J Neurol (2016) 263:2395–2402
DOI 10.1007/s00415-016-8277-y

ORIGINAL COMMUNICATION

Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study

Josephine Heine[1] · Lam-Thanh Ly[1,2] · Ina Lieker[3] · Torsten Slowinski[3] · Carsten Finke[1,4] · Harald Prüss[1,2] · Lutz Harms[1]

Received: 7 July 2016 / Revised: 24 August 2016 / Accepted: 29 August 2016 / Published online: 7 September 2016

Abstract Therapeutic apheresis has emerged as a major treatment option for autoantibody-associated inflammatory diseases of the nervous system. This includes patients with autoimmune encephalitides caused by antibodies against neuronal proteins. Plasma exchange (PE) and immunoadsorption (IA) constitute two possibilities to eliminate pathogenic antibodies from patients' plasma, but their efficacy and safety has not been prospectively assessed in larger patient groups of autoimmune encephalitides. In a prospective observational case control study, we, therefore, investigated the disease courses and treatment effects of 21 patients with autoimmune encephalitis associated with NMDAR, LGI1, CASPR2, GAD, mGluR5 and Hu antibodies. Patients were randomly assigned to receive PE ($n = 11$) or IA ($n = 10$). Symptoms were evaluated using the modified Rankin Scale (mRS). Side effects or adverse events were recorded. Both interventions, IA ($p = 0.014$) and PE ($p = 0.01$), resulted in significant reduction of the median mRS. With IA, 60 % of the patients improved clinically by at least 1 mRS score, none worsened. PE led to a comparable symptom reduction in 67 % of the cases. During 83 PE sessions, three adverse events were documented, while no side effects occurred under IA. Symptom improvement was significantly associated with younger age ($r = -0.58$), but not with disease duration. Therapeutic apheresis was most effective for neuronal surface antigens (83.3 %), followed by intracellular-synaptic antigens (66.7 %). Both IA and PE resulted in moderate to marked clinical improvement, with a low rate of adverse events. Apheresis is well tolerated and effective also as first-line therapy in autoimmune encephalitis, particularly in patients with antibodies targeting neuronal surfaces.

Keywords Autoimmune encephalitis · Immunotherapy · Autoimmunity · Plasma exchange · Immunoadsorption

JH and LTL contributed equally to the work.

✉ Josephine Heine
josephine.heine@charite.de

[1] Department of Neurology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

[2] German Center for Neurodegenerative Diseases (DZNE) Berlin, Charitéplatz 1, 10117 Berlin, Germany

[3] Department of Nephrology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

[4] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Luisenstr. 56, 10117 Berlin, Germany

Introduction

Over the past years, autoimmune encephalitides have emerged as a distinct neuropathology and constitute a heterogeneous group of inflammatory central nervous system (CNS) diseases [1]. Antibodies target intracellular antigens (such as Hu or Ma2) or proteins and receptors on the cell surface and membrane (e.g. NMDAR, LGI1, CASPR2). Following a subacute onset of disorientation and memory deficits, symptoms often progress to seizures, psychosis, sleep disorder and agitation, while the specific disease course, symptomatology [2, 3] and neuroimaging [4, 5] depend on the antibody type.

Case studies and retrospective analyses have established a multimodal treatment protocol for autoimmune encephalitides, comprising high-dose corticosteroids, intravenous immunoglobulins (IVIG), and plasmapheresis (PE) or immunoadsorption (IA) as first-line therapy. Rituximab or cyclophosphamide may be added as second-line treatment in patients without response to first-line therapy or relapsing symptoms. Immunotherapy is most

effective when administered early after symptom onset [6, 7].

Several antibodies are pathogenic by disrupting the structure and function of their antigens. In the case of anti-NMDAR encephalitis, antibodies mediate internalization of NMDAR clusters [8]. Since recovery and symptom remission are accompanied by a decline in titres [9], reducing the number of autoantibodies is a primary treatment approach. PE and IA both provide an opportunity for the extracorporeal elimination of circulating antibodies. While the treated plasma volume is replaced by a human albumin solution or fresh frozen plasma (FFP) in PE, IA follows a more selective approach: the patients' plasma is passed to an adsorber column to remove immunoglobulins and immune complexes and thereupon re-infused into the blood circuit.

Therapeutic apheresis has been shown to result in moderate to marked clinical improvement across several inflammatory autoantibody associated diseases of the central and peripheral nervous system, such as Guillain-Barré syndrome [10] and multiple sclerosis [11, 12]. With regard to autoimmune encephalitides, symptom remission following a treatment regimen that included PE has been reported in patients with anti-NMDAR [6, 13, 14] and voltage-gated potassium channel complex antibodies [15]. In a recent retrospective study in anti-NMDAR encephalitis, the combined treatment with PE and intravenous steroids was found to be more effective than intravenous steroids alone [16]. Likewise, immunoadsorption promoted recovery with no [17] or few adverse events [18].

As previously pointed out, IA may be of similar efficacy and safety compared to the non-selective approach of PE. Data comparing these two apheresis approaches are still scarce in autoimmune encephalitis. In the present study, we, therefore, prospectively analyzed the treatment courses of 21 patients treated with PE or IA and provide information on clinical features, symptom outcome, and safety.

Patients and methods

Patients

Twenty-one patients with autoimmune encephalitis and indication for IA/PE were enrolled in the prospective observational case control study at the Clinic of Neurology at Charité University Hospital Berlin between 2013 and 2015. All patients had an established diagnosis of autoimmune encephalitis based on the typical clinical features, antibody detection, CSF findings, abnormalities in magnetic resonance imaging and the exclusion of relevant differential diagnoses. The study comprised 13 female and 8 male patients with an age range of 16–76 years (mean = 49.0 years, SD = 16.0 years) with antibodies against glutamic acid decarboxylase (GAD, $n = 6$), *N*-methyl-D-aspartate receptors (NMDAR, $n = 5$), the leucine-rich glioma inactivated 1 protein (LGI1, $n = 4$), contactin-associated protein-like 2 (CASPR2, $n = 2$), and metabotropic glutamate receptor 5 (mGluR5, $n = 1$). Three patients had anti-Hu antibodies. Demographic and clinical features of the patients were derived from the review of medical records (Table 1).

Apheresis treatments

In the majority of patients, the decision for the treatment with PE or IA was made after unsuccessful or incomplete recovery from therapy with high-dose cortisone (3–5 days à 1000 mg IV methylprednisolone) and intravenous immunoglobulins (2 g/kg body weight over 5 days). Eleven patients were randomly assigned to receive a series of 5–12 PE sessions (median: 7). Ten patients were treated with IA (3–7 sessions, median: 5.5). All patients received a central venous catheter placed in an internal jugular vein as vascular access. IA treatments were performed using a single-use TR-350 tryptophan adsorber (ASAHI Kasei Medical Tokyo, Japan) and the tubing system PA-420 (Beldico, Belgium). Plasma was separated using a polyethylene OP-05W plasma separator together with Octo Nova SW430.2 technology (DIAMED, Cologne, Germany). Angiotensin-converting enzyme inhibitors were paused 48 h prior to IA to reduce the risk of IA-associated bradykinin release syndrome. For each patient, plasma volume was estimated according to Sprenger's formula [19]. A total of the 1.5-fold plasma volume was treated for PE and 2000–2500 ml per treatment for IA. Treatment was administered every other day. In PE, a 4 % human albumin (HA) solution (diluted from a 5 % HA stock solution, Albutein 5 % Grifols, Frankfurt, Germany) was used as a replacement solution. FFP was used only in patients at risk of bleeding. During treatment, patients were anticoagulated with systemic unfractionated heparin and their vital signs were monitored, including blood pressure, heart rate, and body temperature.

Statistical analysis

Treatment efficacy was evaluated using the modified Rankin Scale (mRS) score before and after the treatment series. A reduction of one point was considered as clinically relevant. The statistical significance of the treatment-related mRS changes was determined using the Wilcoxon signed-rank test for each treatment group. A p value <0.05 was considered significant. The effect size r was calculated based on the z value using the formula $r = z/\sqrt{N}$.

Table 1 Patient characteristics

No.	Ab	Gender	Age	Tumour	MRI	EEG	ICU	Preceding immunotherapy	Cycles	mRS pre	mRS post	Follow-up immunosuppression
Immunoadsorption												
1	NMDAR	f	35	Ovarian teratoma	Mild frontotemporal white matter glioses	(Not evaluable due to fluctuation of vigilance)	Yes	IVIG	7	2	1	–
2	LGI1	f	70	Small intestinal neuroendocrine tumour	Left mesiotemporal hyperintensities, supratentorial leukoencephalopathy	Left temporal seizure pattern (after stopping Keppra)	–	–	6	3	2	Methyl-prednisolone, Rituximab
3	LGI1	m	60	–	Bilateral mesiotemporal hyperintensities	–	–	IV steroids	6	3	2	Methyl-prednisolone, Rituximab
4	LGI1	m	64	–	Bilateral mesiotemporal hyperintensities	Increased cerebral excitability	–	IV steroids, IVIG	5	4	3	Rituximab
5	CASPR2	m	71	–	Bilateral mesiotemporal hyperintensities, periventricular leukencephalopathy	Unremarkable	–	IV steroids, IVIG	5	3	3	Methyl-prednisolone
6	GAD	m	36	–	Moderate global atrophy with mesiotemporal accentuation	Unremarkable	–	IV steroids	6	1	1	Rituximab
7	GAD	f	46	Uterine myoma	Unremarkable	Focal abnormal activity in left temporal lobe	–	–	5	3	2	Rituximab
8	GAD	f	54	–	–	Unremarkable	–	–	7	3	2	Rituximab
9	Anti-Hu	m	58	Small-cell lung carcinoma	–	Unremarkable	–	IV steroids	5	3	3	–
10	mGluR5	f	31	–	Unremarkable	Pathological alpha activity with left hemispheric functional disturbance	–	–	3	2	1	Rituximab
Plasma exchange												
11	NMDAR	f	22	Ovarian teratoma	Unremarkable	–	Yes	–	10	3	1	Methyl-prednisolone, Rituximab
12	NMDAR	f	18	Ovarian teratoma (unilaterally malignant)	Unremarkable	–	Yes	–	8	4	2	Rituximab
13	NMDAR	f	21	Ovarian teratoma	Unremarkable	Increased cerebral excitability	Yes	IV steroids, IVIG	6	3	1	Rituximab
14	NMDAR	f	16	–	Unremarkable	Moderate generalised slowing	Yes	IV steroids, IVIG	6	3	1	Methyl-prednisolone, Rituximab

Table 1 continued

No.	Ab	Gender	Age	Tumour	MRI	EEG	ICU	Preceding immunotherapy	Cycles	mRS pre	mRS post	Follow-up immunosuppression
15	LGI1	m	62	–	Predominantly left mesiotemporal hyperintensities extending to insular cortex	Unremarkable	Yes	IV steroids, IVIG	9	4	3	–
16	CASPR2	m	54	–	Unremarkable	–	–	IV steroids, IVIG	5	3	2	Methyl-prednisolone, Rituximab
17	GAD	f	52	Gallbladder carcinoma	Frontal and mesiotemporal hyperintensities extending to insular cortex	Occipital discontinuous patterns with moderately increased cerebral excitability	Yes	IV steroids	10	4	3	Cyclophos-phamide, Methyl-prednisolone, Rituximab
18	GAD	f	76	–	Mild global atrophy, leukencephalopathic opercular lesion	Unremarkable	–	–	7	4	4	Rituximab
19	GAD	f	74	Benign osteoma of the humerus	Bilateral mesiotemporal and cerebellar hyperintensities	–	–	IV steroids	5	3	2	Rituximab
20	Anti-Hu	m	48	Testicular carcinoma	Left mesiotemporal hyperintensities	Left frontotemporal seizure pattern	–	IV steroids, IVIG	12	1	1	Cyclophos-phamide
21	Anti-Hu	f	61	Mamma carcinoma	–	–	–	IVIG	5	4	4	Cyclophos-phamide

Ab antibody; *MRI* magnetic resonance imaging; *EEG* electroencephalography; *ICU* intensive care unit; *IV* intravenous; *IVIG* intravenous immunoglobulin; *mRS* modified Rankin Scale; *NMDAR N*-methyl-D-aspartate receptor; *LGI1* leucine-rich, glioma-inactivated 1 protein; *CASPR2* contactin-associated protein-like 2; *GAD* glutamic acid decarboxylase; *mGluR5* metabotropic glutamate receptor 5

Differences between categorical variables were analyzed using the χ^2 test, and the results of the Fisher's exact test are reported accordingly. Furthermore, we applied the Mann–Whitney test as a non-parametric equivalent to the independent samples t test. Spearman correlations were calculated for non-parametric ranked data and reported with 95 % confidence intervals (CI). Statistical analysis was performed using IBM SPSS Statistics 22. All figures were created using SigmaPlot 11.0. Error bars show the standard error of the mean.

Results

Symptom severity as baseline characteristic did not differ between patients treated by IA versus patients treated by PE ($U = 81.0$, $p = 0.18$, $r = 0.36$). The median disease duration, defined as the time span between symptom onset and IA/PE treatment, was 14.1 months for IA (range 1–98.6 months, CI [5.3, 48.6]) and 4.7 months for PE (range 0.2–84.3 months, CI [1.7, 9.0]; $U = 25.5$, $p = 0.04$, $r = -0.45$). Across both groups, patients with and without previous IVIG/high-dose corticosteroids benefitted from the treatment. Apathy (100 %), aphasia (100 %), stupor (100 %), sleep disorder (88.9 %), agitation (83.3 %), myoclonus/dystonia (80 %), sensory neuropathy (75 %), apraxia (75 %), and seizures (71.4 %) were the symptoms which responded best to therapeutic apheresis in our sample (Fig. 1). Treatment-related improvement was observed in 83.3 % of the patients with neuronal cell surface antibodies (NMDAR, LGI1, CASPR2, mGluR5), 66.7 % of the patients with intracellular-synaptic (GAD) and none of the cases with intracellular antigens (anti-Hu). The effect of antigen type on treatment responsiveness was statistically significant ($p = 0.032$, Fisher's exact test). Post-hoc analyses revealed a significant difference between the response rates of cell surface and intracellular antigens ($p = 0.022$, Fisher's exact test). Furthermore, patients with a history of tumour resection improved more often (75 %) than patients with a non-paraneoplastic autoimmune encephalitis (50 %; not significant: $p = 0.659$; Fisher's exact test). The magnitude of the mRS decrease was significantly associated with age ($r_S = -0.58$, $p = 0.014$, CI [−0.81, −0.03]; Fig. 2a), but not with the duration of the disease until the time point of treatment ($r_S = -0.31$, $p = 0.17$, CI [−0.70, 0.15]; Fig. 2b).

Immunoadsorption

Out of the ten patients treated with IA (Table 1), three had received high-dose corticosteroids, one intravenous immunoglobulins and two patients had been treated with both prior to IA. In the four remaining patients, IA was the first immunotherapy. The adsorption was well tolerated by all patients, and relevant adverse events (beyond the common transient symptoms of nausea, hypotension or mild hematoma associated with the vascular access) were not observed during the 55 performed sessions. Before IA, patients had a median mRS score of 3 (range 1–4, CI [2.3, 3.2], mean = 2.8). Clinically relevant improvement was observed in 60 % of the patients (Fig. 3). All treatment-responding patients decreased by one mRS point (median = 2, range 1–3, CI [1.8, 2.6], mean = 2.1). None of the patients worsened. The symptom improvement proved to be statistically significant ($T = -2.45$, $p = 0.014$, $r = -0.78$).

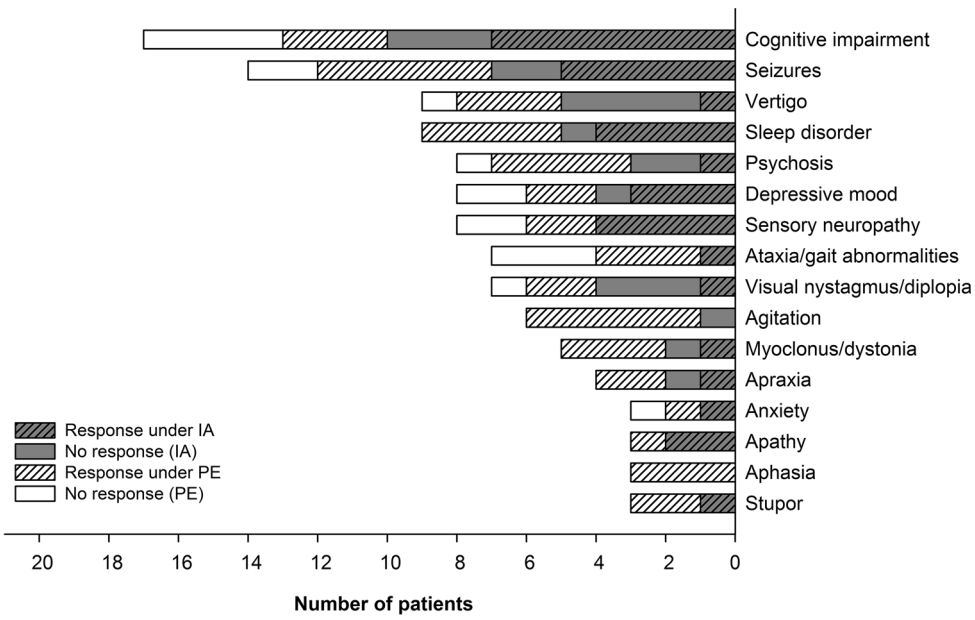

Fig. 1 Frequent symptoms and their responsiveness to treatment

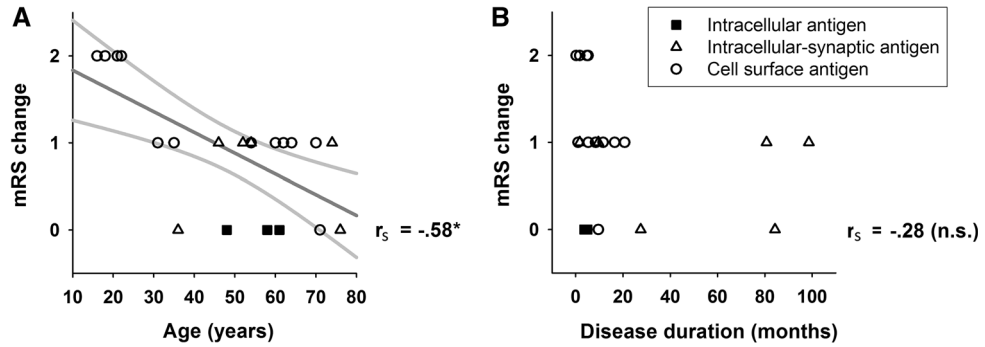

Fig. 2 **a** Treatment-related decline of symptom severity (reduction in points on the modified Rankin Scale, mRS) was significantly associated with age at treatment onset (Spearman correlation with 95 % confidence intervals; $r_S = -0.52$, $p = 0.014$). **b** In contrast, treatment delay (time between the onset of first symptoms and administration of IA/PE) was not significantly associated with a worsened outcome ($r_S = -0.31$, $p = 0.17$), indicating that therapeutic apheresis can be useful for the management of a broader spectrum of disease courses (*ns* not significant)

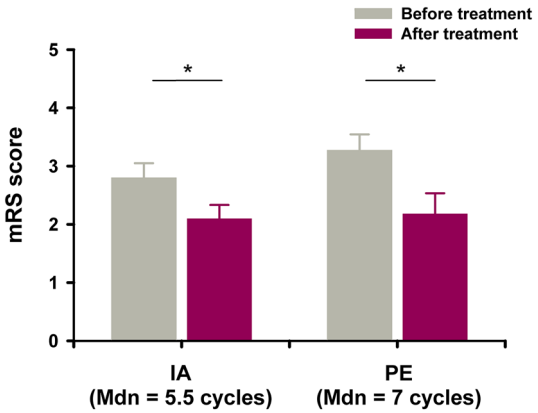

Fig. 3 Symptom severity assessment using the modified Rankin Scale (mRS) before and after treatment. The two groups did not differ in their symptom severity before treatment ($p = 0.18$, $r = 0.36$). Both the immunoadsorption (IA, $p = 0.014$, $r = -0.78$) and the plasma exchange patient group (PE, $p = 0.01$, $r = -0.75$) improved significantly after treatment (Wilcoxon signed rank test)

Plasma exchange

Eleven patients were treated with PE (Table 1). Five patients received PE after incomplete or absent recovery following both IVIG and high-dose corticosteroids. Another two patients had received high-dose corticosteroids only, one patient had a previous treatment attempt with IVIG only, and the remaining three patients had no previous treatment. During the 83 administered PE sessions, no adverse events occurred in the majority of the 11 patients. In one case, catheter-associated infection led to the cessation of treatment. After management of infection and interim IVIG, PE was resumed and she experienced marked symptom improvement. Anaemia was documented in one case. The completion of PE was feasible and the patient improved clinically. A third patient showed a marked fibrinogen decrease and changed from human serum albumin to FFP. A subsequent allergic reaction towards FFP and normalization of the fibrinogen level prompted a return to human serum albumin. Clinical improvement remained absent in this case. 67 % of the PE patients showed a clinically relevant improvement. Four patients decreased by one point on the mRS and five patients, all cases of anti-NMDAR encephalitis, improved substantially by two mRS points (Fig. 3). The median mRS score decreased significantly from 3 (range 1–4, CI [2.5, 3.5], mean = 3.27) to 2 (range 1–4, CI [1.4, 2.6], mean = 2.18; $T = -2.59$, $p = 0.01$, $r = -0.75$). Three patients did not respond to the therapy, none of them worsened.

Discussion

In this prospective observational analysis, we evaluated the treatment outcome under IA or PE in 21 patients with autoimmune encephalitis. 60 % of the patients receiving IA showed a clinically relevant improvement of at least one mRS score. This outcome is comparable to previous findings showing response rates ranging from 47 to 85 % in recent studies of autoimmune encephalitis [17, 18] and an earlier study of paraneoplastic neurological syndromes [20]. Three principal mechanisms of action have been proposed to underlie treatment effects in IA [21]: Autoantibodies are instantly removed from the plasma, their redistribution is induced and provokes succeeding immunomodulatory changes. Out of the 11 patients treated with PE in our study, 67 % showed moderate to marked symptom regression. Case studies have reported successful treatment with PE in autoimmune encephalitis [22, 23]. In other neurological diseases, response rates to PE range from 42 to 60 % in CNS inflammatory demyelinating disease [11, 24] to symptom improvement in all patients in

a study of myasthenia gravis and Guillain-Barré syndrome [10].

We did not observe severe adverse events during IA. In the course of the 83 PE treatments, a fibrinogen decrease and allergic reaction to FFP were observed in one patient during two sessions, another patient developed anaemia and a catheter infection occurred in a further case. As no allo-proteins are substituted in IA, our evaluation suggests good tolerability by reducing the risk for allergic reactions. Similarly, side effects were observed less frequently in IA compared to PE in myasthenic crisis [25]. Beside the potential adverse effects of substitution with foreign plasma, IA precludes the—albeit extremely rare—risk of pathogen transmission [26].

In this patient sample, both treatment options were administered with a comparable number of sessions [median 7 (PE) vs. 5.5 (IA)] and lead to a clinically and statistically significant symptom amelioration. Since both groups did not differ in their mRS scores before the treatment, results of this pilot study suggest that IA and PE constitute two treatment options of equivalent efficacy. This equivalent efficacy was demonstrated despite the fact that IA was performed less frequently and in patients with longer disease duration.

Notably, clinical improvement following therapeutic apheresis was achieved in all cases of anti-NMDAR, mGluR5 and LGI1 encephalitis, and in one of two patients with CASPR2 encephalitis. These findings are in line with observations from a previous study in which 64 % of the patients with cell surface antigens showed symptom improvement [18]. No benefit was seen for intracellular antigens (Fig. 4). Our findings suggest that therapeutic apheresis is particularly effective in patients with antibodies against proteins or receptors on the cell surface, and should be considered as a treatment option in GAD encephalitis. In the same way, the observed association between better treatment outcomes and younger age may be driven by the distinct patient characteristics of the particular encephalitides: In our study, all patients with a remarkable improvement of two mRS points suffered from anti-NMDAR encephalitis, which is in turn predominantly observed in younger women [6].

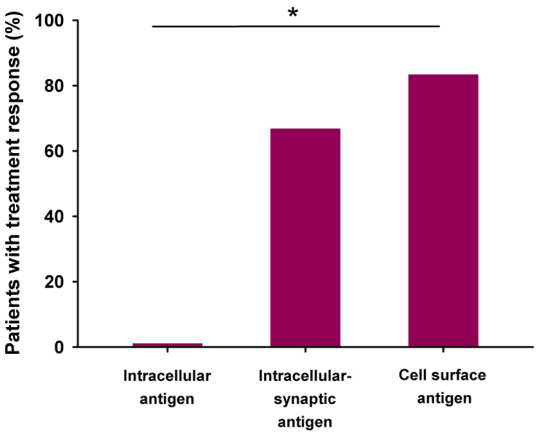

Fig. 4 Treatment-related improvement was observed more often for neuronal cell surface (NMDAR, LGI1, CASPR2, mGluR5) than for intracellular-synaptic antigens (GAD). None of the patients with intracellular antigens (anti-Hu) improved. The effect of antigen type on treatment responsiveness was statistically significant ($p = 0.032$, Fisher's exact test). Post-hoc analyses revealed a significant difference between the response rates of cell surface and intracellular antigens ($p = 0.022$, Fisher's exact test)

Moreover, it is currently unclear whether treatment effects of therapeutic apheresis are limited to an early treatment onset. As there was no association between treatment delay and response in our patients, we propose that therapeutic apheresis can be useful for the management of a broader spectrum of patients. A later treatment was previously not found to be a significant limitation for treatment response in CNS inflammatory demyelination [24, 27]. Nevertheless, early tumour removal in paraneoplastic encephalitides has an important impact on the clinical outcome of the immunotherapy protocol [3].

Autoimmune encephalitides are relatively rare, and severe courses with autonomic instability or poor patient cooperation can potentially complicate a successful administration of therapeutic apheresis. Nonetheless, future prospective and randomized study designs can help to find the ideal number of apheresis sessions and elaborate on antibody titres, neuropsychological and clinical long-term outcomes.

Acknowledgments We thank Dr. Cordula Fassbender and Prof. Reinhard Klingel for helpful comments on the manuscript.

Compliance with ethical standards

Ethical standards All participants or next of kin gave informed written consent for participation. The study was approved by the Ethics Committee of the Charité University Hospital Berlin and conducted in accordance with the principles of the Declaration of Helsinki (1964) and its later amendments.

Conflicts of interests Dr. Slowinski reports Grants from DIAMED, Germany, during the conduct of the study; Grants from Fresenius Medical Care, Germany, outside the submitted work. Dr. Prüss reports Grants from AFI, during the conduct of the study. Dr. Harms reports speaker honoraria from Biogen, Bayer, Genzyme, Roche, Novartis, Grifols and Merck-Serono. He serves on the advisory board for Roche, Biogen, Novartis, Genzyme and TEVA and has received travel support from Bayer, Grifols, Novartis and Biogen; outside of the submitted work.

References

1. Graus F, Saiz A, Lai M, Bruna J, Lopez F, Sabater L et al (2008) Neuronal surface antigen antibodies in limbic encephalitis:

clinical and immunologic associations. Neurology 71(12):930–936. doi:10.1212/01.wnl.0000325917.48466.55
2. Lancaster E, Huijbers MGM, Bar V, Boronat A, Wong A, Martinez-Hernandez E et al (2011) Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 69(2):303–311. doi:10.1002/ana.22297
3. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10(1):63–74. doi:10.1016/S1474-4422(10)70253-2
4. Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C (2015) Imaging of autoimmune encephalitis–Relevance for clinical practice and hippocampal function. Neuroscience 309:68–83. doi:10.1016/j.neuroscience.2015.05.037
5. Finke C, Kopp UA, Scheel M, Pech LM, Soemmer C, Schlichting J et al (2013) Functional and structural brain changes in anti-*N*-methyl-D-aspartate receptor encephalitis. Ann Neurol 74(2):284–296. doi:10.1002/ana.23932
6. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T et al (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12(2):157–165. doi:10.1016/S1474-4422(12)70310-1
7. Finke C, Kopp UA, Prüss H, Dalmau J, Wandinger K-P, Ploner CJ (2012) Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosur Ps 83(2):195–198. doi:10.1136/jnnp-2011-300411
8. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R et al (2010) Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 30(17):5866–5875. doi:10.1523/JNEUROSCI.0167-10.2010
9. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F et al (2014) Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 13(2):167–177. doi:10.1016/S1474-4422(13)70282-5
10. Yücesan C, Arslan Ö, Arat M, Yücemen N, Ayyildiz E, Ilhan O et al (2007) Therapeutic plasma exchange in the treatment of neuroimmunologic disorders: review of 50 cases. Transfus Apher Sci 36(1):103–107. doi:10.1016/j.transci.2006.06.008
11. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW et al (1999) A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 46(6):878–886. doi:10.1002/1531-8249(199912)46:6<878
12. Trebst C, Bronzlik P, Kielstein JT, Schmidt BMW, Stangel M (2012) Immunoadsorption therapy for steroid-unresponsive relapses in patients with multiple sclerosis. Blood Purificat 33(1–3):1–6. doi:10.1159/000332397
13. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M et al (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7(12):1091–1098. doi:10.1016/S1474-4422(08)70224-2
14. Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J (2013) Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apheresis 28:349–355. doi:10.1002/jca.20311
15. Jaben EA, Winters JL (2012) Plasma exchange as a therapeutic option in patients with neurologic symptoms due to antibodies to voltage-gated potassium channels: a report of five cases and review of the literature. J Clin Apheresis 27(5):267–273. doi:10.1002/jca.21233
16. DeSena AD, Noland DK, Matevosyan K, King K, Phillips L, Qureshi SS et al (2015) Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-*N*-methyl-D-aspartate receptor antibody encephalitis: a retrospective review. J Clin Apheresis 30(4):212–216. doi:10.1002/jca.21363
17. Köhler W, Ehrlich S, Dohmen C, Haubitz M, Hoffmann F, Schmidt S et al (2014) Tryptophan immunoadsorption for the treatment of autoimmune encephalitis. Eur J Neurol. doi:10.1111/ene.12389
18. Dogan-Onugoren M, Golombeck KS, Bien C, Abu-Tair M, Brand M, Bulla-Hellwig M et al (2016) Immunoadsorption therapy in autoimmune encephalitides. Neurol Neuroimm Neuroinfl. doi:10.1212/NXI.0000000000000207
19. Sprenger KB, Huber K, Kratz W, Henze E (1987) Nomograms for the prediction of patient's plasma volume in plasma exchange therapy from height, weight, and hematocrit. J Clin Apheresis 3(3):185–190. doi:10.1002/jca.2920030313
20. Batchelor TT, Platten M, Hochberg FH (1998) Immunoadsorption therapy for paraneoplastic syndromes. J Neuro Oncol 40:131–136. doi:10.1023/A:1006136219490
21. Klingel R, Heibges A, Fassbender C (2013) Neurologic diseases of the central nervous system with pathophysiologically relevant autoantibodies–perspectives for immunoadsorption. Atheroscler Supp 14(1):161–165. doi:10.1016/j.atherosclerosissup.2012.10.024
22. Mazzi G, Roia D, Cruciatti B, Matà S, Catapano R (2008) Plasma exchange for anti GAD associated non paraneoplastic limbic encephalitis. Transfus Apher Sci 39(3):229–233. doi:10.1016/j.transci.2008.09.005
23. Mori M, Kuwabara S, Yoshiyama M, Kanesaka T, Ogata T, Hattori T (2002) Successful immune treatment for non-paraneoplastic limbic encephalitis. J Neurol Sci 201(1–2):85–88. doi:10.1016/S0022-510X(02)00188-0
24. Magana SM, Keegan BM, Weinshenker BG, Erickson BJ, Pittock SJ, Lennon VA et al (2011) Beneficial plasma exchange response in central nervous system inflammatory demyelination. Arch Neurol Chic 68(7):870–878. doi:10.1001/archneurol.2011.34
25. Köhler W, Bucka C, Klingel R (2011) A randomized and controlled study comparing immunoadsorption and plasma exchange in myasthenic crisis. J Clin Apher 28:349–355. doi:10.1002/jca.20317
26. Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B et al (2014) Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 384(9956):1766–1773. doi:10.1016/S0140-6736(14)61034-5
27. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker B (2002) Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 58(1):143–146. doi:10.1212/WNL.58.1.143