche, and Biogen and received grant support from Bayer-Schering AG, Novartis, and Chugai Pharma. O. Aktas served on the scientific advisory board of MedImmune and received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Merck Serono, Teva, Sanofi-Genzyme, Roche, and Almirall. H-P Hartung served on the scientific advisory boards of Novartis, Merck Serono, Teva, Biogen, Roche, Genzyme, Bayer, Sanofi, MedImmune, GeNeuro, Opexa, Octapharma, Receptos, Celgene, and Roche; received speaker honoraria from Biogen, Genzyme, Merck, Novartis, and Roche; and served on the editorial boards of *Frontiers Neurology/Immunology*, the *European Journal of Neurology*, *Current Opinion in Neurology*, and *Nature Reviews Neurology*. M. Ringelstein received travel funding and/or speaker honoraria from Novartis, Bayer, Biogen, Genzyme, Teva, Merz, Ipsen, and Merck. C. Geis received travel funding from Merck Serono; served as a guest editor for *Frontiers Neurology*; and received research support from the German Research Council and German Ministry of Education. C. Kleinschnitz reports no disclosures. A. Berthele received travel funding and speaker honoraria from Bayer, Biogen, Genzyme, Merck Serono, Mylan, Novartis, Roche, and Teva. B. Hemmer served on the scientific advisory boards of F. Hoffmann-La Roche, Novartis, Bayer, Genentech, AllergyCare, and TG Therapeutics; received travel funding and/or speaker honoraria from Excemed; served on the editorial boards of *JAMA Neurology* and the *MS Journal*; holds a patent for detection of antibodies and T cells against KIR4 in a subpopulation of MS patients and genetic determinants of neutralizing antibodies to interferon B; received research support from Chugai, the German Research Foundation, German Ministry of Education and Research, and EU Horizon 2020; and he or his institution received speaker honoraria from Biogen, Teva, Merck Serono, MedImmune, Novartis, Destin, and Hoffmann-La Roche. K. Angstwurm received travel funding from Alexion, Bayer, Biogen Idec, Merck Serono, Novartis, and Teva and received research support from Alexion, Chugai, Bayer, Biogen, Merck Serono, Novartis, and Roche. J-P Stellmann served on the scientific advisory board of Genzyme; received speaker honoraria from Genzyme and Biogen; received a travel grant from Novartis; and received research support from Biogen, Genzyme, and DFG Research Fellowship. S. Schuster reports no disclosures. M. Stangel served on the scientific advisory boards of Biogen, Baxalta/Shire, CSL Behring, Grifols, MedDay, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva; received travel funding and speaker honoraria from Bayer, Biogen, CSL Behring, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva; served as an academic editor for *PLoS One*; served on the editorial board of *Multiple Sclerosis International*; received research support from Biogen, Merck Serono, Novartis, Sanofi-Genzyme, Teva, Deutsche Forschungsgemeinschaft,

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Received May 3, 2018. Accepted in final form July 23, 2018.

Appendix 1 Coinvestigators of the Neuromyelitis Optica Study Group (NEMOS) in alphabetical order. All institutions are in Germany, unless otherwise indicated

Name	Affiliation	Role	Contribution
Albrecht, P.	University of Düsseldorf	Site investigator	Collected data
Ayzenberg, I.	Ruhr-University Bochum	Site investigator	Collected data
Bayas, A.	Klinikum Augsburg	Site investigator	Collected data
Bellmann-Strobl, J.	Charité University Medicine Berlin	Site investigator	Collected data
Bischof, F.	University of Tübingen	Site investigator	Collected data
Bittner, S.	Johannes Gutenberg University Mainz	Site investigator	Collected data

Continued

Appendix 1 Coinvestigators of the Neuromyelitis Optica Study Group (NEMOS) in alphabetical order. All institutions are in Germany, unless otherwise indicated (continued)

Name	Affiliation	Role	Contribution
Böttcher, T.	Bonhoeffer Klinikum Neubrandenburg	Site investigator	Collected data
Brettschneider, J.	University of Ulm	Site investigator	Collected data
Buttmann, M.	Caritas Hospital Bad Mergentheim	Site investigator	Collected data
DSouza, M.	Charité University Medicine Berlin	Site investigator	Collected data
Ettrich, B.	University of Leipzig	Site investigator	Collected data
Frank, B.	University of Essen	Site investigator	Collected data
Gass, A.	University hospital Mannheim	Site investigator	Collected data
Grothe, M.	University of Greifswald	Site investigator	Collected data
Guthke. K.	Klinikum Görlitz	Site investigator	Collected data
Haarmann, A.	University of Würzburg	Site investigator	Collected data
Habedank, E.	University of Göttingen	Site investigator	Collected data
Hoffmann, F.	Krankenhaus Martha-Maria Halle	Site investigator	Collected data
Hoffmann, O.	St. Josefs-Krankenhaus Potsdam	Site investigator	Collected data
Hümmert, M.W.	Hannover Medical School	Site investigator	Collected data
Junghans, J.	Krankenhaus Martha-Maria Halle	Site investigator	Collected data
Kaste, M.	Nordwest-Krankenhaus Sanderbusch	Site investigator	Collected data
Kaulen, B.	University of Hamburg	Site investigator	Collected data
Kermer, P.	Nordwest-Krankenhaus Sanderbusch	Site investigator	Collected data
Kern, P.	Asklepios Klinik Teupitz	Site investigator	Collected data
Klotz, L.	University of Münster	Site investigator	Collected data
Köhler, W.	Universitätsklinikum Leipzig	Site investigator	Collected data
Kolesilova, E.	Asklepios Klinik Teupitz	Site investigator	Collected data
Korsen, M.	University of Münster	Site investigator	Collected data
Kowarik, M.	University of Tübingen	Site investigator	Collected data
Langel, S.	Landeskrankenhaus Rheinhessen	Site investigator	Collected data
Lee, D.H.	University of Erlangen	Site investigator	Collected data
Liebetrau, M.	St. Josefs-Hospital Wiesbaden GmbH	Site investigator	Collected data
Luessi, F.	Johannes Gutenberg University Mainz	Site investigator	Collected data
Marouf, W.	University Hospital Bonn	Site investigator	Collected data
Meister, S.	University of Rostock	Site investigator	Collected data
Melms, A.	University of Erlangen	Site investigator	Collected data
Metz, I.	University of Göttingen	Site investigator	Collected data
Münch, C.	Charité University Medicine Berlin	Site investigator	Collected data
Niehaus, S.	Klinikum Dortmund	Site investigator	Collected data
Pawlitzki, M.	University of Magdeburg	Site investigator	Collected data
Pellkofer, H.	Ludwig-Maximilians University Munich	Site investigator	Collected data
Puhlmann, H.U.	Schlosspark-Klinik Berlin	Site investigator	Collected data

Continued

Appendix 1 Coinvestigators of the Neuromyelitis Optica Study Group (NEMOS) in alphabetical order. All institutions are in Germany, unless otherwise indicated (continued)

Name	Affiliation	Role	Contribution
Pul, R.	University of Essen	Site investigator	Collected data
Retzlaf, N.	University of Rostock	Site investigator	Collected data
Riedlinger, A.	Asklepios Klinik Teupitz	Site investigator	Collected data
Rommer, P.	Medical University of Vienna, Austria	Site investigator	Collected data
Röpke, L.	University of Jena	Site investigator	Collected data
Rostásy, K.	Vestische Caritas-Kliniken GmbH	Site investigator	Collected data
Rückriem, L.	MediClin Hedon-Klinik Lingen (Ems)	Site investigator	Collected data
Ruschil, C.	University of Tübingen	Site investigator	Collected data
Schippling, S.	University of Zürich, Switzerland	Site investigator	Collected data
Senel, M.	University of Ulm	Site investigator	Collected data
Sieb, J.P.	Helios Hanseklinikum Stralsund	Site investigator	Collected data
Sommer, C.	University of Würzburg	Site investigator	Collected data
Spreer, A.	Johannes Gutenberg University Mainz	Site investigator	Collected data
Steinbrecher, A.	Helios Klinikum Erfurt	Site investigator	Collected data
Stephanik, H.	University of Magdeburg	Site investigator	Collected data
Stoppe, M.	University of Leipzig	Site investigator	Collected data
Süße, M.	University of Greifswald	Site investigator	Collected data
Tackenberg, B.	University of Marburg	Site investigator	Collected data
Tünnerhoff, J.	University of Tübingen	Site investigator	Collected data
Veauthier, C.	Charité University Medicine Berlin	Site investigator	Collected data
Walter, A.	Klinikum Herford	Site investigator	Collected data
Wandinger, K.P.	University Medical center Schleswig-Holstein Campus Lübeck	Site investigator	Collected data
Warnke, C.	University of Köln	Site investigator	Collected data
Weber, M.S.	University of Göttingen	Site investigator	Collected data
Weissert, R.	University of Regensburg	Site investigator	Collected data
Wiendl, H.	University of Münster	Site investigator	Collected data
Wilke, C.	Nervenzentrum Potsdam	Site investigator	Collected data
Winkelmann, A.	University of Rostock	Site investigator	Collected data
Yalachkov, Y.	University of Frankfurt	Site investigator	Collected data
Young, K.	University of Hamburg	Site investigator	Collected data
Zentner, C.	Krankenhaus Martha-Maria Halle	Site investigator	Collected data
Zipp, F.	Johannes Gutenberg University Mainz	Site investigator	Collected data

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