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Efficacy of double filtration plasmapheresis in the treatment of steroid and/or IVIG unresponsive neuronal surface antibodies associated autoimmune encephalitis

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Abstract

Introduction Whether double filtration plasmapheresis (DFPP) is effective in the patients who do not response to the initial immunotherapy is uncertain. This retrospective study aimed to evaluate the efficacy and safety of DFPP in the treatment of patients who had no improvement after initial immunotherapy (steroids and/or immunoglobulin (IVIG)), and moreover, to investigate the factors associated with the efficacy of DFPP.

Methods From January 1st, 2014, to December 30th,2018, a total of 26 patients who were diagnosed autoimmune encephalitis (AE) and were received the treatment of DFPP after unsuccessful or incomplete recovery from their early immune therapy (including intravenous high-dose cortisone, IVIG and or immunosuppressant) for at least 21 days were investigated. Their plasmapheresis volume, the course of disease, treatment sessions, and complications were recorded. The efficacy of DFPP within a week were assessed by modified Rankin scale (mRS). These patients were followed until six months after the last session of DFPP treatment.

Results The duration between the onset of symptoms and DFPP administration was 54.5 days (range 21—243 days). The median DFPP sessions for each patient were three (range 2–6 sessions), and the mean volume of plasma exchange was 50.5 ± 11.1 ml/kg/session. Total clinically relevant improvement was observed in 57.7% of the patients. The median mRS was decreased from 5 to 4 within one week after DFPP treatment ($P < 0.001$). Only one patient relapsed in the following six months after DFPP. The effectiveness of DFPP has no relationship with age, gender, the type of antibody, with or without neoplasm, clinical course and the volume of plasma exchange. Most patients tolerated well, except 2 cases. One encountered mild allergic reaction and the other had a transient hypotension during DFPP treatment, but both were corrected rapidly.

Conclusion DFPP is an effective and safe treatment option for patients who have poor responsiveness to early immunotherapy).

Keywords Autoimmune encephalitis, Double filtration plasmapheresis

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Introduction

Over the past decades, autoimmune encephalitis (AE), neither caused by viruses nor by bacteria, but caused by antibodies has been recognized and several novel antibodies have been continuously identified [1, 2]. The discovery of non-infectious forms of encephalitis associated with autoantibodies has been a breakthrough in the field of neurology.

AE is classified according to the location of the antigen, either intracellular or on the cell surface, because each classification is associated with different clinical characteristics. Antibodies targeting nuclear and cytoplasmic proteins which are called onconeural antibodies, such as Hu, Ma, and Ri usually accompany malignancy [3]. Patients producing these antibodies respond poorly to immunotherapy, but treatment of the cancer often results in neurological improvement [4, 5]. Antibodies against N-methyl-D-aspartate receptor (NMDAR), leucine-rich, glioma inactivated 1 (LGI1), or contactin-associated protein-2 (CASPR2) are common antibodies against surface antigens [6]. Unlike encephalitis with antibodies to intracellular antigens, AE associated with autoantibodies against cell surface antigens are less frequently accompanied with cancer and respond significantly better to immunotherapy [2, 6].

First-line therapy of AE consists of corticosteroids, intravenous immunoglobulins (IVIG) and therapeutic plasma exchange (TPE) or immunoadsorption (IA). Following these options, some patients are treated with the "second-line" immunotherapies, including intravenous rituximab, cyclophosphamide or other immunosuppressants). In theory, TPE or IA is the most effective way to remove circulating antibodies. However, in the clinical settings, the challenges and delays in diagnosis, the high expense of plasmapheresis, and in addition, the potential complications arising from invasive catheterization and allergic to blood product, have limited its clinical application. Although, the American Society for Apheresis has recommended TPE/IA as the first-line therapy in the treatment of NMDAR antibody encephalitis, there is no broad consensus about the exact order to apply corticosteroids, IVIG, or TPE [7]. There is no compelling evidence to suggest whether TPE is useful in AE patients who poorly response to the initial immune therapy.

In TPE treatment, the target treated plasma volume varied from 1 to 1.4 of patient's plasma volume and was often up to 2.5 L. Thus, TPE has a high clinical demand of fresh-frozen plasma or albumin as replacement fluid. Double filtration plasmapheresis (DFPP) is an approach modified from TPE, with semi-selective removal of auto-immune antibodies, consisting of a primary plasma separator and a secondary fraction plasma separator to separate albumin and other small molecular proteins from plasma and then reclaim them by returning them back to the patient. The larger molecular substances such as pathogenic antibodies, immune complexes and cryoglobulin which are retained in the secondary filter are discarded. DFPP has been shown moderate to marked clinical improvement in certain auto-immune mediated neuromuscular diseases, such as Guillain-Barré syndrome [8], chronic inflammatory demyelinating polyradiculoneuropathy [9], and Neuromyelitis optica (NMO) spectrum disorder (NMOSD) [10], and myasthenia gravis [11]. Selective elimination of autoantibodies and avoiding the disadvantage of plasma substitution is a pathophysiological therapeutic approach.

In this study, we retrospectively assessed the efficacy and safety of DFPP in the treatment of surface antibodies associated autoimmune encephalitis, especially, in the patients who poorly responded to corticosteroids and/or IVIG.

Material and methods

Patients and setting

Patients with AE who were admitted to the Department of Neurology in Huashan Hospital of Fudan University were retrospectively assessed from January 1st, 2014, to December 30th, 2018. Patients who met the following criteria were finally enrolled into the analysis: 1) patients had an established diagnosis of AE [12] based on typical clinical features, surface antibody in either circulation or in CSF, abnormalities in magnetic resonance imaging and the exclusion of relevant differential diagnoses. We used commercially available cell-based assay (CBA) kits to analyze the antibodies; 2) patients who had no improvement after intravenous high-dose steroid (500 mg methylprednisolone for 3–5 days) and/or immunoglobulins (0.4 g/kg/d for 5 days) or other immunotherapy (e.g. intravenous cyclophosphamide) for at least 21 days; 3) patients who were treated with DFPP after first-line therapy (steroid and/or IVIG or other immunosuppressive therapy). All patients except those with contraindications were treated with immunosuppressants for maintenance therapy within two weeks after DFPP (375 mg/m^2 rituximab each week for four weeks or 600 mg, 100 mg D1, 500 mg D2; 750 mg/m^2 cyclophosphamide intravenously every four weeks for six months). Demographic and clinical features of the patients were derived from the review of medical records (Table 1). The efficacy of DFPP was evaluated using the modified Rankin scale (mRS) [13] before and within one week after the last DFPP session (early follow-up). In addition, these patients were

Table 1 Patients' general characteristics and clinical features

Patient No	Gender	Age	Weight (kg)	Antibody	Serum titer	CSF titer	MRI	EEG	Tumor
1	male	30	50	NMDAR	(++)	(++)	Abnormal signal in left occipital and temporal	Normal	None
2	male	47	70	NMDAR	(-)	(+++)	Abnormal signal in pedunculus cerebri, medulla oblongata	Abnormal	None
3	male	16	70	NMDAR	(++++)	(+++)	Abnormal signal in left cerebellum and bilateral hippocampus	Abnormal	None
4	female	28	52	NMDAR	(+++)	(++)	Abnormal signal in bilateral frontoparietal and temporal lobe	Normal	Ovarian teratoma
5	female	29	70	NMDAR	(+++)	(++)	Normal	Abnormal	None
6	male	51	71	AMPAR	(++)	(++)	Abnormal signal in frontal lobe	Normal	None
7	male	64	71	GABA-BR	(+++)	(++)	Abnormal signal in hydrocephalus	Normal	None
8	female	23	80	NMDAR	(+)	(++)	Abnormal signal in bilateral hippocampus	Abnormal	Ovarian teratoma
9	female	16	38	NMDAR	(+)	(++)	Abnormal signal in left temporal lobe and hippocampus	Abnormal	None
10	male	72	40	GABA-BR	(+++)	(+++)	Multiple cerebral ischemia	Normal	esophagus cancer
11	male	59	60	NMDAR	(-)	(+++)	Normal	Abnormal	None
12	female	19	40	NMDAR	(+++)	(+++)	Normal	Abnormal	None
13	female	16	50	NMDAR	(+++)	(+++)	Intensified signal in bilateral pia mater	Abnormal	Ovarian teratoma
14	male	66	65	LGI1	(+)	(+)	Abnormal signal in left hippocampus and frontal lobe	Normal	None
15	male	59	61	LGI1	(++)	(-)	Abnormal signal in right frontal lobe	Abnormal	None
16	male	64	60	GABA-BR	(+++)	(+++)	Normal	Abnormal	Lung cancer
17	female	21	45	NMDAR	(+)	(+++)	Abnormal signal in right frontal and parietal lobes	Abnormal	Ovarian teratoma
18	female	28	56	NMDAR	(+)	(+++)	Abnormal signal in bilateral temporal lobe and basal ganglia region	Abnormal	Ovarian teratoma
19	male	69	60	LGI1	(+++)	(+++)	Mesencephalon, bilateral basal ganglia region ischemia	Abnormal	none
20	male	34	60	NMDAR	(-)	(+++)	Normal	Abnormal	None
21	male	45	90	GABA-BR	(++)	(++)	Normal	Abnormal	Lung cancer
22	male	56	66	NMDAR	(-)	(++)	Bilateral hippocampus, front parietal and periventricular ischemia	Normal	None
23	female	17	51	NMDAR	(-)	(++)	Abnormal signal in left frontal lobe	Abnormal	None
24	male	35	65	NMDAR	(+)	(++)	Abnormal signal in right temporal lobe, insular lobe and brainstem	Abnormal	None
25	male	62	69	AMPAR	(++)	(-)	Abnormal signal in bilateral hippocampus	Abnormal	Thymoma
26	male	52	60	GABA-BR	(++)	(++)	Abnormal signal in right temporal-parietal white matter	Abnormal	None

followed up for six months of DFPP (late follow-up). This study was approved by the Ethics Committee of Huashan Hospital. The protocol was conducted in accordance with the declaration of Helsinki. All patients gave written informed consent (either the patient or guardian).

DFPP procedure

Blood access was set up by insertion of a single dual-lumen catheter into the right internal jugular vein. A blood purification machine (KM8900, Kuraray, Tokyo, Japan) was used for DFPP. The primary filter for plasma separation was Plasmaflo PS-08, and the second filter for plasma fractionation was EC20W filter (both Kuraray) with an albumin sieving coefficient of 0.62. The blood flow was set at 100 ml/min, and the plasma flow rate out of the primary separation was set at 20–30 ml/min. Target volume of plasma exchange was determined by patient's body weight (40–50 ml/kg) with a supplement of 30–40 g albumin during each DFPP session. Heparin was used for anticoagulation. DFPP was performed every other day and each patient received at least three sessions of DFPP.

Statistical analysis

Data was presented as mean ± SD or median (IQR). One point reduction of mRS score was considered as clinically relevant. The statistical significance of the treatment related mRS changes was determined using the paired Wilcoxon signed-rank test. A p value < 0.05 was considered significant. Univariate analyses were employed to examine the differences in each observed indicator between efficacy group and inefficacy group. Binary data were analyzed using Fisher's exact test. Statistical analysis was performed using SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Patients

This study comprised 9 females and 17 male patients with median age 40 years old (range from 16 to 72 years old) with neuronal surface antibodies against N-methyl-D-aspartate receptors (NMDAR, $n=16$, 61.5%), γ-aminobutyric acid receptor (GABA-BR, $n=5$, 19.2%), leucine-rich glioma inactivated 1 (LGI1, $n=3$, 11.5%) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR, $n=2$, 7.7%). At the time of diagnosis, ovarian teratomas were identified in six patients, while additional three patients were diagnosed with neoplasms during the three-month follow-up period. Antibodies were absent in the cerebrospinal fluid (CSF) of two patients, and 5 out of 26 patients (19.2%) exhibited no detectable antibodies in their serum. The laboratory findings were summarized in Table 2.

Double filtration plasmapheresis

Out of the twenty-six patients treated with DFPP, six had only received steroids, one just received intravenous immunoglobulins, and nineteen patients had been treated with both steroids and immunoglobulins prior to DFPP. Among them, two patients were add-on intravenous cyclophosphamide after steroids and IVIG before DFPP. The median DFPP circles for each patient were three (range 2–6 sessions). The median time between the onset of symptoms and DFPP administration was 54.5 days (range 21—243 days). The mean volume of plasma exchange was 50.5 ± 11.1 ml/kg/session. Total clinically relevant improvement was observed in 57.7% of the patients. The clinical response of patients with different neuronal surface antibodies were illustrated in Table 3. Within one week after the last DFPP, the median mRS decreased from 5 to 4 (median pre mRS vs. median post mRS 5 vs. 4, $P<0.001$). The mRS scores were not significantly different between mRS post-DFPP and mRS at 6 months after DFPP. Only one patient relapsed twice in the following six months after DFPP.

There were no differences between efficacy-group and inefficacy-group in age, gender, antibody types, the period from the onset of disease to the treatment of DFPP, the DFPP circles and the volume of plasma change (Table 4). Since most of patients were NMDAR-related AE, we analyzed this group of patients separately. Similarly, the decreased in mRS was not associated with age, gender, the period from the onset of disease till the treatment of DFPP, the DFPP circles, and the volume of plasma change (Table 5).

Adverse events of the DFPP were noted in two patients. One patient encountered mild allergic reaction. The allergic symptom disappeared at the second time when the extracorporeal circuit was flushes with more liters of saline solution. The other patient had a transient hypotension during DFPP treatment, but it was corrected rapidly after increasing the rate of saline infusion.

Discussion

DFPP is a selective apheresis modality for the removal of pathophysiological associated antibodies and immune complexes avoiding plasma substitution. Although it has been widely used in various autoimmune-mediated diseases in Asia, there is a paucity of published reports on the role of DFPP in the treatment of AE. Clinical evidence in AE have accumulated that early, appropriate, and intense treatment is essential for achieving a good outcome [14, 15]. However, the diagnosis of AE is challenging because the rarity of the disease limits clinical experience and the intervention may be delayed if the evidence is not so strong [16, 17].

TPE is currently recommended as a first-line therapy for several neurologic diseases. As a matter of fact, it is difficult to assess the effect of TPE on outcome, because many patients also receive concurrent immunotherapy. So far, the exact order of the treatments (i.e., corticosteroids, IVIG, and TPE) was not defined [2]. A few studies have proved that the steroids followed by TPE was more effective than intravenous steroids alone [6]. DeSena, AD et al. reported that TPE after steroids might be more efficacious than steroids alone in the early stages of anti-NMDA receptor antibody encephalitis [18]. In another study, Heine J et al. found the time between the onset of first symptoms and administration of TPE/IA was not associated with worsened outcome [6]. It is unclear whether treatment effects of DFPP are limited to an early treatment onset. In theory, DFPP can directly remove autoantibodies may show a synergistic effect, even though in late treatment. In the current study, we evaluated the effectiveness of DFPP in treating

Table 2 Treatment therapies, modified rankin scores before and after DFPP

Patient No	Antibody	Preceding Treatment	Age	Period from onset to DFPP (days)	Plasma exchange volume of DFPP (ml/kg/circle)	DFPP circles	mRS Pre-DFPP	mRS Post-DFPP	mRS at 6 months after DFPP	Follow-up immunotherapy	Follow-up for six months after the last DFPP
1	NMDAR	steroids + IVIG	30	96	69	5	5	4	4	/	not relapse
2	NMDAR	IVIG	47	27	41	2	5	4	4	Prednisolone, cyclophosphamide	not relapse
3	NMDAR	steroids + IVIG	16	55	48	6	5	4	4	Prednisolone, Rituximab	not relapse
4	NMDAR	steroids + IVIG	28	54	58	4	5	4	4	Methylprednisolone, Rituximab	not relapse
5	NMDAR	steroids + IVIG	29	155	43	3	4	3	3	Rituximab	not relapse
8	NMDAR	steroids	23	130	38	4	5	5	5	Prednisolone, Rituximab	not relapse
9	NMDAR	steroids + IVIG	16	235	76	3	5	4	4	Methylprednisolone, Rituximab	not relapse
11	NMDAR	steroids + IVIG	59	51	48	3	5	4	4	/	not relapse
12	NMDAR	steroids + IVIG	19	177	75	5	5	4	4	Prednisolone, Cyclophosphamide	not relapse
13	NMDAR	steroids + IVIG	16	42	60	5	5	4	4	Rituximab	not relapse
17	NMDAR	steroids + IVIG	21	28	64	4	4	4	4	Rituximab	relapse twice
18	NMDAR	steroids + IVIG	28	243	54	3	3	3	3	Rituximab	not relapse
20	NMDAR	steroids + IVIG	34	32	43	3	5	6	/	/	/
22	NMDAR	steroids + IVIG	56	123	46	3	4	3	3	Prednisolone, Cyclophosphamide	NA
23	NMDAR	steroids + IVIG	17	62	59	4	5	5	5	Prednisolone, Rituximab	not relapse
24	NMDAR	steroids	35	23	46	3	5	5	5	Prednisolone, Rituximab	not relapse
6	AMPAR	steroids + IVIG	51	25	42	3	5	4	4	Rituximab	not relapse
25	AMPAR	steroids	62	40	44	5	3	1	1	Prednisolone, Cyclophosphamide	not relapse
7	GABA-BR	steroids + IVIG	64	34	38	3	5	5	4	Rituximab	not relapse
10	GABA-BR	steroids + IVIG	72	57	50	2	5	6	/	/	/
16	GABA-BR	steroids	64	21	46	5	5	4	4	Prednisolone, Cyclophosphamide	not relapse
21	GABA-BR	steroids	45	26	33	3	4	4	4	Rituximab	not relapse
26	GABA-BR	steroids + IVIG + Cyclophosphamide	52	60	50	5	5	5	4	Prednisolone, Cyclophosphamide	not relapse
14	LGI1	steroids + IVIG + Cyclophosphamide	66	181	45	5	3	1	1	Prednisolone, Cyclophosphamide	not relapse
15	LGI1	steroids + IVIG	59	150	48	3	4	2	1	Methylprednisolone, Rituximab	not relapse
19	LGI1	steroids	69	35	50	3	4	4	4	Rituximab	not relapse

NA not available

Table 3 The changes of mRS after DFPP treatments within a week for different neuronal surface antibodies

Antibodies	n
NMDAR	16
Effective	10 (62.5%)
No respond	5 (31.3%)
Worse	1 (6.3%)
GABA-BR	5
Effective	1(20%)
No respond	3 (60%)
Worse	1 (20%)
LGI1	3
Effective	2 (66.7%)
No respond	1 (33.3%)
Worse	0 (0.00%)
AMPAR	2
Effective	2 (100%)

patients with surface antibodies associated autoimmune encephalitis, especially, in the patients without steroids and/or IVIG responsiveness. Out of our expectation, more than half of the patients showed considerable clinical improvement within one week. Of note, 10 of 16 cases (62.5%) with NMDAR antibodies clinically ameliorated by at least 1 mRS score reduction. Our findings suggest that DFPP could be useful for the management of the patients who had poorly responded to steroids. Since there was no association between treatment delay and response in our patients, we propose that DFPP effect is not limited to an early treatment onset.

On the other hand, we did not observe severe adverse events during DFPP. During the 92 DFPP treatments, one patient experienced a mild allergic reaction, and another had transient mild hypotension, which was quickly resolved with a saline infusion. It is worth noting that this DFPP is a selective modality for the removal of antibodies and immune complexes avoiding foreign plasma substitution.

This is a retrospective study with some inherent limitations. First, it included patients from a single center and the sample size was small. Nevertheless, this study provides evidence that for patients resistant to initial immunotherapy, DFPP treatment may still be effective in the late stage of disease, rather than the previously reported that the earlier intervention is always better. Second, this was not a control study. It was difficult to establish a control group matched for age and disease severity during the same study period. Moreover, for its retrospective observational nature, patients' follow-up immunotherapies were heterogeneous, it is difficult to isolate the effect of DFPP on the clinical outcome as well as to elucidate the role of DFPP in reducing AE relapse. Prospective randomized controlled studies or real-world studies are needed to gain further data for the application of DFPP. Third, we could not determine the pre- and post-DFPP antibody titers in the patients' serum and/or cerebrospinal fluid, as the assay was not routinely conducted and because of the high expense.

Conclusions

Our study identified one issue that the time of DFPP application was not limited to the early stages of diseases in neuronal surface antibodies associated

Table 4 All of the patients' clinical characteristics and features grouped by the change of mRS

mRS change (ΔmRS) = mRS (pre) – mRS (post)			*P* value
Parameter	**No respond or worse (ΔmRS ≤ 0) (-1,0)**	**Improvement (ΔmRS ≥ 1) (1,2)**	
N	11	15	
Age	41.82 ± 19.894	41.2 ± 19.633	0.938
Gender (female:male)	4:7	5:10	0.873
AE Antibody (n)	NMDAR: 6	NMDAR: 10	
	GABA-BR: 4	GABA-BR: 1	
	LGI1: 1	LGI1: 2	
		AMPAR: 2	
Neoplasm (n%)	45.5%	26.7%	0.32
Serum antibody positive	9	12	0.557
CSF antibody positive	11	13	0.557
the duration of the disease until the time of DFPP (days) (range)	34 (8–243)	75.5 (21–235)	0.183
Plasma exchange volume of DFPP (ml/kg) (range)	46 (33–64)	48 (41–76)	0.317
DFPP circles (IQR)	3 (3,4)	4 (3,5)	0.253

Table 5 Clinical characteristics and features of patients with NMDAR positive grouped by the change of mRS

mRS change (ΔmRS) = mRS (pre) – mRS (post)			*P* value
Parameter	**No respond and worse (ΔmRS = 0) (-1,0)**	**Improvement (ΔmRS ≥ 1) (1,2)**	
N	6	10	
Age (range)	25.5 (17–35)	28.5 (16–59)	0.957
Gender (male %)	33.3%	50%	0.633
Neoplasm (Ovarian teratoma or tumor)	50%	20%	0.299
Serum antibody positive	4	7	1.000
CSF antibody positive	6	10	0.267
Both serum and CSF antibody positive	4	7	1.000
Period from onset to DFPP (days)	67.0 ± 69.6	99.4 ± 70.1	0.433
Plasma exchange volume of DFPP (ml/kg)	47.5 ± 9.8	53.2 ± 12.2	0.325
DFPP circles (IQR)	3.5 (3,4)	3.5 (3,5)	0.606
mRS pre (IQR)	5 (3.75, 5)	5 (4.75, 5)	0.474
mRS post (IQR)	5 (3.75, 5.25)	4 (3.75, 4)	0.041

autoimmune encephalitis. It appears to be a relatively effective and well tolerated in patients who were steroid and/or IVIG unresponsive, even though the onset of disease was quite some time. Further study should be performed to identify the time, frequency, duration as well as the order of DFPP relative to steroids, IVIG, and other immunotherapy.

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Authors' contributions
XWL coordinated the research and drafted the manuscript. CZ collected data. JX analyzed and interpreted data. YZ designed the study, drafted and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Helsinki Declaration. The study protocol was approved by the Human Research and Ethics Committee of Huashan Hospital Affiliated to Fudan University (KY2016-394). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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