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Clinical trial

A retrospective cohort study of plasma exchange in central nervous system demyelinating events in children

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ABSTRACT

Background: Plasma exchange (PLEX) may improve recovery of acute central nervous system (CNS) demyelinating events related to multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), and MOG-antibody associated demyelination (MOG) if recovery with pulse steroids (PS) is incomplete. Although there is a single randomized controlled trial in adults, there are limited case series in children. We aimed to describe the effectiveness and safety of PLEX in children with acute events of MS, NMOSD, TM, ADEM, and MOG with limited improvement after PS.

Methods: This was a retrospective cohort study of children with acute CNS demyelinating events seen at a single tertiary referral center who received PLEX as a second- or third-line therapy between 2006 and 2018. Through chart review of clinical notes, presence of clinical improvement by physician assessment was recorded pre- and post-PS and pre- and post-PLEX. Expanded Disability Status Scale (EDSS) scores were collected pre- and post-PLEX. We evaluated the number who improved clinically with PLEX and compared pre- and post-PLEX EDSS with Wilcoxon matched pairs signed-rank test.

Results: 26 patients followed at the Pediatric MS Center at the University of California, San Francisco received PLEX for acute events of MS ($n = 15$), NMOSD ($n = 7$), MOG ($n = 2$), TM ($n = 1$), and ADEM ($n = 1$). At time of PLEX initiation, median age was 13.5 years (range 3–17) and median time between the acute event onset and PLEX initiation was 22 days (range 3–94). 14 of 24 patients had documented clinical improvement after PS. Of those who improved during PS ($n = 14$), 13 had additional improvement after PLEX. Of those with no improvement after PS ($n = 10$), 8 improved after PLEX. 16 of 26 patients had pre- and post-PLEX EDSS scores available. Median pre-PLEX EDSS score was 4.0 (range 3.0–8.0), and median post-PLEX EDSS score was 3.75 (range 0–8.0) ($p = 0.062$). 5 patients had improved EDSS scores by 1 or more points. Adverse events during PLEX included hypotension ($n = 3$), nausea ($n = 2$), headache ($n = 2$), hypocalcemia ($n = 2$), hypofibrinogenemia ($n = 2$), thrombocytopenia ($n = 1$), spinal cord hemorrhage ($n = 1$), acute non-occlusive thrombosis of internal jugular vein ($n = 1$), occlusion of the central line ($n = 1$), edema of the neck ($n = 1$), and gastrointestinal discomfort ($n = 1$).

Conclusions: PLEX is an overall well-tolerated second-line treatment option for pediatric patients with severe acute CNS demyelinating events with limited response to PS.

1. Introduction

Children with acute central nervous system (CNS) demyelination are typically treated with first-line pulse steroid therapy. (Cortese et al., 2011) Second-line therapies such as intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) are considered in patients with severe events with incomplete or no improvement after high-dose pulse steroids. (Cortese et al., 2011; Reeves and Winters, 2014; Alper, 2012; Brenton and Banwell, 2016) A randomized controlled trial of PLEX in acute CNS demyelinating disease in adults ($n = 22$) demonstrated moderate to marked improvement in neurologic deficits in those receiving active treatment (42.1%) compared to sham therapy (5.9%). (Weinshenker et al., 1999)

To date, only small case series and no randomized controlled trials have evaluated the effectiveness and safety of PLEX in children with CNS demyelinating disorders. The largest case series suggested PLEX

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can be beneficial for pediatric transverse myelitis (TM), with 15 of 19 patients having major improvement in symptoms with PLEX. (Noland and Greenberg, 2018) Another case series (n = 12) suggested that PLEX in acute CNS demyelinating diseases, specifically multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), and TM can improve recovery. In this series, median Expanded Disability Status Scale (EDSS) score decreased by 2 points in the 9 patients who improved after PLEX. (Bigi et al., 2014) Other case reports of the use of PLEX in acute CNS demyelinating events in children have also suggested potential benefit, though most did not detail disease courses after pulse steroids. (Takahashi et al., 1997; Mogami et al., 2011; Bonastre-Blanco et al., 2011)

This study aimed to examine the safety and effectiveness of PLEX in a larger pediatric cohort of acute CNS demyelinating events in the context of pulse steroids effect.

2. Materials and methods

This was a single-center, retrospective cohort study of pediatric patients with acute CNS demyelinating events who received PLEX as a second- or third-line therapy from November 2006 to April 2018. All patients were seen at the Pediatric MS Center at University of California, San Francisco (UCSF), a tertiary referral center. Patients treated with PLEX for an acute CNS demyelinating event were identified through the center's database. This study was approved by the UCSF IRB.

The inclusion criteria were as follows: (1) Diagnosis of MS, neuromyelitis optica spectrum disorder (NMOSD), TM, ADEM, or MOG-antibody associated demyelination (MOG); (2) disease onset before 18 years of age; and (3) received PLEX before age 18 years.

Data collected through chart review included demographics (age, race/ethnicity, and sex), diagnosis, disease duration prior to PLEX, dose and type of pulse steroids, number of PLEX sessions, volume exchanged, and adverse events from PLEX. Presence of clinical improvement post-steroid treatment and post-PLEX based on clinical physician assessment were evaluated. We also collected pre- and post-PLEX EDSS scores. For patients with EDSS scores missing for pre- or post-PLEX, scores were extrapolated by a neurologist (KK) using clinical notes when available, who remained blinded with respect to the timing of PLEX (i.e. pre- or post-).

The primary outcome was the change in EDSS score pre- versus post-PLEX. The secondary outcome was the presence of clinical improvement determined by the treating physician following PLEX, stratified by response to steroids. Patients with clinical improvement were considered responders to PLEX. We examined the trajectory of EDSS scores up to a year following PLEX or until another relapse occurred.

Descriptive statistics were reported as medians and ranges. Wilcoxon matched pairs signed-rank test was used to assess change in EDSS scores following PLEX. Tests were performed in STATA 15 (College Station, TX) with alpha of 0.05.

3. Results

Twenty-six pediatric patients (10 male, 16 female) received PLEX as second- or third-line treatment for an acute CNS demyelinating event. Median age at disease onset was 10.5 years (range 2–17). Median age at first cycle of PLEX was 13.5 years (range 3–17). Median duration between onset of the most recent acute event and PLEX initiation was 22 days (range 3–94). Diagnoses included MS (n = 15), NMOSD (n = 7), MOG (n = 2), TM (n = 1), and ADEM (n = 1) (Table 1).

All patients (n = 26) initially received IV high-dose pulse steroids prior to PLEX with median treatment duration before PLEX of 5 days (range 1–10) (n = 24). 4 patients started PLEX before their last administration of high-dose pulse steroids. All 26 patients received PLEX, and 25 had number of exchanges recorded in the clinical records with a median of 5 exchanges (range 3–10) (Table 2). 9 of 26 patients also received IVIG, 8 of whom were treated with IVIG before PLEX and 1 who started IVIG on the final day of PLEX. The median number of days between initiating IVIG and initiating PLEX was 3, and thus response to IVIG is difficult to evaluate.

Pre- and post-PLEX EDSS scores were available for 16 of 26 patients (Fig. 1). Median pre-PLEX EDSS score was 4.0 (range 3.0–8.0), and

Table 1
Patient characteristics (n = 26).

Characteristics	Number (%) or Median (Range)
Female	16 (61.5%)
Race	
White	9 (34.6%)
Black	7 (26.9%)
Asian	5 (19.2%)
Other	4 (15.4%)
Unknown/Declined to State	1 (3.8%)
Age at disease onset (years)	10.5 (2–17)
Age at PLEX (years)	13.5 (3–17)
Disease duration before PLEX (months)	2.4 (0.2–74.4)
PLEX for first event	13 (50%)
Time between acute event and PLEX (days)	22 (3–94)
Diagnosis	
MS	15 (57.7%)
NMOSD	7 (26.9%)
MOG	2 (7.7%)
TM	1 (3.8%)
ADEM	1 (3.8%)

PLEX = plasma exchange, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder, MOG = MOG-antibody associated demyelination, TM = transverse myelitis, ADEM = acute disseminated encephalomyelitis.

Table 2
Treatment of acute CNS demyelinating events.

Treatment Details	Number (%) or Median (Range)
Number of pulse steroid days before plasma exchange, n = 24	5 (1–10)
Type of pulse steroids	
Methylprednisolone	20 (76.9%)
Dexamethasone	1 (3.8%)
Unknown	5 (19.2%)
Dosage of methylprednisolone (mg/day), n = 14	1000 (400–1285)
Number of plasma exchange sessions, n = 25	5 (3–10)
Plasma volume ratio exchanged per cycle, n = 15	1.0 (1.0–1.5)

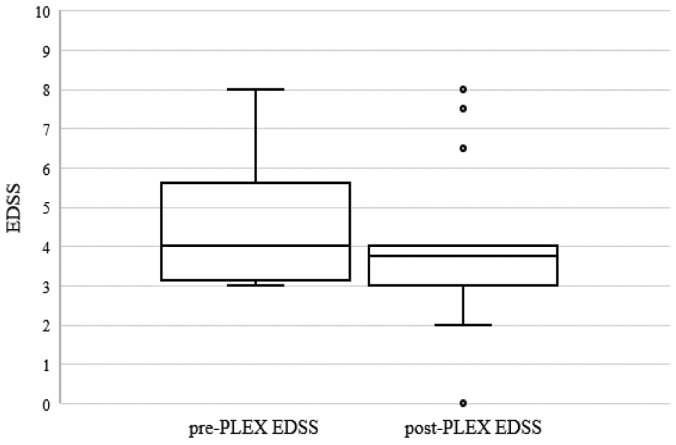

Fig. 1. EDSS score prior to and following PLEX (n = 16).
Figure legend: There was a median EDSS improvement of 0.25 in the subset with EDSS pre- and post-PLEX available (n = 16), although this did not reach statistical significance (p = 0.062).
EDSS = Expanded Disability Status Scale, PLEX = plasma exchange.

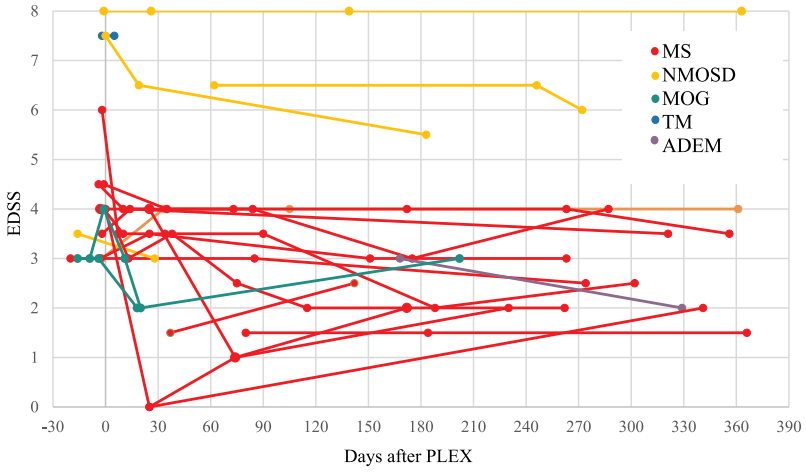

Fig. 2. EDSS trajectory by patient after PLEX by diagnosis (n = 21).
Figure legend: The trajectory of disability as measured by EDSS in individual patients (n = 21) who had at least 2 EDSS scores available in the year after PLEX. Follow-up continued until either a relapse occurred or 1 year after PLEX. The majority had stable or improved EDSS over time.
EDSS = Expanded Disability Status Scale, PLEX = plasma exchange, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder, MOG = MOG-antibody associated demyelination, TM = transverse myelitis, ADEM = acute disseminated encephalomyelitis.

median post-PLEX EDSS score was 3.75 (range 0–8.0) (p = 0.062). The median improvement in EDSS score for the 9 responders to PLEX was 1.0 (range 0.5–4.0), 5 of whom had ≥ 1.0 point improvement. At least two EDSS scores were available for 21 patients over up to one relapse-free year from PLEX, and the EDSS trajectories are displayed in Fig. 2. Most had stable EDSS scores over this period. 13 of 21 patients with follow-up data available did not experience a relapse over the year following PLEX.

Of 26 patients, 10 had no clinical improvement after pulse steroids, while 14 improved (status after steroids is not available for the other 2). Of the 10 patients with no improvement after pulse steroids, 8 improved after PLEX, 1 of whom started PLEX while on pulse steroids. Of the 14 who improved during or after pulse steroids, 13 had additional improvement after PLEX, 2 of whom started PLEX while on pulse steroids. Of the 2 patients with no available physician assessment after pulse steroids, both improved after PLEX, and 1 started PLEX while on pulse steroids (Fig. 3). Overall, 23 of 26 patients experienced improved symptoms following PLEX based on clinical physician subjective assessment. By diagnosis, clinical improvement was seen in 15/15 with MS, 5/7 with NMOSD, 2/2 with MOG, 0/1 with TM and 1/1 with ADEM.

In the 26 patients, 9 had at least one adverse event (AE) while 17 patients had no AEs with PLEX, with a median number of AEs of 0 per patient and a maximum of 3. Adverse events occurred across a range of ages from 3 to 17 years of age, and across diagnoses with at least 1 adverse event in 5 with MS, 2 with NMOSD, and 2 with MOG. Adverse events during PLEX included hypotension (n = 3), nausea (n = 2), headache (n = 2), hypocalcemia (n = 2), hypofibrinogenemia (n = 2), thrombocytopenia (n = 1), acute non-occlusive thrombosis of an internal jugular vein (n = 1), occlusion of the central line (n = 1), edema of the neck (n = 1), and gastrointestinal discomfort (n = 1) (Table 3).

Table 3
Adverse events during PLEX (n = 26).

Adverse Event	Number of cases (%)
Hypotension	3 (11.5%)
Nausea	2 (7.7%)
Headache	2 (7.7%)
Hypocalcemia	2 (7.7%)
Hypofibrinogenemia	2 (7.7%)
Thrombocytopenia	1 (3.8%)
Spinal cord hemorrhage into myelitis	1 (3.8%)
Acute non-occlusive thrombosis of internal jugular vein	1 (3.8%)
Occlusion of the central line	1 (3.8%)
Edema of the neck	1 (3.8%)
Gastrointestinal discomfort	1 (3.8%)

One patient with hypofibrinogenemia had hemorrhage into his NMOSD-related TM lesion, with no recovery following PLEX.

Four of 26 patients treated with PLEX were 5 years or younger in age, with indications at this young age including NMOSD in 3 and TM in 1. Two of these young children with NMOSD improved clinically after PLEX, and 2 of these young children had at least 1 adverse event.

4. Discussion

We found that the majority of children who received PLEX for an acute CNS demyelinating event in our cohort exhibited some degree of clinical improvement after absent or incomplete response to high-dose pulse steroid therapy. While not all improved after PLEX with a median improvement by 0.25 on the EDSS overall, those who were responders to PLEX had a median improvement of 1.0 on EDSS. Improvement was seen for patients across all diagnoses, except for TM (n = 1), with

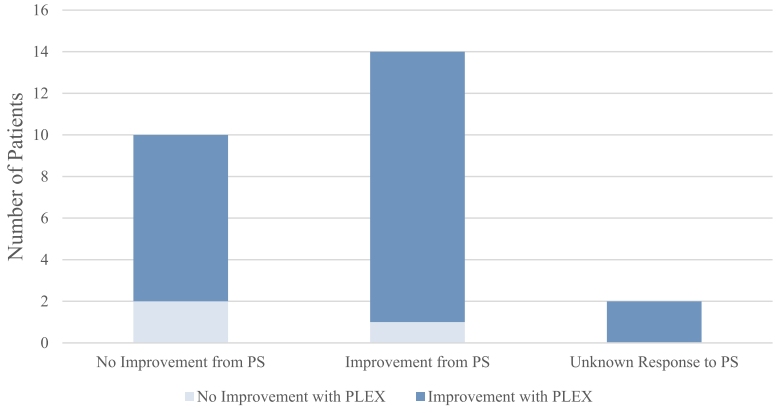

Fig. 3. Clinical improvement per clinical physician assessment after PLEX (n = 26).
Figure legend: The number of patients with clinical improvement with PLEX (dark blue), and the number without clinical improvement with PLEX (light blue) stratified by initial response to steroids. Most patients had at least some clinical improvement during PLEX therapy regardless of initial response to pulse steroids.
PS = pulse steroids, PLEX = plasma exchange.

improvement in all of our cases of MS and MOG. There was also improvement in 11 of 13 initial and 12 of 13 subsequent demyelinating events treated with PLEX. Additionally, the majority experienced a relapse-free year following PLEX, although this may be due to subsequent initiation of disease-modifying therapies not captured by this study.

Compared to a previous similar size cohort which reported a median EDSS improvement of 2.0 following PLEX, the median 1.0 EDSS improvement in our study in PLEX responders was modest. This may be in part due to patients in the previous cohort receiving PLEX in closer proximity to the event onset (2–24 (median 10) days after symptom onset), while some patients in our study received PLEX in a more delayed fashion (3–94 (median 22) days after symptom onset). (Bigi et al., 2014) Previous studies also showed improvement after PLEX in a majority of patients, with 15 of 19 improving in one study. (Noland and Greenberg, 2018) The lack of improvement in the single case of TM in our cohort does not imply no benefit of PLEX in TM, as other series have suggested improvement in pediatric TM with PLEX. (Noland and Greenberg, 2018) Similar to prior studies, 23 of 26 patients in our cohort had subjective clinical improvement following PLEX based on physician assessment. It is not possible to separate improvement related to natural history from improvement related to PLEX in any of these studies.

Adverse events associated with PLEX in our cohort were consistent with those previously reported with PLEX for acute CNS demyelination in adults and children. (Brenton and Banwell, 2016; Weinshenker et al., 1999) Adverse events were associated with central line use, blood volume shifts, replacement products, and anticoagulant effects of PLEX. None of the patients experienced allergic reactions or infections. However, one patient had cord hemorrhage at the level of the myelitis in the setting of hypofibrinogenemia with persistent, severe neurologic deficits. PLEX can deplete coagulation factors, particularly fibrinogen, and bleeding complications have rarely been reported. (Eyre et al., 2018) Fibrinogen should be monitored during PLEX, and supplementation may be required. (Eyre et al., 2018) Additionally, two patients had fewer PLEX sessions than initially planned due to thrombotic events related to central lines. Overall, there is potential for clinically important complications of PLEX that should be discussed with the child and family when initiating PLEX and balanced with potential benefit.

Because of the retrospective nature of the study, there was incomplete data in some clinical records. Unfortunately, only 16 patients had both pre- and post-PLEX EDSS scores available due to lack of EDSS or adequately documented neurologic exam and ambulatory ability to estimate EDSS before and after PLEX. Additionally, EDSS was calculated retrospectively for some cases when there was no documented EDSS. Although this may lead to misclassification of EDSS, the rater was blinded to the EDSS timing, and thus this misclassification is expected to be non-differential with respect to timing around PLEX and would be expected to result in bias towards finding no effect. We also did not systematically collect adverse event data, so those may be under-estimated.

We also lacked a comparator or control group to evaluate the effectiveness of PLEX, but we were able to assess within-patient changes. Additionally, physicians making judgments of clinical response to PLEX and performing neurologic examination and EDSS were not blinded to PLEX treatment, and these assessments have a subjective component. It is not surprising that more benefit was seen based on the subjective physician clinical improvement assessment over EDSS score (as this score may be poorly sensitive to change), although both can be biased by knowledge of treatment receipt. Finally, the improvement in symptoms or changes in EDSS scores did not account for natural history (i.e. recovery without PLEX) or concomitant or subsequent therapies, including steroid tapers, IVIG, and immunomodulating drugs. It is unknown whether these patients would have improved if they had not received PLEX, and we cannot fully evaluate response to PLEX given the lack of a comparator group in this study. It is expected that the natural history may include improvement with or without PLEX, although this cannot be evaluated without a comparison group.

Strengths of this study include evaluation of the use of PLEX in a larger cohort than previously reported for a variety of acute CNS demyelinating events in children. We uniquely evaluated clinical improvement after PLEX in the context of response to pulse steroids and evaluated disability trajectory over the year following PLEX.

5. Conclusions

Although there is consistent reporting of benefit from PLEX in small studies of acute demyelinating events in children, these studies are limited by lack of blinding or a comparator group, and well-designed studies are required to evaluate the effectiveness and safety of PLEX in children. Additional insight could be gained from a prospective, standardized, multi-site study or a randomized blinded, sham-controlled study. In the absence of these studies, PLEX as a second-line therapy is a reasonable option to consider in pediatric patients with a severe acute CNS demyelinating event with limited improvement after pulse steroids after weighing the potential benefits and risks on an individualized basis.

Data statement

Data are available to investigators on request by contacting the corresponding author for the purposes of replicating results.

Declarations of interest

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