Journal of the Neurological Sciences 461 (2024) 123050

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Apheresis treatment in autoimmune neurological diseases: Predictors of good clinical outcome and success of follow-up therapy with B-cell depletion

Mathias Fousse [a], Klaus Fassbender [a], Stefan J. Schunk [b], Tina Schmidt [c], Jakob Stögbauer [a,*]

[a] Department of Neurology, Saarland University Medical Center, 66421 Homburg, Germany
[b] Department of Internal Medicine IV - Nephrology and Hypertension, Saarland University Medical Center, 66421 Homburg, Germany
[c] Department of Transplant and Infection Immunology, Saarland University, 66421 Homburg, Germany

ARTICLE INFO

Keywords:
Plasma exchange
Therapeutic apheresis
Plasmapheresis
Immunoadsorption
Neurological autoimmune disease
B cell depletion

ABSTRACT

Objective: Apheresis treatment (AT) is an established standard of treatment in various neurological autoimmune diseases. Since not all patients equally benefit from AT, we saw the need to investigate the effect of different clinical, paraclinical and technical-apparative factors on the clinical outcome. Additionally, we wanted to find out whether patients who improved due to AT continue to be clinically stable under B-cell depletion (BCD).
Methods: We screened all patients ($n = 358$) with neurological diseases who received AT at the Medical center of the University of the Saarland in the past 20 years. Different factors (e.g., age, sex, duration until onset of AT, type of AT, number of cycles, csf parameters) were analyzed retrospectively. Clinical disability was measured using the modified Rankin scale (mRS), visual acuity and the Expanded Disability Status Scale (EDSS).
Results: 335 patients, categorized into 11 different autoimmune diagnosis groups, received a total of 2669 treatment cycles and showed a statistically significant improvement in mRS with AT ($p < 0.001$). Patients in American Society for Apheresis (ASFA) categories I ($p = 0.013$) and II ($p = 0.035$) showed a significantly greater benefit under AT than those in category III. The clinical outcome was better with shorter duration until AT onset, more cycles of AT, and more plasma volume exchanged and the presence of an autoimmune antibody. Patients who initially profited had a significantly more stable course of the disease after 1-Year-BCD ($p = 0.039$).
Discussion: In the present study, we were able to identify various significant factors influencing the outcome of patients due to AT. Furthermore, we could show that patients with a response to AT can benefit from BCD follow-up therapy.

1. Introduction

Apheresis treatment (AT) is an established standard of treatment for autoimmune, mostly antibody-mediated diseases [1]. The debate of a potential benefit of apheresis procedures in long-COVID syndromes [2,3] has renewed the focus of the scientific community on the as of now poorly understood factors predicting outcome of AT in other autoimmune neurologic diseases in which autoimmune processes, parainfectious or paraneoplastic mechanisms are discussed as underlying causes.

Therapeutic plasma exchange (TPE) is to be distinguished from immunoadsorption (IA) [4]. In TPE, plasma volume is separated from other blood components and replaced by substitute solutions (usually human albumin or Fresh Frozen Plasma (FFP)). This procedure

Abbreviations: AE, Autoimmune encephalitis; AIDP, Acute inflammatory demyelinating polyneuropathy; AN, Autoimmune neuropathy of other kind; ASFA, American Society for Apheresis; AT, Apheresis treatment; BCD, B cell depletion; C, Category; CIDP, Chronic inflammatory demyelinating polyneuropathy; CRP, C-Reactive Protein.; CSF, Cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FFP, Fresh Frozen Plasma; IA, Immunoadsorption; IQR, Interquartile range; LEMS, Lambert-Eaton myasthenic syndrome; MG, Myasthenia gravis; MOGAD, Myelin oligodendrocyte glycoprotein antibody-associated disease; mRS, Modified Rankin Scale; MS, Multiple sclerosis; ab, Antibodies; NMOSD, Neuromyelitis Optica Spectrum Disorder; OCB, Oligoclonal bands; ON, Optic neuritis; PMS, Multiple sclerosis, progressive; PPMS, Primary progressive multiple sclerosis; RMS, Relapsing *multiple sclerosis*; RRMS, Relapsing-remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis; TPE, Therapeutic plasma exchange; TPV, Total plasma volume; TTP, Thrombotic thrombocytopenic purpura.

* Corresponding author at: Saarland University, Department of Neurology, building 90, Kirrberger Straße, 66421 Homburg, Germany
E-mail address: jakob.stoegbauer@uks.eu (J. Stögbauer).

https://doi.org/10.1016/j.jns.2024.123050
Received 23 February 2024; Received in revised form 14 April 2024; Accepted 13 May 2024
Available online 14 May 2024
0022-510X/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

unselectively removes (exchanges) multiple proteins such as antibodies as well as clotting factors, hormones, or various kinds of drugs. In contrast, in IA, immunoglobulins, complementary factors or immune complexes of plasma are selectively bound in an adsorber column. Both procedures are to be understood as a short-term intervention into the immune system and are used in severe neurological - mostly steroid-refractory - autoimmune diseases, primarily used for disease stabilization. The expected extent of success of AT in various autoimmune diagnoses is currently the subject of research projects. The decrease in immunoglobulins due to the procedure depends on the type of immunoglobulins considered as well as intravascular baseline concentration [5], re-synthesis, redistribution from extracorporeal compartments, exchanged plasma volume and possibly the length of a therapeutic cycle and the time interval between cycles [6].

In TPE proteins have to be replaced (with corresponding allergic risk) and there is a greater circulatory burden. Neither is the case with IA. TPE is equivalent to a non-selective AT, whereas IA is more selective, and a larger TPV can be treated per session.

With TPE 1 to 1.5 times the patient‘s total plasma volume can be treated per session, with IA with tryptophan filters 2 to 2.5 l can be treated. A standard of about 5–7 sessions per AT cycle is established [1,7].

Established and modified indications for evidence-based use of AT are made considering American Society for Apheresis (ASFA) guidelines which are continuously updated [1]. The guideline serves as a guide in the treatment of patients, sorting the disease into four categories (CI, CII, CIII, CIV): CI and CII include evidence-based firstline (CI) or secondline therapy (CII) via AT (in each case combined with other therapeutic modalities, if appropriate), whereas in CIII the role of AT remains unclear and in CIV it has been shown to be ineffective or even harmful [1]. In some diseases (e.g., MG), long-term treatment with AT is necessary if other treatment options fail [8,9].

However, AT is generally used in cases of (sub)acute clinical deteriorations. In a vast variety of immunologically mediated neurological diseases [10–12] such as Guillain-Barré syndrome [13–16], chronic demyelinating inflammatory polyneuropathy (CIDP) [17–19], relapsing multiple sclerosis (RMS) [20,21], myasthenia gravis (MG), autoimmune encephalitis (AE) or NMOSD [22,23] indication for AT can be given as first-line therapy or as a second-line treatment after unsuccessful treatment with steroid pulses [1].

We saw the need to investigate the effect of clinical, paraclinical, and technical-apparative factors in patients with different neurological diseases, because not all individuals benefit from AT. The influence of different variables [20] such as patient age, gender, duration until onset of AT, number of cycles, type of relapse has not coherently been investigated in the largely retrospective studies or case series. Existing studies usually only provided results for individual diseases. However, in large neurological departments the treatment of rare diseases must also be taken into account. Therefore, we decided to examine the entirety of patients treated with AT in accordance with the existing diseases, the paraclinical and AT-related parameters. In addition to the parameters mentioned above the response to the different types of AT was of greater interest, as IA does not require plasma substitution and there are particular cases in which IA is more expensive than TPE. Additionally, the role of seropositivity or seronegativity for autoimmune antibodies has not yet been sufficiently investigated when it comes to AT due to small case sizes.

To assess the outcome for all subjects, functional disability was determined via the modified Rankin scale (mRS). Additionally, in some subpopulations the Expanded Disability Status Scale (EDSS) and visual acuity were examined.

Since many neurological autoimmune diseases present with a chronic disease course after AT, there often is a need for follow-up therapy with immunotherapeutics after the initial use of AT. We were interested to investigate whether patients who had received AT benefit from B-cell depletion (BCD), since ultimately both therapeutic concepts aim at reducing antibody-mediated autoimmunity. Pharmacological destruction of B cells is accompanied by several monoclonal antibodies directed against CD19 or CD20. The original substance is Rituximab, which is used in hemato-oncology. Rituximab which is directed against CD20 is also used as an off-label medication in neurology (for RMS, PMS, MG, vasculitis, NMOSD, MOGAD, AE and other diseases as an individual healing attempt). Approved follow-on products against CD20 are ocrelizumab (for RMS and PPMS), ofatumumab (for RMS), ublituximab (for RMS) and inebilizumab against CD19 (for Aquaporin-4 antibody positive NMOSD) [24–28]. The substances directed against CD20 deplete a large part of B cells, while inebilizumab also destroys early forms of B cells and some types of plasma cells [24,28].

2. Patients and methods

2.1. Study design and participants

Every Patient who was in the Department of Neurology from January 2004 to September 2023 and received AT (TPE or IA) was analyzed retrospectively and included in this study. Both methods are based on prior plasma separation by means of a plasma filter or centrifuge. Plasma exchange was performed via a large central venous catheter. In both cases, tryptophan was used for the binding before the residual blood plasma is re-infused [4,5,29] In most cases anticoagulation with heparin or citrates was administered during AT. Calculation of the individual total plasma volume (TPV) was achieved by specifying hematocrit, body height and weight by use of formulas and nomograms [30].

The study was anonymized and conducted with approval of the local ethics committee (Ethikkommission der Ärztekammer des Saarlandes, ethics vote No. 158/14). Active consent was not required. The analysis was based on data documented by the department of neurology and nephrology.

Clinical parameters (diagnoses, age, sex, examination findings, visual acuity, symptom duration) and supportive instrumental examinations as well as common disability scores before and after AT were evaluated (mRS for all, EDSS for myelitis, ON, RMS, PMS and NMOSD/MOGAD, visual acuity for ON of different diseases).

The seven-item modified Rankin scale (mRS), which was originally developed to evaluate outcome post stroke and is utilized in many stroke studies, reflects the extent of disability using a standardized measure [31–33]. This score is beneficial when it comes to determining functional disability in everyday life, which is the decisive factor for all patients, before and after AT regardless of the disease. In the meantime, mRS has been used for a variety of other neurological diseases [24,34–37]. An mRS of 0–2 points reflects a lack of disability or moderate disability, whereas patients with an mRS of 3–5 points permanently depend on assistance (mRS of 6 points corresponds to death due to illness).

Individual diagnoses were combined into 11 diagnostic groups, as shown in Table 1. We also investigated the proportion of ineffective previous steroid therapy. Cerebrospinal fluid (CSF) findings were assessed if available (cell count, pleocytosis, oligoclonal bands (OCB)). Laboratory results (CRP, antibody levels for IgG and IgM in serum) and the presence of pathological autoantibodies were also included in the analysis. AT specific data (type of AT, number of cycles, exchange volume) was collected. The AT was performed in the Department of Nephrology. Tryptophan filters by the company Asahi Kasei Medical (Japan) were used. In TPE, exchange volume was calculated with 40 ml/kg body weight. The exchange volume in IA was 2.5 l for all patients.

2.2. Statistical analysis

To compare unpaired non-parametric data between the different groups (diagnosis group, sex, presence of ocb/pleocytosis/autoantibodies, type of apheresis, stability under bcd) Mann-Whitney-U- and Kruskal-Wallis-test were performed. In case of multiple testing,

Table 1
Patient characterization, laboratory findings and characteristics of apheresis treatment.

n	335	
Years of age at visit, mean ± SD	53.6 ± 17.4	
Sex, female, n (%)	178 (53.1)	
Underlying disease group, n (%)		
• AIDP	65 (19.4)	
• RMS relapses	62 (18.5)	
• CIDP	59 (17.6)	
• Myasthenia gravis/LEMS (n = 48/n = 3) (MG)	51 (15.2)	
• NMOSD/MOGAD (n = 13/n = 8)	21 (6.3)	
• Autoimmune neuropathy of other kind (AN)[1]	21 (6.2)	
• Autoimmune encephalitis (AE)	20 (6.0)	
• Optic neuritis (ON)[2]	10 (3.0)	
• Multiple sclerosis, progressive (PMS)[3]	9 (2.7)	
• Myelitis of other kind[2]	8 (2.4)	
• Other[4]	9 (2.6)	
• initial diagnosis	150 (44.6)	
• recurrence	185 (55.1)	
CRP[&] at apheresis, mg/l (mean ± SD)	16.5 ± 30	
IgG in serum[*], g/dl (mean ± SD)	1 ± 0.43	
• initial diagnosis	1.05 ± 0.46	
• recurrence	0.9 ± 0.36	p = 0.027
IgM in serum[#], g/dl (mean ± SD)	0.11 ± 0.09	
• initial diagnosis	0.12 ± 0.09	
• recurrence	0.1 ± 0.1	p = 0.043
Presence of autoantibody, n (%)	90 (26.9)	
Presence of CSF pleocytosis (≥6/µl) at diagnosis per available CSF analyses (n = 183), n (%)		
• yes	54 (29.5)	
• no	129 (70.5)	
CSF cell count, n/µl (mean ± SD)	18.1 ± 13.7	
Presence of OCB per available OCB analyses (n = 176), n (%)		
• yes[5]	50 (28.4)	
• no	126 (71.6)	
AT modality, n (%)		
TPE	175 (52.1)	
IA	138 (41.1)	
combined	22 (6.5)	
Number of therapy sessions, n (mean ± SD)	8 ± 6.4	
Volume of plasma exchanged, l (mean ± SD)	26.9 ± 60.5	

[1] includes the diagnoses of paraproteinemic demyelinating neuropathy, polyradiculitis, ganglionitis, vasculitic polyneuropathy, paraneoplastic neuropathy, and other immune-mediated polyneuropathy.
[2] without a diagnosis of multiple sclerosis, NMOSD or MOGAD.
[3] Includes primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS) with progression independent of relapse activity (PIRA).
[4] includes the diagnoses thrombotic thrombocytopenic purpura, Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration and neuropathy, stiff person syndrome, neurosarcoidosis.
[5] OCB type 2 (intrathecal) n = 38 (76%), OCB type 3 (intrathecal and additional identical in CSF/serum n = 12 (24%).
[&] Reference <5 mg/l.
[*] Reference 0.7–1.6 g/dl.
[#] Reference 0.04–0.23 g/dl.

Bonferroni correction was used as post hoc-test. Wilcoxon-rank-test was used for statistical analysis of paired non-parametric data (single group benefit in mRS due to AT). Correlations between age, time to treatment, number of sessions, plasma exchange volume on the one hand and ΔmRS on the other hand were analyzed using Spearman's correlation coefficient. A statistical analysis was considered significant if the p-value was <0.05.

2.3. Software

SPSS statistics (version 28.0.1.1) was used for statistical analysis, GraphPad Prism (Version 10.0.2), Microsoft Excel and Power Point (Microsoft 365) were used to create the graphics, and Microsoft Word and Excel (Microsoft 365) were used for word processing.

3. Results

3.1. (K1) Screening procedures and final selection

358 patients received AT in the Department of Neurology from January 2004 to September 2023. After consideration of the final diagnoses, 23 patients were assigned to category IV according to the current American Society for Apheresis (ASFA) guidelines. As no autoimmune pathology and no therapeutic response is assumed in these patients, they were excluded from the sub-analysis below.

3.2. (K2) Clinical characteristics of the included population

A total of 335 patients, 178 female (53,1%), were included in this study. Table 1 provides an overview of patient characteristics, laboratory findings, and apheresis treatment parameters. The mean age of all patients was 53.6 years (±17.4) with a minimum of 18 and maximum of 86 years. Patients with RMS were of the youngest age (37.8 years (±10.4)), patients with autoimmune neuropathy (AN) had the highest average age of 61.9 years (±9.4). Patients included in this study with RMS, PMS, ON, Myelitis, NMOSD/MOGAD or AE suffered from a steroid-refractory worsening of the disease. Over 2/3 disability-causing events were due to AIDP, CIDP, multiple sclerosis, and myasthenia gravis. The events optic neuritis (ON) and myelitis could be assigned to different diseases. In almost 45% of the patients, the neurological manifestation represented the initial diagnosis of the disease. Pathological autoantibodies were found in about 25% of the reported cases (Table 2 contains the name and frequency distribution of the autoantibodies). CSF pleocytosis and/or the detection of oligoclonal bands, both expressing possible inflammation in the CSF space, were found in 16.1 and 14.9% respectively.

A total of 2669 cycles of AT (of which 1461 cycles of TPE and 1208 cycles of IA) were evaluated.

Overall the AT was well tolerated. The most common side effects were allergic reactions after substitution of FFP (8.6%) and hypotension (4.2%). Three patients died of their disease during the hospital observation phase; however this was not a consequence of AT. Two patients experienced an air embolism after removal of their central venous catheter. No other serious adverse events or deaths occurred. Plasma substitution was performed using albumin and FFP. A slight majority of patients received therapeutic TPE. Combination therapy was mostly initiated by switching to IA due to allergic reactions to FFP during TPE. 5 cycles were usually planed with the option of discontinuation in case of deterioration or additional cycles in case of a favourable response; on average, 8 cycles of AT (± 6.4) were performed.

3.3. (K3) Treatment outcome

3.3.1. (K3a) Functional outcome through apheresis treatment according to the ASFA categories

Indications for AT were made during hospitalization based on initial

Table 2
Presence of autoantibodies (above) and comparison of the groups with and without detection of pathological autoantibodies (below). Change in mRS before/after TA (ΔmRS). Different groups were defined by presence of antibody. Statistical analysis carried out using Mann-Whitney-*U* test.

Presence of autoantibodies (name)	n (%)
Acetylcholine receptor	35 (10.4)
Aquaporin-4	4 (1.2)
NMDA receptor	7 (2.1)
MOG	9 (2.7)
Antiganglioside	10 (3.0)
Yo	4 (1.2)
VGCC	5 (1.5)
Paraproteins	5 (1.5)
Other*	11 (3.3)

Group comparison	n (%)	ΔmRS (mean ± SD)	Median	Min	Max	p
Antibody	90 (26.9)	1.02 ± 0.9	1	−1	4	
No antibody	245 (73.1)	0.75 ± 0.8	1	−3	3	
	335					0.029

Different antibodies found in the patients underwent AT. *Other consists of LGI-1 ($n = 1$), ADAMTS-13 ($n = 1$), GAD ($n = 2$), DPPX ($n = 1$), CASPR2 ($n = 1$), MuSK (n = 1), MAG (n = 1), AMA (n = 1), LRP4 (n = 1), Amphiphysin 2 (n = 1).

suspected diagnoses. However, our evaluation takes into account the final diagnoses (Table 1 and Fig. 2). Each disease was assigned to a category (I to IV) according to the current American Society for Apheresis (ASFA) guidelines [1]; notes in table S1 in the supplement. The diagnoses polyradiculitis, vasculitic and other autoimmune polyneuropathy as well as ganglionitis and neurosarcoidosis were assigned to category CIII due to their autoimmune pathophysiology and the therefore possible but not yet sufficiently investigated efficiency of apheresis therapy. The assignment allows an estimation of the probability of response to the AT.

A total of 358 patients were screened (Fig. 1), the Categorization was made according to the ASFA guideline: CI 197 patients, CII 104 patients, CIII 34 and CIV 23 patients. Fig. 2 is a multidimensional diagram and represents an alternative visualization to a flow chart. It symbolizes each individual's response to AT. The same numbers are assigned to the same diseases. The outcome was colored by the improvement or worsening of mRS (ΔmRS). Patients in green (dark green ΔmRS>1, light green ΔmRS = 1) benefited best, gray (ΔmRS = 0) and red (ΔmRS<0) symbolize unchanged or worsened condition. In line with good clinical practice, the categories with the best therapeutic response according to ASFA (CI and CII) contained the most patients. Deterioration under AT was found in the CI and CIV categories. No patient with improvement was found in CIV. With ascending category, the proportion of patients with response

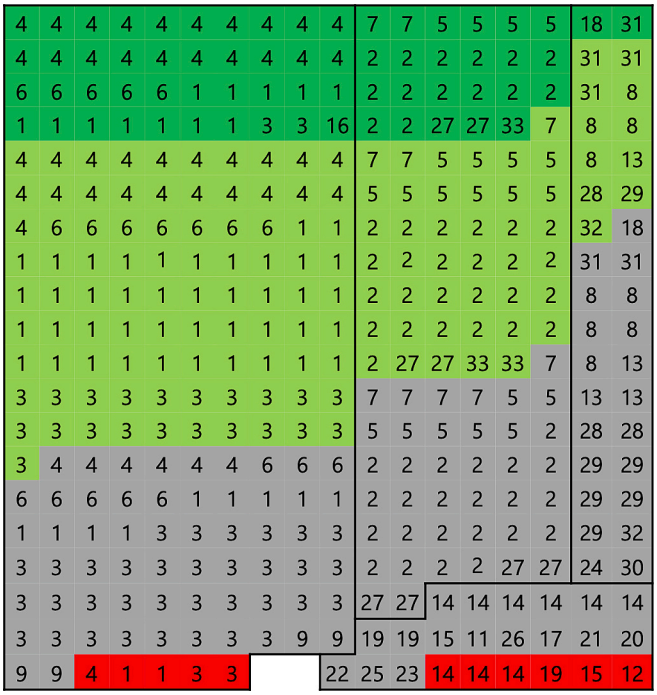

Fig. 2. Multidimensional diagram with final diagnosis (numbers 1–32) assignment to ASFA categories (CI-CIV) and change in functional disability (ΔmRS) after AT.

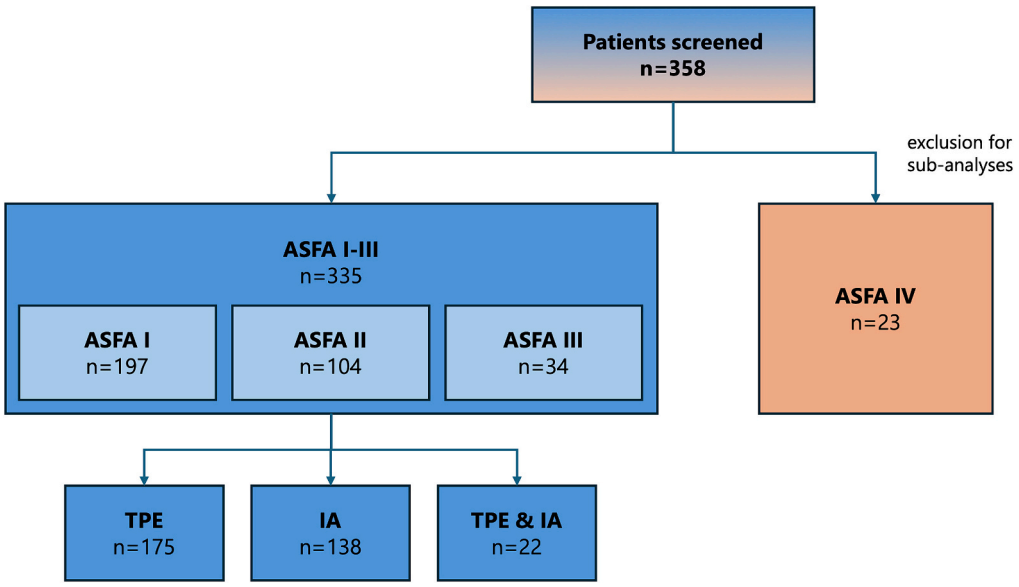

Fig. 1. Flowchart with the screened patients. Patients with ASFA category IV diagnoses were excluded from the sub-analysis if no therapeutic response was expected. The remaining patients were assigned to ASFA categories I, II and III. The distribution of the various AT procedures is shown below.

(green) decreased with CI 66.5%, CII 62.5%, and CIII 38.2%. The proportion of patients with a very good outcome (dark green) was highest in CII with 22.1% and lowest in CIII with 5.9%. As expected, all 23 patients of CIV showed a lack of improvement or even a worsening of the mRS.

Each ASFA category from I to IV (CI, CII, CIII, CIV) was outlined in black. Each square symbolizes a patient.

The number denotes the underlying disease (final diagnosis) according to the legend: (1) AIDP, (2) multiple sclerosis (acute relapse), (3) CIDP, (4) myasthenia gravis, (5) NMOSD/MOGAD, (6) autoimmune encephalitis, (7) optic neuritis, (8) multiple sclerosis (chronic), (9) paraproteinemic demyelinating neuropathy, (11) dystonia, (12) cns lymphoma, (13) paraneoplastic cerebellar degeneration, (14) amyotrophic lateral sclerosis, (15) spinalis anterior syndrome, (16) TTP, (17) critical illness polyneuropathy, (18) stiff person syndrome, (19) meningeosis, (20) toxoplasmosis, (21) stroke, (22) meningitis, (23) Leber's hereditary optic neuropathy, (24) paraneoplastic neuropathy, (25) ethyltoxic neuropathy, (26) spinocerebellar ataxy, (27) myelitis, (28) polyradiculitis, (29) vasculitic polyneuropathy, (30) ganglionitis, (31) autoimmune polyneuropathy, (32) neurosarcoidosis, (33) Lambert-Eaton myasthenic syndrome.

Clinical response, defined by the change in mRS by apheresis, is highlighted in color in the legend: Dark green symbolizes a marked clinical improvement (decrease in mRS by >1 point), light green a slight clinical improvement (decrease in mRS up to 1), gray an unchanged state, and red a worsening (increase in mRS).

Patients in category IV with non-autoimmune-mediated diseases were excluded for further analysis in the absence of an expected response to AT. With the comparison of the ASFA categories CI, CII and CIII, the change in mRS was significantly different in the statistical analysis using the Kruskal-Wallis test ($p = 0.016$). The Bonferroni correction was used as post hoc-test. Patients classified in ASFA CI or ASFA CII showed a significantly greater benefit under AT than patients in ASFA CIII (ASFA CI vs. ASFA CIII: $p = 0.013$; ASFA CII vs. ASFA CIII: $p = 0.035$). Between categories ASFA CI and ASFA CII, we did not find a significant difference in terms of functional outcome after AT (ASFA CI vs. ASFA CII: $p > 0.9$).

3.3.2. *(K3b) Improved outcome through apheresis treatment in different diagnostic groups*

The final individual diagnoses of the included patients (ASFA categories I-III) were summarized into eleven diagnostic groups for statistical analysis (Table 1). 62.38% of patients from ASFA CI, II, III showed a response (defined as improvement in mRS ≥ 1). The median mRS for all 335 patients before AT was 4 (range 1–5), with the median in the AE group being the highest at 5 (range 2–5). The median for the total cohort after AT was 3 (range 0–6), this improvement was statistically significant ($p = 0.001$). Figure Supplement 1 shows a spherical cluster diagram for each of the 11 groups. The mRS value before AT is assigned to an mRS value after AT. No diagnostic group had a majority of patients in the range that reflects a deterioration. However, the visualization suggests that in certain groups, e.g. CIDP, many patients did not benefit from AT.

The statistical analysis using the Wilcoxon rank test showed a significant difference in mRS for all 335 patients as a result of AT. The single group analysis showed significant improvements ($p < 0.001$) for patients with AIDP, RMS, MG/LEMS and NMOSD/MOGAD (Fig. 3). Patients with AE ($p = 0.002$) and AN ($p = 0.011$) also benefited. The improvement for ON ($p = 0.038$) and PMS ($p = 0.046$) was significant, but the group size was small. The myelitis and "other" groups showed no significant difference due to AT. Fig. 3 shows the graphical

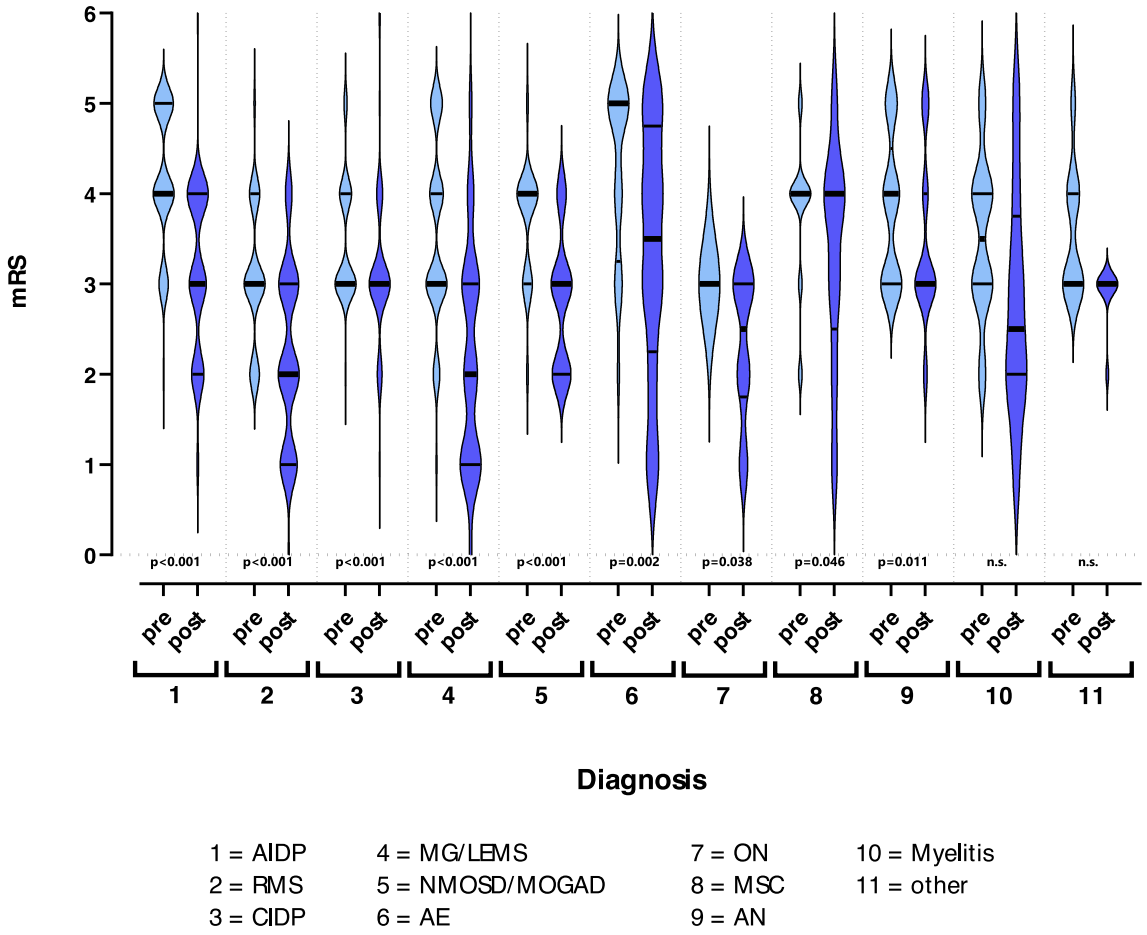

Fig. 3. Violin plots diagram for final diagnosis groups with mRS pre-AT and post-AT.

representation of the distribution of the mRS per diagnosis group in the before-after comparison.

Violin plots show the frequency distribution of the mRS data in the 11 diagnosis groups before (light blue) and after AT (dark blue). Distribution medians and quartiles are depicted as bold and narrow lines, respectively: G1 AIDP ($n = 65$), G2 RMS ($n = 62$), G3 CIDP ($n = 59$), G4 MG/LEMS ($n = 51$), G5 NMOSD/MOGAD ($n = 21$), G6 AE ($n = 20$), G7 ON (n = 20), G8 PMS ($n = 8$), G9 AN (n = 21), G10 Myelitis (n = 8), G11 other ($n = 9$). Statistical analysis was performed using the Wilcoxon rank test.

Comparing the ΔmRS for all groups, the Kruskal-Wallis test also showed a statistically significant result ($p < 0.001$), with the mean ΔmRS being highest for the MG/LEMS (ΔmRS = 1.35 ± 0.93) and AIDP (ΔmRS1.02 ± 0.74) groups and lowest for the AN (ΔmRS = 0.38 ± 0.59) and CIDP (ΔmRS = 0.34 ± 0.78) groups. When comparing demyelinating neuropathies, the post hoc analysis using Bonferroni correction showed a significant result in favour of AIDP (vs. CIDP: $p < 0.001$). The ΔmRS comparisons of the groups AN vs. AIDP ($p = 0.027$), AN vs. MG/LEMS (p < 0.001), and CIDP vs. MG/LEMS (p < 0.001) were also significantly different.

3.4. (K4) Predictors of treatment outcome

3.4.1. Age and sex

When analyzing the epidemiological factors of age and sex, no significant correlation was found for either factor (age: Spearman's $r = -0{,}06$, $p = 0.305$; sex: Mann-Whitney-U test $p = 0.955$) with the change in mRS by AT (ΔmRS). At most, there was a trend for a greater ΔmRS change with younger patients (Spearman's $r = -0.23$, $p = 0.08$) in the RMS group.

3.4.2. Pleocytosis and OCB in CSF and presence of autoantibodies

Whether pleocytosis was present in the CSF at the time of the diagnosis ($n = 53$) or not ($n = 129$) had no significant influence ($p = 0.51$) on the functional outcome (mRS). Similarly, the presence of OCB type 2 or type 3 in the CSF did not significantly influence the functional outcome ($p = 0.51$).

26.9% of patients treated with AT previously had evidence of a pathological autoantibody. Anti-acetylcholine receptor antibodies were most frequently found in patients in the context of MG disease (35 Patients). Table 2 provides further details. Patients with evidence of an autoimmune antibody showed a more significant benefit under AT than patients without ($p = 0.029$) (Table 2). There was no statistical difference in the outcome regarding the presence of IgM- or IgG-antibodies, with the IgM group only consisting of 5 subjects. The differentiation of autoantibodies with regard to their presence or absence of properties directly influencing cell function (e.g. directed against receptors, transmembrane protein) did not yield any significant results.

3.4.3. Apheresis treatment: Time to treatment, number of sessions, plasma exchange volume and type of apheresis

We examined paraclinical parameters in relation to the individual disease groups. Table 3 provides information on the extent to which the time from symptom onset to the start of AT (delta time in days) correlates with an improvement in the mRS. For all patients with a documented time interval, there was a negative correlation (the faster AT is started, the higher the improvement in mRS) with Spearman's $r = -0.255$ ($p < 0.001$). The subgroup analysis showed that, particularly in the groups with CIDP and MG/LEMS, a rapid start of therapy is associated with an improved outcome. There also was a non-significant trend in the NMOSD group. The PMS group showed a significant result, but the group size was too small for a meaningful statistical analysis.

On average, 8.01 ± 6.44 cycles of AT were performed in all patients. On average, patients in the ON group received the fewest cycles (mean ± SD = 6.3 ± 1.83) and patients in the NMOSD group received the most treatment cycles (mean ± SD 11.8 ± 9.15). However, the subgroup analysis showed that the positive correlation between the number of cycles and functional outcome was only significant in the CIDP group (Spearman's $r = 0.53$, $p < 0.001$).

Table 3
Correlation of the time interval from symptom onset to the start of AT (Δtime in days (d)) with ΔmRS per disease group. Expressed as mean ± SD. A negative correlation factor Spearman's r means that a shortened time interval leads to an improved outcome.

	n	time d (x ± SD)	ΔmRS (x ± SD)	r	p
AIDP	44	14 ± 12.2	1.02 ± 0.74	−0.095	0.541
RMS	54	41.9 ± 67.3	0.87 ± 0.81	0.011	0.94
CIDP	24	957.3 ± 1537.4	0.34 ± 0.78	−0.628	**0.001**
MG/LEMS	35	116.7 ± 433.7	1.35 ± 0.93	−0.388	**0.021**
NMOSD/ MOGAD	17	55.6 ± 82	0.86 ± 0.73	−0.438	0.079
AE	17	161.9 ± 212.8	0.9 ± 0.912	−0.044	0.866
ON	10	21.6 ± 9.3	0.7 ± 0.82	−0.58	0.881
PMS	6	156.3 ± 289.8	0.44 ± 0.53	0.878	0.021
AN	12	329.8 ± 738.3	0.38 ± 0.59	−0.078	0.81
Myelitis	8	52.9 ± 95.9	0.75 ± 0.89	−0.026	0.952
other	5	117.2 ± 186.4	0.67 ± 0.87	−0.791	0.111
all	231	171.4 ± 611.1	0.82 ± 0.85	−0.255	**<0.001**

The total plasma exchange volume (in liters (l)) of AT was investigated with regards to the functional outcome. While patients in the MG group had the highest average volume of plasma exchanged/filtered (mean ± SD = 45.1 ± 153.2 l), patients in the PMS group had less than half the volume exchanged/filtered (mean ± SD = 18.5 ± 6.3 l). However, the exchange volume only correlated significantly with the functional outcome ΔmRS (Spearman's $r = 0.506$, $p = 0.001$) in the CIDP group (mean = 25.4 ± 36.1 l). Details on the number of AT cycles and exchange volumes can be found in Tables S2 and S3 in the Supplement.

Furthermore, we investigated the influence of the type of AT on the extent of functional improvement (ΔmRS). We found no significant difference between patients treated with TPE ($n = 175$), IA ($n = 138$) or with a combination of both procedures ($n = 22$). In the Kruskal-Wallis test, no procedure (TPE: median = 1, range − 3–4; IA: median = 1, range − 1–3; combination: median = 1, range − 1–2) was more effective ($p = 0.29$) for both the total of patients and the different diagnostic groups.

3.4.4. Alternative disability scores: EDSS and visual acuity

In the observed patient population of patients diagnosed with RMS, PMS, NMOSD/MOGAD, ON or Myelitis, we found a highly significant correlation (Spearman's $r = 0.852$, $p < 0.001$) between the change in mRS and the change in the EDSS (ΔEDSS) due to the AT. EDSS after AT was significantly lower than before (median before and after AT = 3, mean 4.1 resp. 3.4, $p < 0.001$, Wilcoxon rank test).

However, with the (para-)clinic and apheresis related parameters (age of patient, time to treatment, pleocytosis, OCB, type of AT, number of cycles, and exchange volume) better correlations were shown using mRS as the clinical outcome parameter for the above-mentioned diagnoses.

As various diseases can lead to optic neuritis, we used the parameter of visual acuity determined by ophthalmologists. With regards to the parameter of visual acuity change due to AT (**Δ** visual acuity), we also found significant improvement after undergoing therapy (median 0.1 resp. 0.25, mean 0.18 resp. 0.36, $p < 0.001$, Wilcoxon rank test). No Group differences were found in the Kruskal-Wallis test, therefore the group sizes were too small.

Similar to the EDSS, the change in the visual acuity correlated significantly with the ΔmRS as well (Spearman's $r = 0.907$; $p < 0.001$). Time point of prior steroid therapy did not influence the improvement of visual acuity in the given cohort (Spearman's $r = -0.09$; $p = 0.81$), neither did the dose of it (Spearman's $r = -0.35$; $p = 0.32$).

3.5. (K5) Benefit of apheresis treatment as an indicator of stability under B cell depletion

After initial AT, 76 of 335 patients received long term B cell depletion (BCD), using rituximab, ocrelizumab or ofatumumab. Concerning these patients, we analyzed if initial profit through AT correlates with later disease stability under BCD, which is defined as a constant or improved mRS one year after starting therapy. We had follow up data on 50 of the 76 patients undergoing b cell depletion. The patient characteristics can be found in Table S4 in the Supplement.

Fig. 4 shows the course of the mRS values of the 50 patients in the color beam. Initially, there is a clear improvement in disability due to AT (decrease in the mRS sum score by 43 points) and stabilization during the variable time between the end of AT and the start of BCD (mean time between end of AT and start of BCD was 14.7 days). In the follow-up after one year of BCD, however, there was again a worsening of disability (increase in the mRS sum score by 17 points).

Patients who initially showed response to AT had a significantly more stable course through later BCD in the statistical analysis using the Mann-Whitney U test ($p = 0.039$) (Supplement Table 4).

In particular, patients with RMS and AE who benefited from AT appear to be stable under BCD. However, patients with NMOSD/MOGAD or MG/LEMS who benefited from AT show a variable response to BCD (Table S4). In the post hoc analysis, the AE subgroup was significantly more stable than the NMOSD/MOGAD and MG/LEMS subgroups ($p < 0.001$ in each case).

4. Discussion

The complication rate of AT was very low in our study, most frequently allergic reaction to FFP. The data were congruent with the known good tolerability [38].

In our analysis, we were able to reproduce the benefit of AT for the diagnoses that could be assigned to ASFA categories I and II. Likewise, the demonstration of unchanged or worsened mRS for all individuals in ASFA category IV, for whom no therapeutic response was expected according to ASFA criteria, allowed the exclusion of these patients from the detailed follow-up analysis [1]. While there was no difference between groups CI and CII in terms of mRS outcome, both groups were significantly superior to CIII. This is probably due to the heterogeneous composition of this group, in which the proportion of patients with a very good response was lowest, but on the other hand no patients deteriorating under AT were included.

The epidemiological data mean age of 53 years and predominance of the female sex is consistent with other AT studies in neurological diseases [11,39] and were not significantly influencing variables. In contrast, younger age appears to be advantageous in other studies for individual subgroups, e.g. AE [37]. We could show a similar trend for the RMS subgroup.The CSF parameters presence of pleocytosis or detection of intrathecal OCB did not play a relevant role for the outcome and is consistent with the fact that inflammatory signs cannot be detected in CSF in all diseases.

While smaller studies have reported varying response rates of >50% to almost 90% [11,12,39]. Our patients from ASFA CI, II, III showed a similar improvement but the different diagnoses and heterogeneous composition of the collective and requires more detailed data analysis:

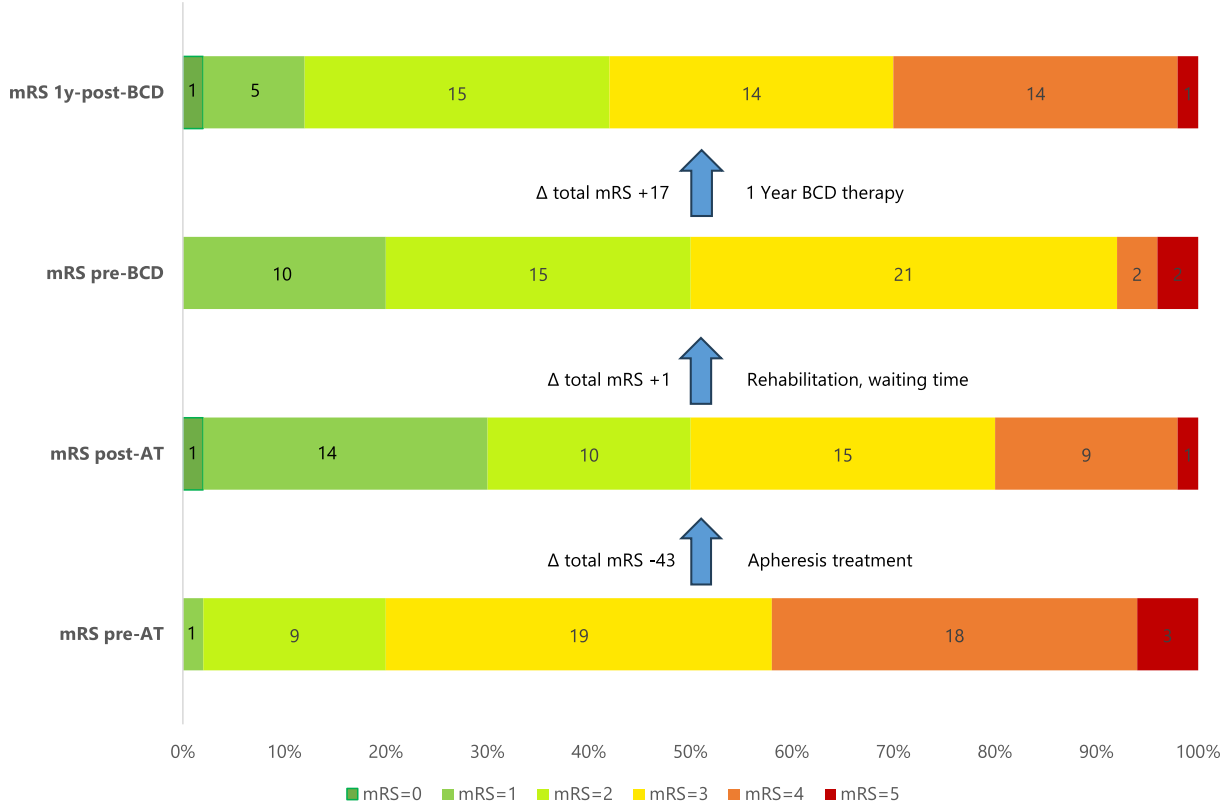

Fig. 4. Representation of the distribution of 50 patients on the mRS values 0–5 in the color scale (green, yellow, orange, red) over the course of the study at four points in time. Low mRS values (green) reflect low disability and high values reflect severe functional disability (orange/red). The absolute number of patients per mRS value is shown; the percentage distribution is presented below. The values are measured at the time before AT (mRS pre-AT), after completion of AT (mRS post-AT), before the start of BCD (mRS pre-BCD) and after one year of therapy with BCD (mRS 1Y-post-BCD). Decrease (**Δ**mRS total score) due to AT and slight increase in total disability in the follow-up after one year of BCD. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In the disease-related subgroup analysis, patients with AIDP, RMS, CIDP, MG/LEMS and NMOSD/MOGAD (each $p < 0.001$) and AE ($p = 0.002$) and AN ($p = 0.011$) showed the most significant improvement (even if before and after data on instrumental diagnostics (e.g. MRI) were unfortunately not available). This reflects the results of other studies [11,39–42], some of which, in contrast, have shown no therapeutic response in CIDP [11,12]. In this disease group and MG/LEMS, a faster onset of AT (time to treatment) was associated with a better outcome. It should be noted here that the time of deterioration tends to be recorded by patients as a rough time period. Diagnosis groups "myelitis of other kinds" and "other"did not appear to benefit from AT, which is probably due to the heterogeneous composition. The CIDP group was the only group in which a higher number of AT sessions or a higher exchanged plasma volume was beneficial for the functional outcome (ΔmRS).

Optic neuritis occurs in various diseases: isolated, in RMS [21], in MOGAD, in NMOSD, and double-negative NMOSD. Especially in the latter group, TPE does not seem to lead to a reliable improvement of vision, whereas a combination of rapid onset of TPE and few previous ON episodes in Aquaporin-4 antibody positive NMOSD patients show the best chances of improvement [43]. In our study, visual acuity was significantly better after AT, but there were no statistically significant differences between the subgroups.

We saw no difference in outcome when using TPE, IA or a combination of both ($p = 0.29$). However, smaller studies may suggest an advantage for IA (better effect and/or fewer complications) for individual disease groups [18]. There is evidence that TPE and IA lead to similar clinical improvements in MS and NMOSD patients [1], with levels of proinflammatory cytokines (Interferon-y, Tumor-necrosis-factor-α, Interleukin-12 and others) appearing to be lowered during IA [44].

We were able to show that the subgroup of patients with pathological autoantibodies (26.9%), regardless of whether the cell function is impaired, benefited more from AT than patients with no successful antibody detection. The most common antibody detected was anti-acetylcholine-Ab in MG patients (10.4%). It is already known that MG patients like in our collective show a rapid regression of symptoms and a decrease in acetylcholine antibody titres due to IA [45].

Unfortunately, the number of autoantibody-positive patients was too small to be able to make a statement on the improved effectiveness of TPE, IA or combination.

With regard to diseases triggered by autoantibodies, there is an important follow-up aspect for treatment: AT is mostly aimed at the treatment of autoimmune diseases in which pathological autoantibodies are detected or suspected. However, B cells, which mature into antibody-producing plasma cells, are not affected by AT. Thus, from a pathophysiological point of view, it appears conclusive that patients who respond to AT should also stabilize under BCD treatment. For the first time, we investigated the relationship between response to AT and subsequent stability under BCD in neurological diseases: We were able to show that the majority of patients who clinically benefit from AT ($\Delta mRS \geq 1$) are also stable or improve under BCD ($\Delta mRS \geq 0$). This fact must be interpreted with caution due to the limited long-term data of only one year of BCD to date and the small patient population. Nevertheless, the combination of short-term antibody reduction (through AT) and the long-term targeted reduction of pathological antibodies through BCD appears to be a promising therapeutic concept.

Of course, this study has some weaknesses. For example, it is a purely retrospective data analysis, which can lead to distortions in the interpretation. The same applies to the fact that the respective diagnoses were made by different physicians over a long period of time, not by a single physician in a standardized manner. Larger populations need to be studied in order to take into account the heterogeneity of the different diagnoses and also the different BCD therapies, which influence the B-cell populations and antibody-levels differently [24,26]. A prospective design and the additional use of disease-specific scores would be desirable, even though the mRS correlated well with functional disability across diseases [12,37,39], and with EDSS and visual acuity in our own cohort. For now, we were able to show that EDSS and visual acuity are good parameters for detecting AT-related improvement in suitable patients.

5. Conclusion

Our real-world data from the large cohort of 335 included patients and >2500 cycles of TPE and/or IA reflects the benefit of AT in many neurological autoimmune diseases. In particular, functional disability, measured via the mRS, improves in patients with AIDP, RMS, CIDP, MG/LEMS, NMOSD/MOGAD, AE, but to a lesser extent also in ON, AN and PMS. The presence of pathological autoantibodies in the serum is a predictor for a better response to TPE, IA or a combination, in contrast to the detection of inflammatory findings in the CSF. Patients with a response to AT are significantly more stable in long-term treatment with BCD.

Funding

No funds, grants, or other support were received.

Availability of data and material

All figures have associated raw data. The data that supports the findings of this study is available from the corresponding author upon reasonable request.

Ethics approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Ethikkommission der Ärztekammer des Saarlandes (vote No. 158/14). Written consent for the retrospective study and publication was not required by the ethics committee.

CRediT authorship contribution statement

Mathias Fousse: Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Investigation, Conceptualization. **Klaus Fassbender:** Writing – review & editing, Supervision, Conceptualization. **Stefan J. Schunk:** Writing – review & editing, Investigation. **Tina Schmidt:** Writing – review & editing, Supervision, Software. **Jakob Stögbauer:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of financial or non-financial interests.

Acknowledgements

The authors are grateful to all participants, who helped us gain knowledge regarding this subject.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123050.

References

[1] L. Connelly-Smith, C.R. Alquist, N.A. Aqui, et al., Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the writing Committee of the American Society for apheresis: the ninth special issue, J. Clin. Apher. 38 (2023) 77–278, https://doi.org/10.1002/jca.22043.

[2] S.R. Bornstein, K. Voit-Bak, T. Donate, et al., Chronic post-COVID-19 syndrome and chronic fatigue syndrome: is there a role for extracorporeal apheresis? Mol. Psychiatry 27 (2022) 34–37, https://doi.org/10.1038/s41380-021-01148-4.

[3] M. Achleitner, C. Steenblock, J. Dänhardt, et al., Clinical improvement of long-COVID is associated with reduction in autoantibodies, lipids, and inflammation following therapeutic apheresis, Mol. Psychiatry (2023), https://doi.org/10.1038/s41380-023-02084-1.

[4] E. Strasser, Principles of therapeutic apheresis in neurological disease, Transfus. Med. Hemother. 50 (2023) 88–97, https://doi.org/10.1159/000529463.

[5] C. Hafer, P. Golla, M. Gericke, et al., Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study, Int. Urol. Nephrol. 48 (2016) 133–138, https://doi.org/10.1007/s11255-015-1137-3.

[6] P.R. Bauer, M. Ostermann, L. Russell, et al., Plasma exchange in the intensive care unit: a narrative review, Intensive Care Med. 48 (2022) 1382–1396, https://doi.org/10.1007/s00134-022-06793-z.

[7] V. Schettler, Standard der Therapeutischen Apherese 2019, Deutsche Gesellschaft für Nephrologie e.V, Göttingen, 2019.

[8] M. Haas, N. Mayr, J. Zeitlhofer, et al., Long-term treatment of myasthenia gravis with immunoadsorption, J. Clin. Apher. 17 (2002) 84–87, https://doi.org/10.1002/jca.10023.

[9] S. Wagner, R. Janzen, C. Mohs, et al., Langzeitbehandlung der therapierefraktären Myasthenia gravis mittels Immunadsorption, Dtsch. Med. Wochenschr. 133 (2008) 2377–2382, https://doi.org/10.1055/s-0028-1100928.

[10] K. Gwathmey, R.A. Balogun, T. Burns, Neurologic indications for therapeutic plasma exchange: 2013 update: neurologic indications for therapeutic plasma exchange, J. Clin. Apher. 29 (2014) 211–219, https://doi.org/10.1002/jca.21331.

[11] E. Kaya, M. Keklik, M. Şencan, et al., Therapeutic plasma exchange in patients with neurological diseases: multicenter retrospective analysis, Transfus. Apher. Sci. 48 (2013) 349–352, https://doi.org/10.1016/j.transci.2013.04.015.

[12] I. Nieto-Aristizábal, A.J. Vivas, P. Ruiz-Montaño, et al., Therapeutic plasma exchange as a treatment for autoimmune neurological disease, Autoimmune Diseases 2020 (2020) 1–6, https://doi.org/10.1155/2020/3484659.

[13] Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome Study Group, Neurology 35 (1985) 1096–1104.

[14] A. Marn Pernat, J. Buturović-Ponikvar, V. Švigelj, R. Ponikvar, Guillain-Barré syndrome treated by membrane plasma exchange and/or Immunoadsorption, Ther. Apher. Dial. 13 (2009) 310–313, https://doi.org/10.1111/j.1744-9987.2009.00730.x.

[15] I. Cortese, V. Chaudhry, Y.T. So, et al., Evidence-based guideline update: plasmapheresis in neurologic disorders: report of the therapeutics and technology assessment Subcommittee of the American Academy of neurology, Neurology 76 (2011) 294–300, https://doi.org/10.1212/WNL.0b013e318207b1f6.

[16] H.J. Willison, B.C. Jacobs, P.A. Van Doorn, Guillain-Barré syndrome, Lancet 388 (2016) 717–727, https://doi.org/10.1016/S0140-6736(16)00339-1.

[17] P.J. Dyck, J. Daube, P. O'Brien, et al., Plasma exchange in chronic inflammatory demyelinating Polyradiculoneuropathy, N. Engl. J. Med. 314 (1986) 461–465, https://doi.org/10.1056/NEJM198602203140801.

[18] I. Lieker, T. Slowinski, L. Harms, et al., A prospective study comparing tryptophan immunoadsorption with therapeutic plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy*, J. Clin. Apher. 32 (2017) 486–493, https://doi.org/10.1002/jca.21546.

[19] N. Galldiks, L. Burghaus, C. Dohmen, et al., Immunoadsorption in patients with chronic inflammatory demyelinating Polyradiculoneuropathy with unsatisfactory response to first-line treatment, Eur. Neurol. 66 (2011) 183–189, https://doi.org/10.1159/000331011.

[20] Pfeuffer Rolfes, Ruck, et al., Therapeutic apheresis in acute relapsing multiple sclerosis: current evidence and unmet needs—a systematic review, JCM 8 (2019) 1623, https://doi.org/10.3390/jcm8101623.

[21] M.J. Koziolek, D. Tampe, M. Bähr, et al., Immunoadsorption therapy in patients with multiple sclerosis with steroid-refractory optical neuritis, J. Neuroinflammation 9 (2012) 80, https://doi.org/10.1186/1742-2094-9-80.

[22] T. Srisupa Olan, S. Siritho, K. Kittisares, et al., Beneficial effect of plasma exchange in acute attack of neuromyelitis optica spectrum disorders, Mult. Scler. Relat. Disord. 20 (2018) 115–121, https://doi.org/10.1016/j.msard.2018.01.010.

[23] T. Songthammawat, T. Srisupa Olan, S. Siritho, et al., A pilot study comparing treatments for severe attacks of neuromyelitis optica spectrum disorders: intravenous methylprednisolone (IVMP) with add-on plasma exchange (PLEX) versus simultaneous ivmp and PLEX, Mult. Scler. Relat. Disord. 38 (2020) 101506, https://doi.org/10.1016/j.msard.2019.101506.

[24] R. Marignier, J.L. Bennett, H.J. Kim, et al., Disability outcomes in the N-MOmentum trial of Inebilizumab in Neuromyelitis Optica Spectrum disorder, Neurol. Neuroimmunol. Neuroinflamm. 8 (2021) e978, https://doi.org/10.1212/NXI.0000000000000978.

[25] P. Barreras, E.S. Vasileiou, A.G. Filippatou, et al., Long-term effectiveness and safety of rituximab in Neuromyelitis Optica Spectrum disorder and MOG antibody disease, Neurology 99 (2022), https://doi.org/10.1212/WNL.0000000000201260.

[26] I. Roos, S. Hughes, G. McDonnell, et al., Rituximab vs Ocrelizumab in relapsing-remitting multiple sclerosis, JAMA Neurol. 80 (2023) 789, https://doi.org/10.1001/jamaneurol.2023.1625.

[27] S.L. Hauser, A. Bar-Or, G. Comi, et al., Ocrelizumab versus interferon Beta-1a in relapsing multiple sclerosis, N. Engl. J. Med. 376 (2017) 221–234, https://doi.org/10.1056/NEJMoa1601277.

[28] M.J. Furman, S.G. Meuth, P. Albrecht, et al., B cell targeted therapies in inflammatory autoimmune disease of the central nervous system, Front. Immunol. 14 (2023) 1129906, https://doi.org/10.3389/fimmu.2023.1129906.

[29] R. Zhang, A.B. Dahl, B. Marchant, et al., Optimizing management of replacement fluids for therapeutic plasma exchange: use of an automated mathematical model to predict post-procedure fibrinogen and antithrombin levels in high-risk patients, J. Clin. Apher. 35 (2020) 41–49, https://doi.org/10.1002/jca.21758.

[30] K.B.G. Sprenger, K. Huber, W. Kratz, E. Henze, Nomograms for the prediction of patient's plasma volume in plasma exchange therapy from height, weight, and hematocrit, J. Clin. Apher. 3 (1987) 185–190, https://doi.org/10.1002/jca.2920030313.

[31] T. Quinn, J. Dawson, M. Walters, Dr John Rankin; his life, legacy and the 50th anniversary of the Rankin stroke scale, Scott. Med. J. 53 (2008) 44–47, https://doi.org/10.1258/RSMSMJ.53.1.44.

[32] T.J. Quinn, M. Taylor-Rowan, A. Coyte, et al., Pre-stroke modified Rankin scale: evaluation of validity, prognostic accuracy, and association with treatment, Front. Neurol. 8 (2017) 275, https://doi.org/10.3389/fneur.2017.00275.

[33] B. Farrell, J. Godwin, S. Richards, C. Warlow, The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results, J. Neurol. Neurosurg. Psychiatry 54 (1991) 1044–1054, https://doi.org/10.1136/jnnp.54.12.1044.

[34] A. Osen, D. Stefoski, T. Shoemaker, et al., Cyclophosphamide for severe acute forms of central nervous system inflammatory disorders, J. Neurol. Sci. 451 (2023) 120693, https://doi.org/10.1016/j.jns.2023.120693.

[35] M.E. Farrugia, C. Carmichael, B.J. Cupka, et al., The modified Rankin scale to assess disability in myasthenia gravis: comparing with other tools, Muscle Nerve 50 (2014) 501–507, https://doi.org/10.1002/mus.24214.

[36] S.-P. Lin, A. Calcagno, S.L. Letendre, Q. Ma, Clinical treatment options and randomized clinical trials for neurocognitive complications of HIV infection: Combination antiretroviral therapy, central nervous system penetration effectiveness, and adjuvants, in: L.A. Cysique, S.B. Rourke (Eds.), Neurocognitive Complications of HIV-Infection, Springer International Publishing, Cham, 2020, pp. 517–545.

[37] J. Heine, L.-T. Ly, I. Lieker, et al., Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study, J. Neurol. 263 (2016) 2395–2402, https://doi.org/10.1007/s00415-016-8277-y.

[38] A. Gala-Błądzińska, K. Mazur, A. Dębiec, et al., Safety and tolerability of therapeutic plasma exchange in autoimmune neurological diseases — a retrospective single-Centre analysis, Neurol. Neurochir. Pol. 54 (2020) 344–349, https://doi.org/10.5603/PJNNS.a2020.0045.

[39] Y. Lin, S. Oji, K. Miyamoto, et al., Real-world application of plasmapheresis for neurological disease: results from the Japan-Plasmapheresis outcome and practice patterns study, Ther. Apher. Dial. 27 (2023) 123–135, https://doi.org/10.1111/1744-9987.13906.

[40] J. Das, V.D. Chauhan, D. Mills, et al., Therapeutic plasma exchange in neurological disorders: experience from a tertiary neuroscience Centre, Transfus. Apher. Sci. 58 (2019) 102654, https://doi.org/10.1016/j.transci.2019.09.007.

[41] B.G. Weinshenker, P.C. O'Brien, T.M. Petterson, et al., A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease, Ann. Neurol. 46 (1999) 878–886, https://doi.org/10.1002/1531-8249(199912)46:6<878::aid-ana10>3.0.co;2-q.

[42] S.M. Magaña, Beneficial plasma exchange response in central nervous system inflammatory demyelination, Arch. Neurol. 68 (2011) 870, https://doi.org/10.1001/archneurol.2011.34.

[43] J. Fu, Y. Wang, H. Li, et al., Efficacy of plasma exchange treatment for demyelinating optic neuritis associated with various serum antibodies: a prospective cohort study, Neurol. Ther. 11 (2022) 797–813, https://doi.org/10.1007/s40120-022-00344-w.

[44] S.C. Boedecker, F. Luessi, S. Engel, et al., Immunoadsorption and plasma exchange—efficient treatment options for neurological autoimmune diseases, J. Clin. Apher. 37 (2022) 70–81, https://doi.org/10.1002/jca.21953.

[45] C. Loschiavo, M. Grecò, A. Polo, R. Del Colle, The use of therapeutic apheresis in neurological diseases and comparison between plasma exchange and immunoadsorption, G. Ital. Nefrol. 32 (2015) gin/32.1.10.