Therapeutic Apheresis in Pediatric Patients with Acute CNS Inflammatory Demyelinating Disease

Michael Koziolek\(^a\)  Johannes Mühlhausen\(^a\)  Tim Friede\(^b\)  David Ellenberger\(^b\)  Matthias Sigler\(^c\)  Brenda Huppke\(^d\)  Jutta Gärtner\(^d\)  Gerhard-Anton Müller\(^a\)  Peter Huppke\(^d\)

Departments of \(^a\)Nephrology and Rheumatology, \(^b\)Medical Statistics, \(^c\)Pediatric Cardiology and Pediatric Intensive Care Medicine and \(^d\)Pediatrics and Pediatric Neurology, University Medical Center, Georg August University Göttingen, Göttingen, Germany

Key Words
Plasma exchange · Immunoadsorption · Multiple sclerosis · Neuromyelitis optica · Acute disseminated encephalomyelitis

Abstract

Background/Aims: In adults, plasma exchange (PE) has been shown to be an efficient treatment for severe relapses of acute inflammatory CNS demyelinating diseases. The aim of this study was to evaluate the safety and efficacy of this treatment in pediatric patients. Methods: We retrospectively analyzed a single-center cohort of pediatric patients with inflammatory CNS demyelinating disorders who underwent apheresis between 2007 and 2011. Results: Ten patients (mean age: 11.6 ± 3.4 years) with an acute relapse of multiple sclerosis (n = 5), neuromyelitis optica (n = 2) or acute disseminated encephalomyelitis were included. All received methylprednisolone prior to treatment with either PE (n = 5) or immunoadsorption (n = 5). Apheresis-related side effects were either self-limiting or easily managed. EDSS (Expanded Disability Status Scale) improved in 7 of 8 patients during apheresis and in all patients within 30 days from a median of 7.5 to 1 (p < 0.01). The visual acuity initially worsened during the procedure in 3 of 7 affected eyes (mean 0.09), but improved in all at follow-up (mean: 0.5; p = 0.008). Conclusions: Apheresis was well tolerated and associated with a favorable outcome in all pediatric patients similar to reports in adults.

Introduction

Therapeutic apheresis has become a well-established tool in modern medicine. In neurology, usage of therapeutic apheresis is especially recommended in Guillain-Barré syndrome and for the short-term management of chronic inflammatory demyelinating polyneuropathy [1]. Two randomized sham-controlled studies have shown a beneficial effect of plasma exchange (PE) in adult patients with acute CNS demyelinating diseases failing to respond to treatment with ACTH or high-dose corticosteroids, respectively [2, 3]. Additionally, one uncontrolled prospective study [4] and several case series [5, 6]

Michael Koziolek and Johannes Mühlhausen contributed equally to this article.
have shown comparable effects of immunoadsorption (IA) in such cases. The International Pediatric Multiple Sclerosis (MS) Study Group states: ‘Children with severe relapses not improving after high-dose IVMP pulse or with contraindications to glucocorticosteroids might benefit from a treatment with plasma exchange’ [7]. In a recent article on children in US hospitals, 53 patients with diagnosed MS are mentioned, 5 of which were treated with therapeutic PE [8]. However, published experience on the outcome of this treatment is limited to one retrospective study of 6 patients with acute disseminated encephalomyelitis (ADEM) showing a positive effect of PE and case reports on patients with ADEM or severe attacks of MS [9–14]. Therapeutic apheresis is used as an escalation procedure in our center for very severe acute attacks of inflammatory CNS demyelinating disease that fail to respond to steroids. In this article, we summarize our experience with this procedure.

**Patients and Methods**

**Data Collection**

The data was derived from the institutional review board-approved Database for Inflammatory Demyelinating Disorders of the German Centre for Multiple Sclerosis in Childhood and Adolescence in Göttingen (Ethics Approval No. 21/12/03). Written informed consent was obtained from the guardians of the patients participating in the study. Diagnoses of ADEM, MS and neuromyelitis optica (NMO) were made according to the recommendations of the International Pediatric MS Study Group [15].

**Patients**

- **Inclusion criteria**: age 16 years or younger, and apheresis therapy for an acute attack of a presumed demyelinating CNS disease between 2007 and 2011.

- **Exclusion criteria**: diagnostic criteria of ADEM, NMO or MS not fulfilled during the follow-up period, and a diagnosis other than ADEM, NMO or MS made during the follow-up period.

**Outcome Measures**

EDSS (Expanded Disability Status Scale) was assessed prior to the acute attack, before methylprednisolone treatment, before apheresis, day 1 after apheresis, and 3 and 6 months after apheresis [16]. EDSS was not assessed in patients presenting with optic neuritis (ON) alone. Changes of visual acuity were monitored using the Snellen chart before high-dose steroid treatment, before apheresis, day 1 after the last apheresis, and 3–5 and 6–12 months after the last apheresis [17].

**Apheresis Treatment**

Apheresis therapy was performed using Octo Nova extracorporeal circuit technology (SW 4.30.2, front 4.30.0; Diamed Medizintechnik, Cologne, Germany) combined with a single-use tubing and filter system. Membrane plasma separation was performed with a polyethylene plasma separator. The plasma separator volume was chosen individually depending on the patient’s weight and height using an OP-02, -05 or -08 filter (Asahi Kasei Kuraray, Tokyo, Japan), respectively. Blood flow rates ranged from 50 to 150 ml/min and plasma flow rates from 15 to 20 ml/min. Anticoagulation with unfractionated heparin was administered for all treatments. Internal jugular (4 of 10 patients) or femoral veins (6 of 10 patients) were used for central vascular access with double-lumen catheters in all patients. Vascular access was administered under generalization (n = 6) or local anesthesia (n = 4). One-fold plasma volume was treated or exchanged, respectively, per session calculated by the formula: plasma volume (in liters) = 0.065 × body weight (in kg) × (1 – hematocrit). In total, 5 sessions were performed on each patient on alternate days. In the event of complications or a fall in fibrinogen below 100 mg/dl, treatment-free intervals were extended for the individual. Human albumin mixed with Sterofundin® to a final human albumin concentration of 4% was used as replacement fluid in PE. In the case of IA, the single-use tryptophan-linked polyvinyl alcohol adsorber TR-350 (Diamed Medizintechnik) was used.

**Classification of Side Effects**

Side effects were defined as any unexpected or symptomatic event, which had a possible, probable or definite causal relationship with apheresis treatment and were classified as mild, moderate or severe as described before [18] with small modifications. Mild side effects included those of a transient nature with little or no clinical significance not necessitating any temporary interruption of the procedure. Side effects that required medical intervention but were not life-threatening were classified as moderate. Unstable and life-threatening events requiring termination of the procedure were classified as severe.

**Clinical Chemistry**

All laboratory parameters were measured using standardized methods.

**Statistics**

Descriptive statistics such as median and range were computed for outcomes including EDSS and visual acuity. For evaluation of treatment efficacy, EDSS prior to apheresis was compared with EDSS the day after apheresis, as well as 30 and 90 days after apheresis using the nonparametric rank-based t test for paired samples [19]. Visual acuity was compared using the same test, comparisons were made between preapheresis and 1 day after the last apheresis as well as 90–150 days (3–5 months) and 180–360 days (6–12 months) after apheresis. In these analyses, the eyes were independent units of analysis. This assumption was checked in sensitivity analyses. Due to the exploratory nature of this study, p values were not adjusted for multiple comparisons. Comparisons with p < 0.05 are referred to as statistically significant.

**Results**

Between 2007 and 2011, 12 pediatric patients were treated with apheresis for a suspected attack of an inflammatory CNS demyelinating disease that failed to re-
respond to corticosteroid treatment. Two patients had to be excluded from the study. In one patient with bilateral vision loss unresponsive to treatment, Leber hereditary optic neuropathy was diagnosed by mutation analysis. In the second patient, a Turkish boy of consanguine parents who presented with recurrent encephalopathy, a mitochondrial disorder was suspected at follow-up due to the results of metabolic testing; however, no definite diagnosis was confirmed. Ten patients aged 6–16 years (mean age: 11.6 ± 3.4 years), 7 of them female, were included in the study. Five were treated with PE and 5 with IA (table 1). Diagnoses of the included patients were: ADEM (n = 2), recurrent ADEM (n = 1), relapsing remitting MS (n = 5) and NMO-IgG-negative NMO (n = 2). In the MS cohort, 4 patients presented at the time of the second relapse (patients 1, 2, 3 and 5) and 1 during the first relapse (patient 4). One patient was treated with interferon-β (patient 2). Patient 10 had been receiving natalizumab, but treatment was discontinued prior to the first presentation in Göttingen. The leading symptoms were tetraparesis (n = 3), paraparesis (n = 4), hemiparesis (n = 1), bilateral ON (n = 3) and unilateral ON (n = 1). Corticosteroids had been administered prior to apheresis in all patients within 1–30 days (median 3) of symptom onset at a dosage of 20 mg/kg methylprednisolone per day (maximum dose = 1 g) for 5–15 days (median: 10). The majority (n = 6) received two pulses lasting 5 days. Indications for apheresis were EDSS ≥6 (patients 2–7 and 9) or severe vision loss (≤0.2) in one eye (patients 2 and 10) and no change or worsening of symptoms after at least 5 days of high-dose prednisolone. Patient 8 received methylprednisolone for 10 days and initially improved dramatically; however, 12 days later his tetraparesis worsened again and he received a further 5 days of steroids. Apheresis was commenced following continued deterioration despite steroid treatment. Apheresis therapy was initiated between 8 and 90 days (median: 27) of onset of symptoms and 1–10 days (median: 4) after corticosteroid treatment. The data is summarized in table 1. None of the patients received any additional therapies to apheresis such as IVIG or cyclophosphamide.

**EDSS**

EDSS in the patients with motor symptoms was 0 in all patients prior to the attack (n = 8). At initiation of corticosteroid treatment, the median EDSS was 8 (mean: 6.9; range: 3.5–9.5). In 7 patients the EDSS remained unchanged or increased after steroid treatment. EDSS improved initially in patient 8, but then increased again de-

---

**Table 1. Clinical data**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age, years</th>
<th>Underlying disorder</th>
<th>Leading symptoms</th>
<th>MP therapy prior to apheresis, days</th>
<th>Interval symptom onset and MP therapy, days</th>
<th>Interval symptom onset to apheresis, days</th>
<th>Interval MP therapy to apheresis, days</th>
<th>Apheresis procedure</th>
<th>Treated plasma volume/session, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>12</td>
<td>MS</td>
<td>ON</td>
<td>5</td>
<td>6</td>
<td>15</td>
<td>4</td>
<td>IA</td>
<td>2,000</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>16</td>
<td>MS</td>
<td>paraparesis</td>
<td>10</td>
<td>2</td>
<td>26</td>
<td>10</td>
<td>IA</td>
<td>2,000</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>16</td>
<td>MS</td>
<td>paraparesis</td>
<td>10</td>
<td>14</td>
<td>31</td>
<td>7</td>
<td>IA</td>
<td>2,500</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>12</td>
<td>MS</td>
<td>paraparesis, ataxia</td>
<td>15</td>
<td>30</td>
<td>90</td>
<td>1</td>
<td>PE</td>
<td>1,500</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>11</td>
<td>MS</td>
<td>hemiparesis, dysarthria</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>PE</td>
<td>3,000</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>11</td>
<td>NMO</td>
<td>tetraparesis, ON</td>
<td>11</td>
<td>4</td>
<td>28</td>
<td>5</td>
<td>IA</td>
<td>1,500</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>6</td>
<td>NMO</td>
<td>tetraparesis, ON</td>
<td>10</td>
<td>2</td>
<td>48</td>
<td>9</td>
<td>PE</td>
<td>1,200</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>10</td>
<td>ADEM</td>
<td>tetraparesis, ON</td>
<td>15</td>
<td>3</td>
<td>32</td>
<td>3</td>
<td>IA</td>
<td>1,500</td>
</tr>
<tr>
<td>9</td>
<td>f</td>
<td>15</td>
<td>ADEM</td>
<td>coma, tetraparesis</td>
<td>8</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td>PE</td>
<td>2,500</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>7</td>
<td>recurrent ADEM</td>
<td>ON</td>
<td>10</td>
<td>1</td>
<td>25</td>
<td>6</td>
<td>PE</td>
<td>1,250</td>
</tr>
</tbody>
</table>

MP = Methylprednisolone.
In spite of steroid treatment, at initiation of apheresis, the median EDSS was 7.5 (mean: 7.1; range: 3.5–9.5), decreasing to a median EDSS of 5 (mean: 5.1; range: 2–9) on the day after the last apheresis procedure (p = 0.0088), to a median EDSS of 1 (mean: 1.6; range: 0–6.5) 30 days after apheresis (p = 0.0003) and to a median EDSS of 0 (mean: 0.87; range: 0–3.5) 90 days after apheresis (p < 0.0001). The individual time-courses of EDSS are shown in Table 2.

**Visual Acuity**

Seven eyes were affected with ON. Visual acuity measured in 5 eyes prior to corticosteroid treatment showed a median of 0.025 (mean: 1.4; range: 0.025–0.6). Visual acuity (n = 7) before apheresis showed a median value of 0.09 (mean: 0.15; range: 0.025–0.5). On day 1 after apheresis, a decrease in visual acuity was observed in 3 eyes and improvement in 2 (median: 0.1; mean: 0.21; range: 0.02–0.6; p = 0.7093). Ninety to 150 days after apheresis, initiation median visual acuity improved to 0.5 (mean: 0.49; range: 0.05–0.9; p = 0.0078). Six to 12 months following apheresis, visual acuity further improved in 5 eyes to a median of 1 (mean: 0.86; range: 0.5–1; p = 0.089). Patient 10 experienced a further attack of bilateral ON within this time interval. The individual time-courses of visual acuity are shown in Table 3.

**Side Effects**

Apheresis-related side effects were either mild (n = 3) or moderate (n = 1). They included transient hypotension (n = 1, IA), acute dyspnea (n = 1, IA), catheter dislocation (n = 1, PE) and decreased serum-fibrinogen. Serum-fibrinogen was lower in patients who underwent PE (129 mg/dl after the first PE, 168.75 mg/dl after the 5th) compared to patients treated with IA (306 mg/dl after the first IA, 239.3 mg/dl after the 5th). In one case, a PE cycle was delayed due to reduced serum-fibrinogen levels.

**Table 2. Time-course of EDSS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>EDSS before the attack</th>
<th>EDSS before MP therapy</th>
<th>EDSS before apheresis</th>
<th>EDSS 1 day after apheresis</th>
<th>EDSS 30 days after apheresis</th>
<th>EDSS 90 days after apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0</td>
<td>5.5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>6.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>3.5</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>8.5</td>
<td>9</td>
<td>8</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>6.5</td>
<td>3.5</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>3.5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>8.5</td>
<td>3.5</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>9.5</td>
<td>9.5</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>8</td>
<td>7.5</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**MP = Methylprednisolone.**

**Table 3. Time-course of visual acuity assessed by standard charts**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>VA before MP therapy</th>
<th>VA before apheresis</th>
<th>VA 1 day after apheresis</th>
<th>VA 90–150 days after apheresis</th>
<th>VA 180–360 days after apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6/0.025</td>
<td>0.5/0.025</td>
<td>0.5/0.025</td>
<td>0.5/0.05</td>
<td>1.0/0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.025/1.0</td>
<td>0.025/1.0</td>
<td>0.2/1.0</td>
<td>0.5/1.0</td>
<td>0.8/1.0</td>
</tr>
<tr>
<td>7</td>
<td>n.d.</td>
<td>0.2/0.16</td>
<td>0.6/0.1</td>
<td>0.9/0.6</td>
<td>1.0/1.0</td>
</tr>
<tr>
<td>10</td>
<td>0.025/0.025</td>
<td>0.05/0.09</td>
<td>0.02/0.05</td>
<td>0.6/0.3</td>
<td>0.05/0.025</td>
</tr>
<tr>
<td>Median</td>
<td>0.025/0.025</td>
<td>0.125/0.125</td>
<td>0.35/0.075</td>
<td>0.55/0.45</td>
<td>0.9/0.525</td>
</tr>
</tbody>
</table>

**MP = Methylprednisolone; VA = visual acuity; n.d. = not done.**
Discussion

Pediatric patients with an acute severe attack of a CNS demyelinating disease who do not seem to respond to high-dose corticosteroids are a therapeutic dilemma for the treating physician. The patients face the risk of permanent disability at a time in life where both personal and professional stability have not yet been achieved. On the other hand, there are no clear treatment recommendations or studies that support either cyclophosphamide, immunoglobulins or plasmapheresis as a superior treatment option. While apheresis is an established treatment in adults, there is only limited literature and experience regarding apheresis use in pediatric patients. The challenges in performing apheresis on pediatric patients arise from differences in physiology with respect to plasma volume, body mass, vascular access and metabolic properties. To the knowledge of the authors, the number of reported cases of pediatric patients who have been treated with apheresis for an acute severe attack of a CNS demyelinating disease encompasses 9 patients with ADEM and 5 with MS. In all but one case the treatment led to an improvement of symptoms [9–12, 14, 20, 21]. We report here on our experience with 10 such patients treated since 2007. The underlying disorders encompassed MS (n = 5), ADEM (n = 3) and NMO-IgG-negative NMO (n = 2). All patients had received at least 5 days of high-dose methylprednisolone prior to apheresis. The patients that were selected for apheresis had a mean EDSS of 7.5 or a visual acuity ≤0.2. Among the patients treated for tetra-, para- or hemiparesis, all but one improved significantly during apheresis treatment with an improvement observed in all patients within 30 days of treatment. In the patients with severe reduction of visual acuity, the response was not as immediate. Visual acuity of 3 eyes even decreased initially; however, an improvement in the months following apheresis was seen in all patients. Such a delayed effect of PE was not seen in a study on adult patients with ON [22], but it has been reported in IA [4, 23]. However, ongoing evaluations on adults treated with either PE or IA in our center seem to show that this delayed effect is not dependent on the applied procedure [Mühlhausen et al., manuscript in preparation]. In our cohort, a long interval between symptom onset and the start of apheresis treatment was not associated with a worse outcome. In fact, EDSS was 0 three months after apheresis in all 3 patients with an interval greater than 1 month. It has been reported previously in adult patients that patients treated after 60 days can have a favorable response [24].

Therapeutic apheresis in children, including its indications, modalities and side effects, is still a rather unexplored chapter in current medicine. Established treatment standards are still missing, with apheresis modalities in pediatric patients mostly derived from adult treatment protocols [25]. Performing apheresis therapy on children requires a multidisciplinary approach involving expertise in pediatrics, intensive care medicine and nephrology, as well as specialty knowledge in apheresis techniques. Thus, a collaboration of specialized medical departments is necessary to overcome the challenges of pediatric apheresis with respect to indication, technical management, vascular access, anticoagulation and the monitoring of side effects. Concerning treatment safety, De Silvestro et al. [26] described a 5.6% rate of adverse events in apheresis therapy in children, analyzing a survey from 2005. In a retrospective study from 2007, Michon et al. [27] detected a much higher complication rate in 186 pediatric apheresis patients of which 73.7% were treated with either PE or IA (55% of all procedures) compared to adults with neurological disorders (16.2% of all procedures, n = 86 patients) [18]. In our cohort, three relevant side effects occurred in 50 procedures at a rate (6%) comparable to the study by De Silvestro et al. [26].

Fortunately, very severe attacks of inflammatory demyelinating CNS disorders are rare events in pediatric patients. As a consequence, although the Göttingen University serves as a tertiary center for large areas of Germany, the number of patients in this cohort remains small and the symptoms and underlying disorders differ in each patient. Moreover, most patients were transferred to us some time after symptom onset and following variable treatment courses with high-dose methylprednisolone, making it difficult to judge if the improvement observed during or after apheresis in each individual case was not an effect of the preceding corticosteroid treatment or the natural course of events. The latter is especially true for patients treated for ADEM or ON. Since the symptoms in these disorders are often self-limiting, apheresis may have only accelerated improvement. Due to the small number of patients, we also cannot comment if a specific disorder or symptom reacts more responsively to treatment with apheresis than others. Finally, as we did not use cyclophosphamide or immunoglobulins, we cannot comment if using these drugs alone or in combination with apheresis would lead to an even more favorable outcome. To overcome these limitations, prospective studies comparing different standardized treatment protocols are clearly warranted. Since the burden of permanent disability is especially high in this age group, the need for optimizing treatment is essential.
In conclusion, we report on the largest series published to date of pediatric patients undergoing apheresis treatment for a severe attack of a CNS demyelinating disorder. Apheresis treatment was associated with a favorable outcome in all patients and the procedure was well tolerated. The positive outcome was not limited to the patients treated within the first 4 weeks, but also seen in patients treated up to 90 days following symptom onset. Due to the nature of the study, we cannot exclude that the positive outcome was a delayed effect of the steroid treatment.

Acknowledgements

The authors thank the staff of the ICUs 1022 and 0123.

Disclosure Statement

A previous study was supported by a research grant of Diamed Medizintechnik M. Koziolek. The authors have no financial interest in this manuscript.

References


17 Hetherington R: The Snellen chart as a test of visual acuity. Psychol Forsch 1954;24:349–357.


