SHORT COMMUNICATION

Tryptophan immunoadsorption for the treatment of autoimmune encephalitis

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Background and purpose: Detection of autoantibodies against neuronal surface antigens and their correlation with the pattern and severity of symptoms led to the definition of new autoimmune-mediated forms of encephalitis and was essential for the initiation of immunotherapies including plasma exchange. The elimination of autoantibodies using selective immunoadsorption (IA) is a pathophysiologically guided therapeutic approach but has not yet been evaluated in a separate analysis.

Methods: A retrospective analysis was performed of patients with autoimmune encephalitis who were treated with tryptophan IA in six neurological clinics between 2009 and 2013. The modified Rankin scale (mRS) was used to evaluate neurological status before and after IA.

Results: Data on 13 patients were documented. Twelve patients were positive for specific autoantibodies (NMDA-R, GABA, GAD, Lgl1). Patients received a series of a median of six IA treatments. Median mRS of all patients was 3.0 before IA and 2.0 after IA ($P < 0.001$). Eleven patients improved by at least one point in mRS after IA.

Conclusion: For autoimmune-mediated forms of encephalitis rapid elimination of autoantibodies with selective IA seems to be an effective therapeutic option as part of multimodal immune therapy.

Introduction

The discovery of autoantibodies against neural surface antigens was essential for the identification of new non-infectious autoimmune encephalitis entities. Major examples are antibodies against the *N*-methyl-D-aspartate receptor or voltage-gated potassium channel complex which are probably directly pathogenic [1,2]. The clinical syndrome of anti-*N*-methyl-D-aspartate receptor encephalitis develops in several stages, often with prodromal symptoms followed by a rapid change of behavior or psychosis, seizures and variable signs of autonomic instability, hypoventilation or both and reduction in consciousness. Other antibodies are associated with autoimmune encephalitis with a different clinical pattern. Diagnosis requires the combination of characteristic paraclinical findings [magnetic resonance imaging, cerebrospinal fluid (CSF), histopathology] with the detection of specific antibodies [2]. Early start of immunotherapy correlates with good outcome and is strongly recommended [3]. First-line therapy consists of corticosteroids, intravenous immunoglobulin (IVIG) or plasma therapy [plasma exchange (PE), immunoadsorption (IA)], alone or combined, followed by cyclophosphamide or rituximab [2–6]. PE is a non-selective apheresis method with elimination of the entire plasma and subsequent

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Table 1 Clinical features and medical treatment of patients with autoimmune encephalitis treated with immunoadsorption (IA)

Patient sex/age (years)		Antibody	IA [n]	i.v. steroid pulse (3 days, 1000 mg)	IVIG	Immunosuppression	Tumor	Prodromal symptoms	Epileptic seizures	Movement disorder	Psychiatric symptoms	Neurological symptoms	Reduced consciousness	Autonomic disorder
1[a]	F 19	NMDA	5	–	–	–	–	+	+	+	+	+	+	+
2[a]	F 27	NMDA	6	+	–	–	–	–	–	–	+	+	–	–
3[a]	F 20	NMDA	8	+	5×0.4g before IA	Rituximab	–	+	–	–	+	+	–	–
4[a]	F 19	NMDA	6	+	5×0.4g before IA	–	–	–	+	+	+	+	+	+
5	F 23	NMDA	10	+	After IA	–	–	+	–	+	+	+	–	–
6	F 56	NMDA	6	+	5×0.4g before IA	Rituximab, Cyclophosphamide	–	+	+	+	+	+	+	+
7	F 22	NMDA	6	+	–	–	Teratoma	+	–	–	+	+	+	–
8	M 83	NMDA	3	100 mg oral after IA	–	Azathioprine	Adenocarcinoma	–	+	+	+	+	+	–
9	F 19	NMDA	8	100 mg oral before IA	5×0.4g before IA	–	–	+	+	+	+	+	–	–
10	M 37	GAD	6	+	–	–	–	–	–	–	–	+	–	–
11[a]	M 71	GABA	4	+	–	–	Basalioma	+	–	+	+	+	–	–
12	F 77	Lgl1	5	100 mg oral concomitant to IA	–	Azathioprine	–	–	+	–	–	+	–	–
13	F 66	–	4	+	–	–	–	–	+	+	+	+	+	–

NMDA-R, *N*-methyl-D-aspartate receptor; GAD, glutamic acid decarboxylase; GABA, γ-aminobutyric acid; LGl1, Leucine rich Glioma-inactivated Protein 1. [a]Details of these patients have been published in part elsewhere [4].

substitution using human plasma products. Selective extracorporeal elimination of autoantibodies and immune complexes with IA is increasingly replacing PE for the treatment of autoimmune neurological diseases of the peripheral and central nervous system due to its equivalent efficacy and advantageous safety profile [7,8]. The use of IA for patients with autoimmune encephalitis has not yet been investigated separately.

Methods

A retrospective analysis was performed of patients with autoimmune encephalitis who were treated with tryptophan IA. Standardized questionnaires were used. Details of clinical features, examination results and treatment modalities were documented (Table 1). IA treatments were performed using the single-use tryptophan adsorber TR-350 in combination with the OP-05W plasma separator (Asahi Kasei Medical Tokyo, Japan) together with Octo Nova technology (Diamed, Cologne, Germany). Patient informed consent was obtained. According to local regulations, approval of the institutional review board was not needed. The Wilcoxon test was used for analysis of change in the modified Rankin scale (mRS) because variables could not be assumed to be normally distributed. $P < 0.05$ was defined as significant. A decrease in mRS of at least one point was defined as clinically relevant. Descriptive statistics are provided as median and interquartile range (IQR).

Results

Thirteen patients (10 females) with autoimmune encephalitis were treated with tryptophan IA between 2009 and 2013 in six clinics. Median age was 27 years (range 19–83 years). Clinical features are summarized in Table 1. Tumor resection (one adenocarcinoma, one teratoma) was performed before immunosuppressive therapy in two patients. In 12 patients specific autoantibodies were detected in serum, in eight patients also in CSF. One patient was positive for glutamic acid decarboxylase, associated with non-paraneoplastic progressive encephalomyelitis with rigidity and myoclonus. In one patient with no detectable autoantibody the diagnosis of autoimmune encephalitis was based on the specific syndrome and exclusion of other differential diagnoses. Patients received a median of six IA treatments (IQR = 1) within a median period of 8 days (IQR = 7 days). Median treated plasma volume was 2500 ml (IQR = 500 ml). No severe adverse events related to IA treatment were observed. Minor adverse events typically associated with apheresis treatment and vascular access, e.g. transient hypotension, dizziness or nausea, hematoma, were not recorded. Peripheral vascular access was used in one patient; in all other patients a Shaldon catheter was used. Anticoagulation was done with heparin. IA treatment was done after steroid pulse in 10 patients. One patient was treated with steroids concomitant to IA. Four patients received IVIG before IA but did not respond. One patient improved after IA and then received in addition IVIG. In two cases IA was used as sole treatment (no steroids, no IVIG). These patients were positive for *N*-methyl-D-aspartate receptor antibody and improved from mRS 5 to 2 and 5 to 3 respectively after IA. Four patients received other immunosuppressive drugs after IA (Table 1). Time between mRS evaluation before and after IA was a median of 20 days (IQR = 9); median time between last IA and last mRS was 5 days (IQR = 14). Eleven patients (85%) improved by at least by one point (range 1–4) of the mRS; no patient worsened (Fig. 1).

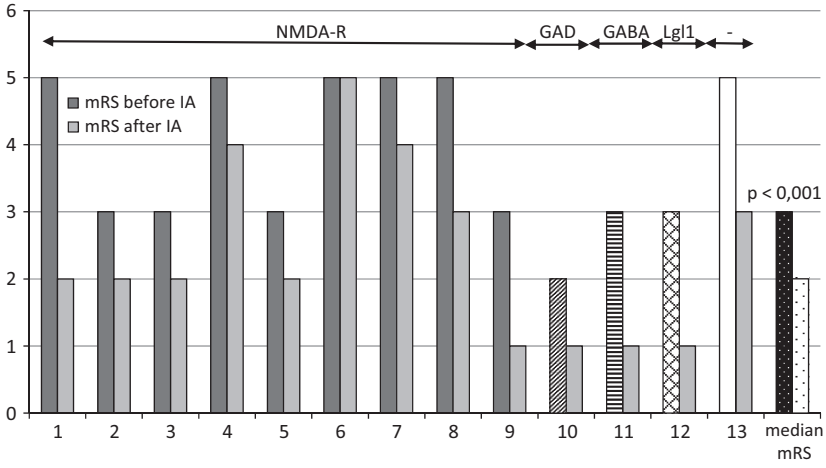

Figure 1 Individual modified Rankin scale (mRS) before and after tryptophan immunoadsorption of 13 patients with autoimmune encephalitis. Specific autoantibodies are illustrated in different patterns. The mRS decreased significantly (Wilcoxon test, $P < 0.001$).NMDA-R, *N*-methyl-D-aspartate receptor; GAD, glutamic acid decarboxylase; GABA, γ-aminobutyric acid; LGl1, Leucine rich Glioma-inactivated Protein 1.

Median mRS of all patients improved from 3.0 (IQR = 2.0) before IA to 2.0 (IQR = 2.0) after IA, $P < 0.001$ (97.75% confidence interval −2.000 to −1.000, $z = -2.56$, $U_{min} = 34$).

Discussion

In this study tryptophan IA resulted in clinically relevant neurological improvement in 11 of 13 patients (85%). In 11 patients IA was combined with corticosteroids, in four cases IA was performed after no response to IVIG. Two patients received only IA and improved substantially. In a recent retrospective analysis of patients with autoimmune encephalitis who were treated with PE as part of a multimodal immune therapy nine of 21 patients improved (43%) [4]. Tryptophan IA seems to be at least as effective as PE, avoiding the need and potential risks of plasma substitution.

Previous studies provided evidence for a direct immunopathology of specific IgG antibodies to neuronal cell surface proteins and revealed a correlation of the antibody titer with the clinical outcome [1,2]. IgG have a relatively long half-life as well as a large volume distribution in the body. Only 50% of IgG is intravascular. Thus intravascular reduction of autoantibody concentration after IA is followed by pulsed induction of antibody redistribution and subsequent immunomodulatory changes. IA is a drug-free treatment option and due to good tolerability compares advantageously with PE and aggressive immunosuppressive therapies.

Rapid elimination of autoantibodies with tryptophan IA seems to be an effective therapeutic option alone or as part of a multimodal immune therapy for autoimmune forms of encephalitis. Further studies with larger numbers of patients should confirm these encouraging results.

Acknowledgement

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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