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Plasma exchange: an effective add-on treatment of optic neuritis in neuromyelitis optica spectrum disorders

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Abstract
Purpose To evaluate the efficiency of plasma exchange (PE) add-on on optic neuritis (ON) in neuromyelitis optica spectrum disorders (NMOSD).
Methods Our ambispective, nonrandomized study was performed in Southwest Hospital, Southwest Eye Hospital, Army Medical University. We studied 31 consecutive NMOSD patients characterized by ON and hospitalized from September 2015 to May 2018. Their clinical features were assessed, and efficiency of PE add-on treatment in ON of NMOSD was evaluated. Correlation was assessed between the effect of steroid pulse therapy (SPT) and the number of ON episodes in NMOSD.
Results All 31 NMOSD patients accepted SPT; 15 patients of them accepted SPT and PE add-on. In these 15 patients, after PE add-on treatment, the patients' visual acuity was further significantly improved ($P = 0.000$, $N = 23$), including 3 no light perception (NLP) patients. After the treatment, the visual function recovered quickly in the first 2 months and then gradually slowed down; the visual function remained stable about 6 months later. The correlation coefficient between visual acuity improvement of SPT and the number of ON episodes was -0.311 ($P = 0.030$, $N = 49$).
Conclusion One clinical feature of NMOSD can be repeated vision impairment. In NMOSD patients characterized by ON, efficacy of SPT is limited as the number of episodes increased, and PE add-on is more effective. Even though the visual acuity of NMOSD patients decreases to NLP during episodes, there is still a chance to restore vision by PE add-on treatment.

Keywords Neuromyelitis optica spectrum disorder · Optic neuritis · Steroid pulse therapy · Plasma exchange

Introduction

Neuromyelitis optica (NMO) is a demyelinating disease caused by autoimmune disorders that predominantly presents optic neuritis (ON) and transverse myelitis (TM) [1, 2]. The presence of Aquaporin-4 immunoglobulin G antibodies (AQP4-IgG), also called NMO-IgG, distinguishes NMO and similarly related disorders from multiple sclerosis (MS) [3]. The discovery of the association between AQP4-IgG and NMO offers a significant diagnostic basis for NMO. In 2007, the concept of neuromyelitis optica spectrum disorder (NMOSD) was proposed; it contained NMO,

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limited or inaugural forms of NMO with NMO-IgG seropositive and autoimmune disorders with NMO-IgG seropositive, even brain concerned otherwise typical NMO [1]. Because there is no significant difference between NMO and NMOSD in biological characteristics and treatment, and the vast majority of limited forms of NMO with NMO-IgG seropositive ultimately develop into NMO, Wingerchuk et al. [4] published new diagnostic criteria for NMOSD, incorporate NMO into NMOSD in 2015.

As a central nervous system demyelinating disease, risk of NMOSD is higher in Asian populations than in western countries compared with MS [5, 6]. Repeated vision impairment caused by ON could be the initial or only symptom of NMOSD. Differently from MS, NMOSD hardly ever takes a progressive course of disease, and inflammatory damage from attacks can accumulate disabilities in NMOSD [7]. Compared with most MS patients, ON of NMOSD often manifests severe visual loss and results in permanent blindness [8]. Timely intervention and effective treatment are crucial. Current treatment for acute attacks of ON includes steroid pulse therapy (SPT), also called methylprednisolone therapy, and plasma exchange (PE). Immunosuppressive drugs are used to reduce the recurrence rate of ON but with side effects. In this study, we studied the clinical characteristics of 31 NMOSD patients characterized by ON, compared and followed up the efficacy of SPT and PE add-on, assessed the correlation between the effect of SPT and the number of episodes, hoped to find more effective treatment for ON of NMOSD and reduced the blindness caused by NMOSD.

Subjects and methods

We studied 31 consecutive NMOSD patients characterized by ON whose chief complaint was vision loss and hospitalized in Southwest Eye Hospital from September 2015 to May 2018. Informed consent was obtained from all the 31 patients. The study was approved by the Ethics Committee of Southwest Hospital and was in accordance with the Helsinki Declaration. All the patients had complete medical histories, ophthalmological examinations and neurological examinations. Unaffected eyes, eyes with optic atrophy and had been NLP for a long time were not included in this analysis.

All 31 patients accepted SPT, SPT here means 3–5-day administration of high-dose intravenous methylprednisolone [9, 10]; 15 of 31 patients accepted PE. PE was performed when the visual acuity of patients had no or poor improvement after SPT. The average interval between SPT and PE was 1.6 days. PE was performed 2–3 times a week. The volume of plasma was associated with weight and physical condition of the patients. In the process of PE, plasma was removed, and frozen plasma, 0.9% sodium chloride solution and 10% calcium gluconate solution were infused into as substitutions.

Decimal visual acuity values were converted to LogMAR values for statistical analysis. The LogMAR value for count fingers (CF) was 1.85, hand movement (HM) was 2.30, light perception (LP) was 2.70, and no light perception (NLP) was 3.00 [11]. Standard automated perimetry examinations were performed by Humphrey Field Analyzer II (Carl Zeiss Meditec). Visual electrophysiology examinations were performed by Vision Monitor Mon2014D (Metrovision). Statistical analysis was performed using SPSS 22, and statistical significance was defined as $P < 0.05$. A paired samples t test was applied to assess the effects of PE add-on treatment in 15 patients (23 eyes). Correlation analysis was used to analyse the relationship between the effect of SPT and the number of episodes.

Results

Demographic and clinical characteristics

All 31 NMOSD patients were enrolled. All 31 patients were Chinese; 3 patients were male, and other 28 patients were female. Among the 31 patients, 3 patients were first attacked and the others were recurrent. The number of total episodes of the 31 patients was 84, the number of ON episodes was 74, the number of TM episodes was 14, and ON and TM could also occur simultaneously in one episode. NMOSD patients were characterized by ON; most of them suffered from binocular vision impairment after repeated ON episodes. Recurrent ON of NMOSD in these patients is the focus of our study. The age of the first episode of the patients was from 12 to 67 years old. It took on average 29.10 ± 33.35 months to diagnose NMOSD (Table 1). Sharp vision loss,

Table 1 Demographic and clinical characteristics of NMOSD patients characterized by ON

Evaluated patients ($N = 31$)	
Gender M/F	3/28
Race	Chinese
First episode/recurrent episode	3/28
Monocular/binocular vision impaired (patients)	5/26
Age at first episode (years) (M ± SD) (min–max)	36.13 ± 15.83 (12–67)
Age at diagnosis (years) (M ± SD) (min–max)	38.52 ± 15.86 (12–70)
Period from first episode to diagnosis (months) (M ± SD) (min–max)	29.10 ± 33.35 (1–121)
Number of total episodes (M ± SD) (min–max)	2.71 ± 1.35 (1–7)
Number of ON episodes (M ± SD) (min–max)	2.39 ± 1.20 (1–5)
Serum AQP4-IgG positive/negative/patient refused to test	28/0/3
ON as initial episode (%)	90.32
Papilloedema (%)	17.86
Suffer from Sjogren's syndrome	3
Suffer from systemic lupus erythematosus	1
Suffer from hyperthyroidism	2

recurrent attacks and female are high risk factors for diagnosing NMOSD. The high specificity of AQP4-IgG assay gave us the chance to identify whether ON with high risk factors is NMOSD. In recent years, less time is taken to diagnose NMOSD because of AQP4-IgG assay. Serum AQP4-IgG was positive in 28 of the 31 patients, and other 3 patients refused to test AQP4-IgG by the reasons of economy and family. Papilloedema can be observed in the course of some ON in NMOSD. It is worth mentioning that 3 patients were diagnosed with Sjogren's syndrome during hospitalization. A patient with chronic nephritis was diagnosed with systemic lupus erythematosus. Two patients had history of hyperthyroidism. These diseases are all related to autoimmune disorders.

Effect of plasma exchange add-on treatment

All 31 patients accepted SPT, and 15 patients (23 eyes) of them accepted PE add-on. In these 15 patients, the number of episodes was 3.13 ± 1.59 and the number of PE was 4 ± 1.37. Seven of 15 patients had no visual improvement after SPT, but vision of the 7 patients was all improved after PE add-on. Vision of other 8 patients was improved after SPT, and their vision was further improved after PE add-on treatment. In summary, in these 15 patients, after PE add-on treatment, the patients' visual acuity was further significantly improved ($P = 0.000$, $N = 23$) (Table 2). In this study, the visual acuity of the 5 patients (5 eyes) was regained from NLP, of which 2 patients' visual acuity (2 eyes, NLP) was improved after SPT and further improved after PE add-on treatment. The visual acuity of other 3 patients (3 eyes, NLP) did not improve after SPT until after PE add-on treatment. In this study, we followed up for 6 months after the treatment of SPT and PE add-on. Visual acuity and visual field of the patients were both significantly improved. After the treatment, visual acuity of patients recovered fast during the first 2 months, then slowed down and maintained stable (Fig. 1). Improvements in visual field indices (VFI) and changes in mean deviation (MD) are echoed with vision recovery; all the data suggest the recovery of visual function in patients. In Fig. 2, we present the 17-month follow-up of one NMOSD patient' left eye. This is a 52-year-old female patient. Vision of her right eye had been NLP for more than 1 year because of the attacks of ON in NMOSD. Her left eye visual acuity had been decreased to 0.2 when she went to our hospital and was admitted. The day after admission, vision of her left eye dramatically decreased to NLP. After SPT, her vision was restored to light perception. (Light location was inaccurate.) After PE add-on treatment, her vision of left eye restored to 0.5 (ETDRS 70). In early several months follow-up, vision of her left eye restored quickly to 0.8. Four months after the previous attack, the patient experienced a relapse, and her vision decreased from 0.8 to 0.6. After the addition of immunosuppressive drug mycophenolate mofetil,

Table 2 Effects of steroid pulse therapy and plasma exchange add-on in 15 patients (23 eyes)

No. of episodes (M ± SD)	No. of PE (M ± SD)	Effectiveness of SPT (%)	Effectiveness of PE (%)	VA (LogMAR) before treatment (M ± SD)	VA (LogMAR) after SPT (M ± SD)	VA (LogMAR) after PE (M ± SD)	P 1	P 2	P 3
3.13 ± 1.59	4 ± 1.37	53	100	1.94 ± 0.83	1.78 ± 0.83	1.26 ± 0.66	0.019	0.000	0.000

VA, visual acuity; SPT, steroid pulse therapy; PE, plasma exchange; P1, visual acuity before treatment versus visual acuity after SPT; P2, visual acuity after SPT versus visual acuity after PE; P3, visual acuity before treatment versus visual acuity after SPT and PE add-on

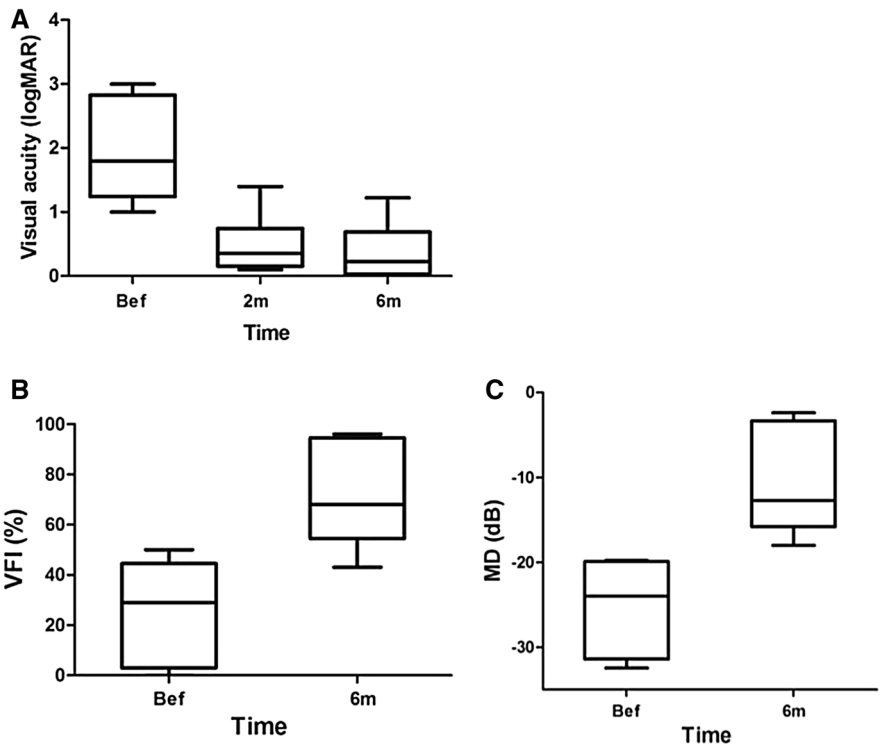

Fig. 1 Follow-up of visual acuity and visual field after treatment of SPT and PE add-on. Bef, before treatment; 2 m, 2 months after treatment; 6 m, 6 months after treatment; VFI, visual field index; MD, mean deviation

vision of her left eye was restored again and remained relatively stable during subsequent 12-month follow-up. VFI of the patient before treatment, 3 months and 17 months is, respectively, 39%, 93%, and 96%, suggesting the visual function recovery of her left eye (Fig. 2b). Pattern visual evoked potential (P-VEP) results further support this conclusion. During the follow-up, waves of both reversal 60′ and 15′ LE stimulation of P-VEP are more stable, amplitudes of P100 are increased, and latencies are shortened with the recovery of visual function (Fig. 2c).

Correlation between the effect of steroid pulse therapy and the number of ON episodes

We reviewed records of the 31 patients admitted to our hospital. According to the profiles of the patients, we found that SPT appeared to be more effective in the early episodes of ON in NMOSD. However, the effect of SPT became increasingly insignificant with the number of ON episodes increased. We thus performed a correlation analysis between the effect of SPT and the number of episodes. The correlation coefficient between visual acuity improvement after SPT

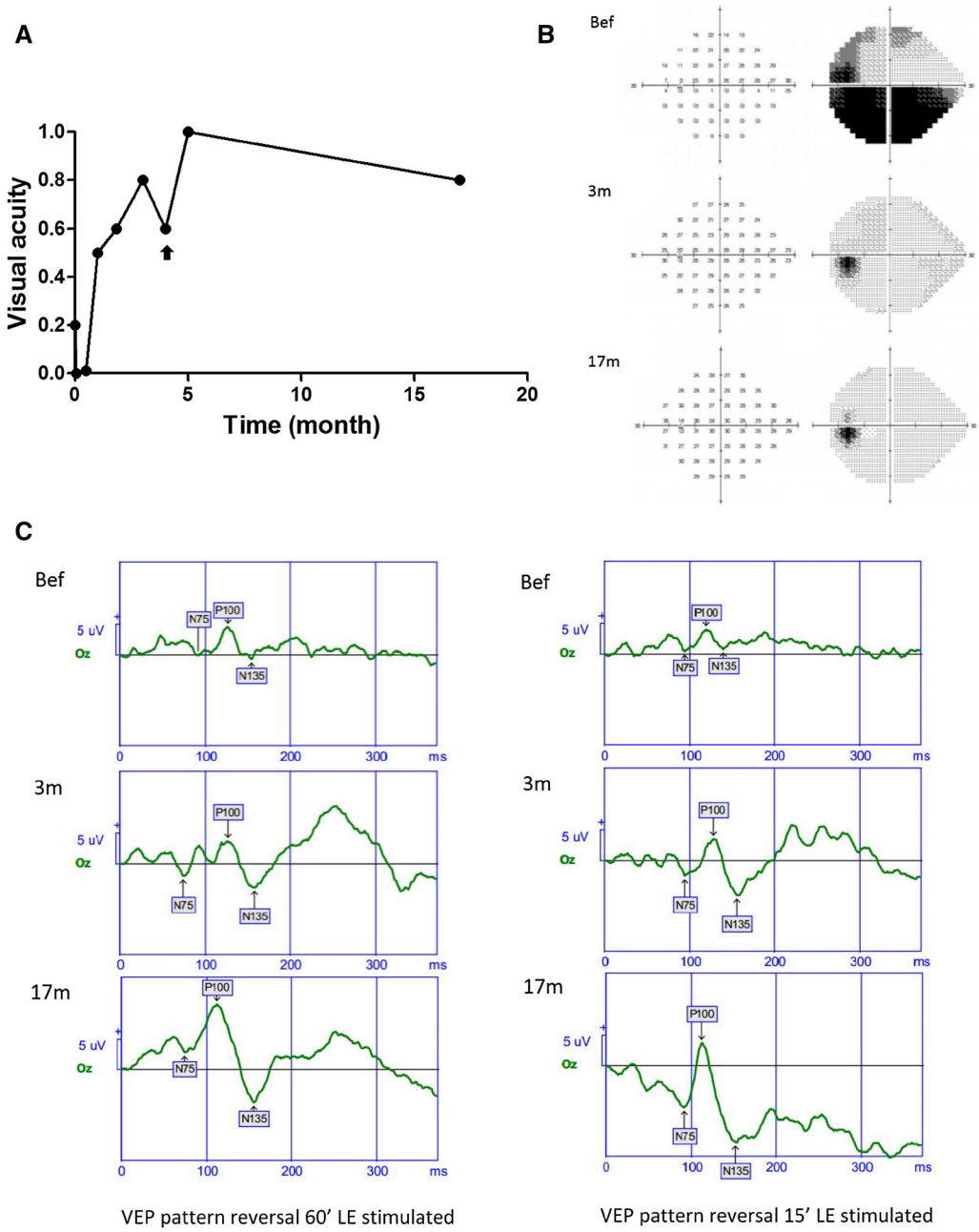

Fig. 2 Visual function follow-up (17 months) of one NMOSD patient' left eye who accepted SPT and PE add-on treatment. Vision of her right eye has been NLP for more than 1 year. **a** Visual acuity changes in treatment and follow-up. The arrow represents the addition of immunosuppressive drug mycophenolate mofetil. **b** Follow-up of visual field. Bef, before treatment; 3 m, 3 months; 17 m, 17 months. **c** Follow-up of P-VEP

and the number of episodes was -0.311 ($P = 0.03$, $N = 49$) (Fig. 3). This result indicates that SPT treatment is less effective as the number of episodes increases. In the later stages, patients had poor vision after repeated episodes of ON, SPT treatment alone is insufficient, and PE add-on provides hope for saving the patients' residual vision and avoiding blindness. In this part, the number of episodes of right and left eyes was counted, respectively.

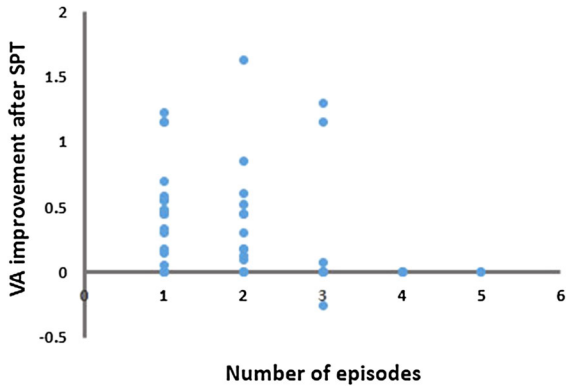

Fig. 3 Scatterplots of visual acuity improvement after SPT at different numbers of episodes. Visual acuity improvement after SPT became less significant with the number of ON episodes increased. Correlation coefficient between visual acuity improvement of SPT and the number of ON episodes was − 0.311 ($P = 0.030$, $N = 49$). VA, visual acuity; SPT, steroid pulse therapy. The points of same X, Y coordinates in the figure were represented as one point

Discussion

SPT is regarded as the typical pharmacotherapy for acute attacks of NMOSD. It is adopted from the treatment of optic neuritis and MS, although the efficiency and mechanism of steroids have not been accurately investigated [12]. NMOSD is a demyelinating disease caused by autoimmune disorders. May immunosuppression and anti-inflammatory effects of steroid therapy contribute to limit the development of NMOSD? In the correlation analysis between the effect of SPT and the number of episodes, we found that visual acuity improvement of SPT and the number of episodes were negatively correlated. In some patients, the efficacy of SPT is not significant, especially in the later stages.

Compared with the application of steroids to ON attacks of NMOSD, PE add-on is more efficient. Merle H et al. came to a same conclusion [13]. In active NMOSD, IgG, IgM and C9neo deposition can be demonstrated, capillaries hyalinize, and immune cells infiltrate lesions [14, 15]. In the presence of complement proteins or immune cells, NMO-IgG can induce complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) [16–19]. PE can remove pathogenic antibodies and complements and, meanwhile, immunomodulate and input normal plasma components. From the perspective of pathophysiology and immunology, the efficiency of PE is reasonable. We recommend that PE should be performed 5 times. NMO-IgG in NMOSD patients could be cleared up to 80% or more after 5 PE [10, 20]. In our study, the number of PE was 4, because after several PE visual acuity of patients improved though, some of them refused subsequent PE treatment due to financial difficulties, family factors, and so on, this is regrettable. In our study, the visual acuity of all 15 patients (23 eyes) was all improved after PE. One precondition of vision restoration is that the optic nerve is not destroyed completely, so PE could not work on eyes that have been NLP for a long time. In addition, it is worth mentioning a disadvantage of PE that multiple uses of PE could cause hypoproteinemia. In the process of PE, some beneficial substances are lost and fresh frozen plasma is imported. It may also cause paraesthesia, abnormal clotting, anaphylaxis, hypernatremia and metabolic alkalosis [21, 22]. In our study, two patients had leukocytosis—one of them had anaphylaxis, and one patient had hypoproteinemia after PE. After symptomatic treatment, all these symptoms disappeared.

NMOSD may spontaneously relieve after attack; however, this kind of relief is quite limited. In NMOSD, inflammatory damage from attacks can accumulate disabilities [7]. NMOSD patients with multiple optic neuritis attacks, pallor and atrophy of optic nerve can be observed in the later stage. So timely and effective intervention, shortening of the course of disease and improvement in the rate of visual recovery all contribute to the control of the development of ON in NMOSD. Moreover, PE therapy has been proven to be effective in NMOSD patients with NMO-IgG positive or negative [23, 24]. In our study, visual acuity was improved after PE add-on, and the improvement indicates a better prognosis. PE is effective for both neuritis and myelitis, brings good news to patients suffered from relapse and, from the point of view of ophthalmology, can reduce blindness caused by ON in NMOSD.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Informed consent Informed consent was obtained from all the 31 patients. The study was approved by the Ethics Committee of Southwest Hospital and was in accordance with the Helsinki Declaration.

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