Clinical application of plasma exchange in pediatric anti-N-methyl-D-aspartate receptor encephalitis

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Received May 3, 2017; Accepted June 6, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: To retrospectively analyze the efficacy and adverse events of plasma exchange (PE) in the treatment of children with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Methods: A retrospective case analysis was conducted on the medical records of plasma exchanges in children with Anti-NMDAR encephalitis in the Blood Purification Room, Pediatric Department, The West China Second University Hospital of Sichuan University between January 2013 and December 2015. The replacement fluid was homotypic fresh frozen plasma. The patients' therapeutic effect and adverse reactions were measured and analyzed. Results: A total of 12 children aged 5-14 years were included in the study. The time from clinical symptoms onset to PE treatment was 12-300 days (mean 61 d). All the patients were given immunoglobulin and high dose methylprednisolone before PE. Each patient received 3-7 sessions of PE, with overall 54 sessions for all the cases. Ten patients showed confirmed effectiveness, with an effective rate of 83.33%. The Glasgow Coma Scale (GCS) scores were different before and after PE (P<0.05). Fifteen adverse events occurred in the patients (27.78%), mostly anaphylaxis. Conclusion: PE is well tolerated by children and appears to be beneficial to children with anti-NMDAR encephalitis.

Keywords: anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, plasma exchange, children

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a type of immune-mediated encephalitis presented with characteristic neuropsychiatric symptoms. The disease occurs in patients at any age, most frequently in children and young women. It is the most common pediatric autoimmune encephalitis [1, 2]. The overall mortality of the disease was approximately 7%, of which children accounted for 2.8%-5% [3, 4]. The clinical course of the disease is virulent in most patients and it takes months even years for them to recover. Nevertheless, 75%-83% of the patients have good prognosis after aggressive treatment [5-7].

Early detection and immunotherapy intervention are crucial for a favorable outcome [2, 5, 8, 9]. The first-line immunotherapy for anti-NMDAR encephalitis in adults was defined as the use of corticosteroids, intravenous immunoglobulin (IVIG) or plasma exchange (PE) alone or combined [3, 5, 7, 10]. But as for the treatment of pediatric anti-NMDAR encephalitis, no optimum protocol is agreed [10-12]. In this study, we made a retrospective analysis on 12 cases of pediatric anti-NMDAR encephalitis received PE treatment, with an aim to investigate, efficacy, safety and adverse reactions of PE in treatment of pediatric anti-NMDAR encephalitis.

Subjects and methods

Selection of study subjects

This retrospective study was conducted in the Pediatric Department, West China Second University Hospital of Sichuan University. Approval from the Hospital Ethics Committee and the informed written consents from all the guardians were obtained. The children who had been diagnosed as having anti-NMDAR encephalitis were given corticosteroids and IVIG followed by PE in the blood purification room of
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Pediatric Department from January 2013 to December 2015. The guardians promised to participate in the follow-ups and provide detailed information of the children during treatment. The subjects were required to make regular clinic visits after discharge. The modified Ranke scale (MRS) was used to assess the patients' outcomes during follow-ups. MRS ≤2 indicated good prognosis but MRS ≥3 poor prognosis. The diagnosis of anti-NMDAR encephalitis was performed based on the diagnostic criteria proposed by Dalmau et al. in 2011 [10].

Information extraction

The clinical data of the patients were obtained from the Division of Medical Records Management and blood purification room of the West China Second University Hospital of Sichuan University. Follow up data were collected from the medical records management system of the pediatric outpatient clinic. Descriptive analysis was performed on the following clinical data: demographic data, clinical features, details of the plasma exchange procedure, efficacy and adverse reactions of PE therapy, as well as follow-ups after discharge.

Plasma exchange

All the children underwent PE on alternate days with Gambro PRISMAFLEX extracorporeal circulation line and plasma filter. The replacement fluid was homotypic fresh frozen plasma (FFP). Vascular access was established by inserting an indwelling double-lumen catheter into the femoral vein. PE volumes of 1.2- to 1.5-fold the child's plasma volume per procedure were used [14]. Nadroparin calcium (Fraxiparine, manufactured by GlaxoSmithKline) was used as the only anticoagulant for all the procedures at an initial dose of 60-80 IU/kg, and did not require to be maintained. At the initiation of PE procedure, the blood pathway was pre-flushed with normal saline to prevent hypotension. Before the PE procedure, 5-10 mg of dexamethasone and 5-10 mg of calcium gluconate were intravenously infused to prevent anaphylaxis. Furthermore, during the PE procedure 10 ml of 10% calcium gluconate per 1000 ml fresh frozen plasma was continuously administrated by intravenous drop for prophylaxis of hypocalcemic toxicity.

The heart rate, respiration, blood pressure, transcutaneous oxygen saturation and temperature were constantly monitored during PE treatment. In addition, whether there was anaphylaxis and hemorrhagic tendency were observed. After PE, the site of femoral vein puncture was observed to see if there was the presence of complications like errhysis or infection, or signs of venous thrombosis. The patients' blood routine test, blood electrolytes, albumin, globulin, blood coagulation were re-examined on the second day after PE.

Outcome measures

Primary outcome measures were the therapeutic effects of PE treatment, including the clinical manifestations, the Glasgow Coma Scale (GCS) scores and NMDAR antibody titers in cerebrospinal fluid (CSF) and serum before and after PE and the time from the end of PE treatment to discharge. Other outcomes included adverse reactions to PE and follow-up MRS score. The adverse reactions to PE were categorized into four grades: Grade 1 (mild), Grade 2 (moderate: requiring medication or other interventions), Grade 3 (severe: PE must be discontinued) and Grade 4 (leading to death) [13].

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 17.0. Data were expressed as mean ± standard deviation (mean ± SD). Comparison of data before and after treatment was done with the use of the paired t-test. P<0.05 was considered to represent statistically significant difference.

Results

General information

A total of 12 children were included in this study. There were 6 males and 6 females, with a mean age of 10 years (range 5-14 years). All the children had psychiatric and neurologic deficits and sleep disorders before PE; ten patients presented seizures; eight disturbance of consciousness; five superficial coma; six ataxia; three paresthesia; two associated with central hypoventilation; two oral ulcer. CSF NMDAR antibodies were found in all 12 patients, and serum NMDAR antibodies in 6 patients. No abnormalities in thyroid functions were found and no one was screened to be tumor positive.
## Table 1. PE for anti-NMDAR encephalitis in children

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Pre-PENM-DAR antibody titers in CSF</th>
<th>Pre-PE NMDAR antibody titers in serum</th>
<th>Time from presence of clinical symptoms to confirmed diagnosis (d)</th>
<th>Time from presence of clinical symptoms to PE (d)</th>
<th>Sessions of PE</th>
<th>Post-PENM-DAR antibody titers in CSF</th>
<th>Post-PE NMDAR antibody titers in serum</th>
<th>Time from last session of PE to discharge (d)</th>
<th>Discharge outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>8.8</td>
<td>++</td>
<td>–</td>
<td>25</td>
<td>30</td>
<td>1</td>
<td>No reexamination</td>
<td>No reexamination</td>
<td>1</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>2*</td>
<td>Male</td>
<td>9.3</td>
<td>++</td>
<td>–</td>
<td>25</td>
<td>40</td>
<td>5</td>
<td>+</td>
<td>–</td>
<td>3</td>
<td>Better</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>13.9</td>
<td>+</td>
<td>+</td>
<td>17</td>
<td>20</td>
<td>5</td>
<td>±</td>
<td>±</td>
<td>9</td>
<td>Better</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>13.1</td>
<td>+</td>
<td>–</td>
<td>10</td>
<td>13</td>
<td>4</td>
<td>±</td>
<td>–</td>
<td>42</td>
<td>Better</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>10.9</td>
<td>+</td>
<td>–</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>±</td>
<td>–</td>
<td>6</td>
<td>Better</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>6.3</td>
<td>++</td>
<td>+</td>
<td>20</td>
<td>25</td>
<td>5</td>
<td>+</td>
<td>–</td>
<td>5</td>
<td>Better</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>9.8</td>
<td>++</td>
<td>+</td>
<td>23</td>
<td>31</td>
<td>3</td>
<td>+</td>
<td>±</td>
<td>5</td>
<td>Better</td>
</tr>
<tr>
<td>8*</td>
<td>Female</td>
<td>13.5</td>
<td>+</td>
<td>+</td>
<td>240</td>
<td>300</td>
<td>5</td>
<td>±</td>
<td>–</td>
<td>2</td>
<td>Better</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>5.2</td>
<td>+</td>
<td>–</td>
<td>8</td>
<td>15</td>
<td>5</td>
<td>±</td>
<td>–</td>
<td>5</td>
<td>Better</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>9.5</td>
<td>++</td>
<td>++</td>
<td>10</td>
<td>18</td>
<td>4</td>
<td>+</td>
<td>±</td>
<td>4</td>
<td>Better</td>
</tr>
<tr>
<td>11*</td>
<td>Female</td>
<td>11.8</td>
<td>++</td>
<td>+</td>
<td>40</td>
<td>200</td>
<td>5</td>
<td>+</td>
<td>–</td>
<td>3</td>
<td>Better</td>
</tr>
<tr>
<td>12*</td>
<td>Female</td>
<td>8.1</td>
<td>+</td>
<td>–</td>
<td>19</td>
<td>28</td>
<td>2+5</td>
<td>±</td>
<td>–</td>
<td>2</td>
<td>Better</td>
</tr>
</tbody>
</table>

Note: a: Out-of-hospital diagnosis and out-of-hospital IVIG and methylprednisolone; b: Received prednisone instead of methylprednisolone due to hypertension; *: Patients were discharged when they got better without PE, and underwent PE after re-admission due to relapse. #: Patients were discharged when they got better after two sessions of PE, and underwent five sessions of PE after re-admission due to relapse. Note: "++" denotes strong positive; "+" positive; "±" weakly positive; "-" negative.
Timing of plasma exchange

Case 2 had received methylprednisolone and IVIG therapy in other hospital. Case 8 was only given oral prednisone without methylprednisolone due to high blood pressure, and the remaining 10 patients received high dose methylprednisolone and IVIG in our hospital. All the 12 children underwent PE treatment within 1 to 150 days after methylprednisolone and IVIG treatment. Each patient received 3-7 PE sessions, with 54 sessions in total for all the cases. The period from the presence of clinical symptoms to the confirmatory diagnosis lasted for 8-240 days, with an average of 37 days. The period from the presence of clinical symptoms to PE lasted for 12-300 days, with an average of 61 days. Clinical data are shown in Table 1.

Efficacy of plasma exchange therapy

Clinical manifestation: Of 12 patients, Case 1 withdrew from the therapy after one PE session; Case 4 continued to use ventilator for 15 days after 5 PE sessions, due to central hypoventilation and pulmonary infection. After PE treatment, the remaining 10 patients showed significantly improved clinical symptoms: recovered consciousness, improved sleep disorders, reduced involuntary movement, improved ataxia, and reduced dysarthria. Clinical manifestations at different stages are shown in Figure 1.

Glasgow coma scale

As shown in Figure 2, GCS scores were 9.58±3.29 before PE, but 13.33±3.06 after PE, and the difference was statistically significant (P<0.001).

Timing of plasma exchange

Case 2 had received methylprednisolone and IVIG therapy in other hospital. Case 8 was only given oral prednisone without methylprednisolone. Except Case 1 withdraw from PE treatment, the CSF and serum NMDAR antibodies titers of the remaining children after sessions of PE de-
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**Table 2. Grading of adverse reactions to PE**

<table>
<thead>
<tr>
<th>Grading in severity</th>
<th>Clinical symptoms</th>
<th>Sessions</th>
<th>Inventions adopted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (Mild)</td>
<td>Hypothermia</td>
<td>2</td>
<td>Keeping warm</td>
</tr>
<tr>
<td>Grade 2 (Required medication or other interventions)</td>
<td>Hypotension</td>
<td>2</td>
<td>Reduce blood flow rate of the extracorporeal blood circulation</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>2</td>
<td>Himostasis by compression</td>
</tr>
<tr>
<td></td>
<td>Errhysis at the site of femoral vein catheterization</td>
<td>2</td>
<td>Himostasis by compression</td>
</tr>
<tr>
<td>Grade 3 (Required to discontinue PE)</td>
<td>Cather-related infection</td>
<td>2</td>
<td>Remove the catheter</td>
</tr>
<tr>
<td>Grade 4 (Death)</td>
<td>None</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

**Figure 4. Follow-up MRS score of patients.**, compared with the scores at discharge, *P*<0.01.

Increased or resolved compared with those before PE (**Table 1**).

**Time from completion of plasma exchange to discharge**

Except Case 1 (withdrew from the treatment and discharged one day after the first session of PE) and Case 4 (discharged 42 days after PE), for the remaining 10 patients, the time from the last session of PE to discharge was 2-9 days. The time windows for PE treatment were seen in **Figure 3**.

**Adverse reactions to plasma exchange**

All the 54 sessions of PE were successfully completed, without death or other serious adverse reactions. A total of 15 adverse events (27.78%) were recorded in 54 PE procedures, including low temperature, hypotension, anaphylaxis, errhysis at the catheter exit site and catheter-associated infection. **Table 2** shows severity rating of the adverse reactions in all patients.

Seven episodes (12.96%) of anaphylaxis occurred in the children, manifested as pruritus, urticaria rashes, without tachypnea, dyspnea, hypotension and abnormal lung auscultation. Allergic symptoms were relieved after intravenous drip of diphenhydramine; two episodes (3.70%) of hypotension occurred at the time when blood was drawn out of the body and the blood pressure returned to normal after the blood flow rate decrease; two episodes (3.70%) of hypothermia occurred when the children complained of chills and their body temperature returned to normal after they were kept warm.

Catheter-related complications included two episodes (3.70%) of errhysis at catheter exit site and two episodes (3.70%) of catheter-associated infection.

**Mid-and-long-term follow-ups**

Apart from Case 1 withdraw from therapy and follow-ups, the remaining 11 patients completed the 18-month follow-ups and showed substantial improvement after discharge. Two patients (Case 2 and 11) presented relapse, and the symptoms relieved immediately after receiving prednisone. One year after discharge, all the 11 patients returned to school. The Modified Rankin scale is shown in **Figure 4**.

**Discussion**

PE is a technique of in vitro blood purification, which can remove antibodies (IgG, IgM, etc.) of autoimmune disease, the immune complexes deposited in the tissues, as well as protein-binding toxins [15]. Anti-NMDAR encephalitis is a type of immune-mediated nervous system disease. Anti-NMDAR IgG1 and IgG3 presented
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in patients’ serum and CSF. What’s more, B and T cells are also involved in mediation of this disease. Therefore, theoretically, PE is advisable for the treatment of anti-NMDAR encephalitis [7, 16-18]. It is speculated that PE may play a role in treatment of anti-NMDAR encephalitis by directly scavenging antibodies in the blood plasma [16]. In the present study, the NMDAR antibody titers in CSF after PE decreased compared with those before PE, which suggests the benefit of PE.

In most previous studies, neurological status was assessed with MRS [5, 15, 19, 20]. However, one study held that MRS was not a sensitive marker in the assessment of cognitive dysfunction and neurological abnormalities, particularly in very young children [4], as MRS is a marker of activities of daily living, which is not optimum for patients with acute stroke [21]; whereas the GCS is mainly used for quantitative evaluation of patients with disorders of consciousness. The subjects of this study were children, and the youngest one was 5 years. Among the patients, 8 had disorder of consciousness and 5 had superficial coma. Therefore, GCS was more appropriate than MRS in presenting the real conditions of patients in acute stage.

Of the 12 children, 10 responded to PE treatment, with an effective rate of 83.33%. The state of consciousness was improved significantly after PE; the GCS score after PE greatly increased compared with that before PE which was statically significant. The NMDAR antibody titers in CSF decreased after PE as compared with those before PE. It is of note that after PE treatment, apart from one patient voluntarily discharged from hospital and one prolonged hospitalization due to central hypoventilation and pulmonary infection, all the remaining 10 children discharged very soon. These results suggest that PE is effective, especially in the rapid improvement of symptoms, which is consistent with the results of previous studies [11, 15, 16]. But in some studies, PE is not recommended as the first-line therapy for pediatric anti-NMDAR encephalitis [4, 6], which may be related to the fact that PE had not be done in children in some medical centers. In addition, children’s poor cooperation, relatively larger extracorporeal volumes related to low patient body weight, more difficultly in establishing venous access than adult patients as well as catheter-related complications, all lead to the restriction of PE use in children.

Of 54 sessions of PE, 15 adverse events (27.78%) were observed and the adverse reactions were primarily grade I and II. The methods to resolve the events were simple and effective, which was consistent with the results reported in the previous literature [14, 22, 23]. Incidence of complications associated with PE in adults was 5% to 12% reported [23, 24], with some even as low as to 2.7% or as high as up to 45% [14, 25]. A large sample study reported a high incidence (55%) of complications associated with PE in children [26]. Factors that impact on the complication rate include low body weight, disease type, replacement fluid type and anticoagulant type. FFP is associated with a higher risk of adverse events relative to albumin [14, 23]. In this study, as the major adverse reaction, the rate of allergic reaction was 12.96%, which was consistent with that reported in the literature using FFP as replacement fluid (13%) [23]. Of paramount importance to avoid allergic reactions is the intravenous infusion of dexamethasone (0.5 mg/kg, not exceeded the maximum of 10 mg) and 10% calcium gluconate (0.5 ml/kg, not exceeded the maximum of 10 ml) prior to PE procedure. If the patient had an allergic reaction, diphenhydramine was used in addition to the above-mentioned prophylactic medications. The allergic symptoms gradually disappeared after diphenhydramine was administered. Quick resolution of allergic symptoms was observed which showed diphenhydramine was effective in treating anaphylaxis.

Studies report a rate of catheter-associated infection ranging from 16.1% and 18.75% in children [26, 27]. Catheter-associated infection (positive blood culture) occurred in 16.67% (2/12) of patients in the present study, which was consistent with those reported in the literature. Diligent catheter exit site care with chlorhexidine and dressing changed daily is of importance to prevention of infection. If children had fever or other signs of infection, the possibility of catheter-associated infections should be taken into account.

FFP contains citrate which chelates free ionized calcium, soprophylactic intravenous calcium administration is required to reduce the incidence of hypocalcemia induced by citrate. In the present study, all of the children did not
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appear any complications due to hypocalcaemia, including numbness, tingling, muscle spasms. Calcium gluconate infusion given during the PE procedure is a simple and effective means of decreasing hypocalcemic toxicity. Nadroparin calcium was used as anticoagulants instead of citrate, and just a single intravenous injection was enough to achieve adequate anticoagulation of the circuit without a continuous infusion. In addition, the serum ionized calcium need not be frequently monitored. The use of nadroparin calcium was more convenient in operation and reduced the incidence of hypocalcemia compared with citrate. Blood coagulation measured on the second day after PE were normal and all the patients had no systemic haemorrhagic manifestations which indicated nadroparin calcium a utilized choice.

The most frequently observed complication in children is hypotension during PE procedures [17, 22, 26, 27]. However, in the present study, only 2 patients presented mild hypotension. Selecting proper extracorporeal circulation line and plasma filter in terms of age and body weight is crucial to prevent hypotension. In addition, at the initiation of PE, pre-flushing the extracorporeal circulation line with normal saline can effectively reduce the incidence of hypotension. Each of the children completed the whole PE procedure, and no life-threatening adverse events occurred, indicating that PE is well tolerated by the children and it is a safe and effective treatment.

It is noteworthy that, compared with medication, although the PE therapy is more effective and more rapid in clearance of etiologic agents, resulting in temporary relief of the disease, it is not a radical cure. Oral administration of corticosteroids after PE treatment is still an essential protocol. Eleven children discontinued corticosteroids within half a year after discharge and showed gradual recovery. Although relapse occurred in two patients, the symptoms were mild and resolved quickly.

This study has limitations, with respect to the small numbers and that was not prospective and PE use was administered after IVIG and corticosteroids. Further studies should be performed to identify the opportune time for PE, and the order of PE relative to corticosteroids and IVIG.

PE is an effective, safe treatment option in paediatric anti-NMDAR encephalitis. Adverse reactions associated with PE are mostly mild to moderate, and are manageable. PE can be used as an alternative when corticosteroids and IVIG medication are ineffective.

Disclosure of conflict of interest

None.

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