ORIGINAL ARTICLE

WILEY

Plasma exchange therapy for acute necrotizing encephalopathy of childhood

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Funding source
This study was supported by Capital's Funds for Health Improvement and Research of Beijing Children's Hospital, Capital Medical University (No. 2020-2-2094) and the CAMS Innovation Fund for Medical Sciences (No. 2019-I2M-5-026).

Received: 8 April, 2021
Accepted: 20 May, 2021

ABSTRACT

Importance: Acute necrotizing encephalopathy (ANE) is a rare disease with high mortality. Plasma exchange (PLEX) has recently been reported to treat ANE of childhood (ANEC), but its efficacy is uncertain.

Objective: This study aimed to investigate the effectiveness of PLEX on ANEC.

Methods: A retrospective study was conducted in four pediatric intensive care units from December 2014 to December 2020. All patients who were diagnosed with ANEC were included; however, these patients were excluded if their length of stay was less than 24 h. Participants were classified into PLEX and non-PLEX groups.

Results: Twenty-nine patients with ANEC were identified, 10 in the PLEX group and 19 in the non-PLEX group. In the PLEX group, C-reactive protein, procalcitonin, alanine aminotransferase, and aspartate aminotransaminase levels were significantly lower after 3 days of treatment than before treatment (13.1 *vs*. 8.0, $P = 0.043$; 9.8 *vs*. 1.5, $P = 0.028$; 133.4 *vs*. 31.9, $P = 0.028$; 282.4 *vs*. 50.5, $P = 0.046$, respectively). Nine patients (31.0%, 9/29) died at discharge, and a significantly difference was found between the PLEX group and non-PLEX group [0 *vs*. 47.4% (9/19), $P = 0.011$]. The median follow-up period was 27 months, and three patients were lost to follow-up. Thirteen patients (50.0%, 13/26) died at the last follow-up, comprising three (33.3%, 3/9) in the PLEX group and ten (58.8%, 10/17) in the non-PLEX group, but there was no significant difference between the two groups ($P = 0.411$). Three patients (10.3%, 3/29) fully recovered.

Interpretation: PLEX may reduce serum C-reactive protein and procalcitonin levels and improve liver function in the short term. PLEX may improve the prognosis of ANEC, and further studies are needed.

KEYWORDS

Acute necrotizing encephalopathy, Children, Plasma exchange, Prognosis

DOI: 10.1002/ped4.12280

INTRODUCTION

Acute necrotizing encephalopathy (ANE) is a distinctive type of acute encephalopathy with rapid progression of brain dysfunction and a disastrous outcome.[1] ANE mainly occurs in children, especially those with an influenza virus infection,[2] and which could be an important cause of death or disability due to a critical influenza infection. Cytokine storm,[3-5] hereditary susceptibility,[6,7] immune etiology,[8] and other unknown factors are related to ANE pathogenesis. The prognosis of ANE was poor. The mortality of ANE was around 30%, and only 10% of patients fully recovered.[2,9-11]

A unified treatment schedule for acute necrotizing encephalopathy of childhood (ANEC) has not been established. Steroids and intravenous immunoglobulin (IVIG) for immunomodulation therapy are the most commonly used drugs to treat ANEC,[9,12,13] and early steroid pulse therapy has been recommended.[14] Moreover, plasma exchange (PLEX) has recently been reported for some ANEC patients, which could be an effective treatment to remove inflammatory mediators and other harmful substances that are caused by ANEC, but the outcome has been variable.[9,15,16] In this study, a multicenter retrospective study was conducted at four pediatric intensive care units (PICUs) in China, and it aimed to investigate the efficacy of PLEX therapy in treating ANEC.

METHODS

Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board for Beijing Children's Hospital, Capital Medical University (approval number: 2019-k-384), with waiver of the requirement for informed consent.

Patients

This retrospective study was conducted at four PICUs from December 2014 to December 2020. The four participating centers were Beijing Children's Hospital, Capital Medical University (Beijing, China), Shengjing Hospital of China Medical University (Shenyang, China), Hebei Children's Hospital affiliated to Hebei Medical University (Shijiazhuang, China), and Bao'an Maternity & Child Health Hospital (Shenzhen, China), respectively.

The inclusion criteria for ANEC were as follows: 1) all patients were 29 days to 18 years old; 2) acute encephalopathy followed by a febrile disease, with rapid deterioration of consciousness and convulsions; 3) commonly increased cerebrospinal fluid (CSF) protein without pleocytosis, and elevated serum aminotransferases with variable degrees, but no hyperammonemia; 4) cranial imaging showing symmetric and multifocal brain lesions with involvement of bilateral thalami, and possible involvement of cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum, and cerebellar medulla; and 5) exclusion of similar diseases.[2] PLEX is a complex invasive treatment, and patients whose length of stay was less than 24 h were excluded to allow better observation of PLEX efficacy in treating ANEC. The participants were classified into PLEX and non-PLEX groups.

Data collection

The demographics, clinical manifestations, laboratory examination results, therapeutic schedules, and clinical outcomes were collected. The demographic information included age, sex, family history, and underlying diseases. Clinical manifestations included symptoms, Glasgow coma scale score (GCS), and ANE severity score (ANE-SS)[17] on admission. Laboratory examination results including serum C-reactive protein (CRP) and procalcitonin (PCT) levels, routine blood test results, and liver enzyme levels were collected when patients were admitted to the PICU and 3 days after treatment. The results of routine CSF, cranial imaging, and etiology (respiratory virus antigen or nucleic acid detection) tests were also collected. The therapeutic schedules included the main drugs that were administered after hospitalization in the PICU. Follow-up was performed by telephone interview or outpatient service to evaluate the neurological function in surviving children with pediatric cerebral performance category scale (PCPC) and pediatric overall performance category scale (POPC).

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or as the median (interquartile range) depending on whether the data were parametric or nonparametric. Categorical variables were expressed as numbers and percentages. A student's *t*-test was used for parametric variables and Mann–Whitney *U* test was used for nonparametric continuous variables. Categorical variables were analyzed using Fisher's test. The Wilcoxon test was used to identify differences for the same variables at different times. All analysis was conducted using SPSS statistical software version 24 (IBM, Armonk, NY). A two-sided P value < 0.05 was considered to be statistically significant.

RESULTS

Fifty-one children with ANE were eligible for this study, and 29 patients were identified, 10 in the PLEX group and 19 in the non-PLEX group (Figure 1). Table 1 shows the characteristics of all the ANEC patients. The median onset age was 30 months. Thirteen patients were males, and the male-to-female ratio was 1:1.2. Winter was the most common season. One patient had idiopathic uveitis, and began to take cyclosporine and methylprednisolone

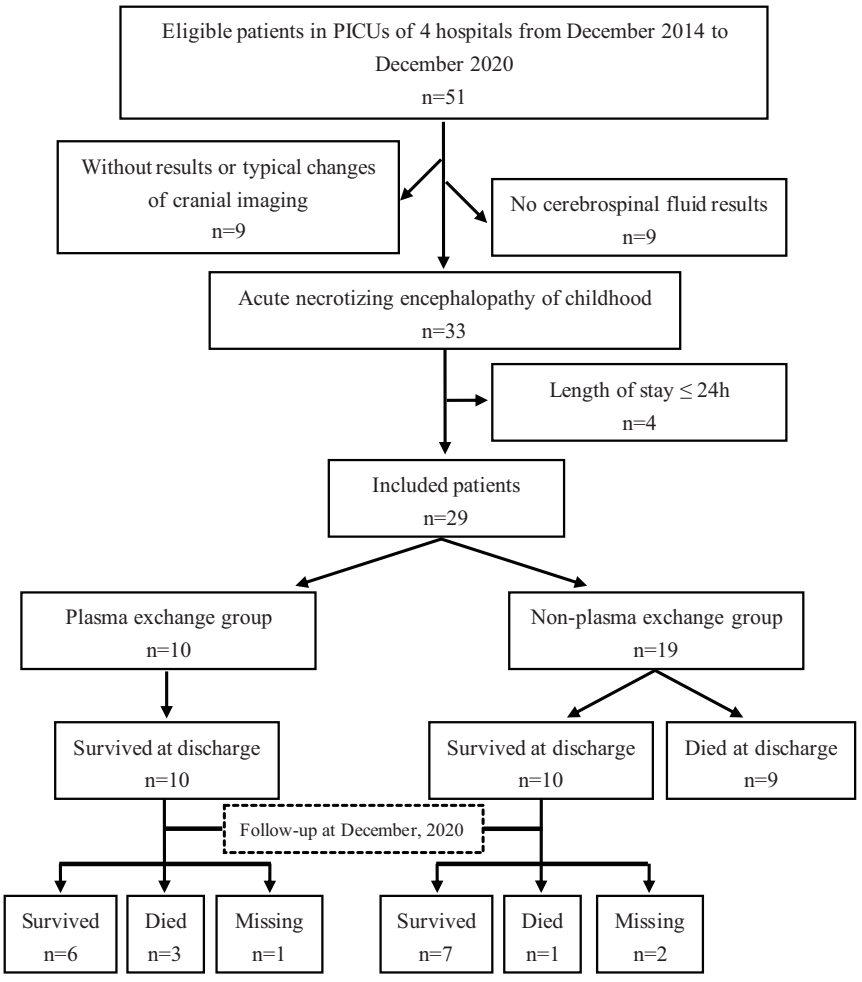

FIGURE 1 Patients with acute necrotizing encephalopathy in this study.

tablets orally 5 months before admission. The median time from disturbance of consciousness to admission was 24 h. During the acute phase, fever, convulsion, and disturbance of consciousness were the most common presentations.

TABLE 1 Clinical characteristics of children with acute necrotizing encephalopathy

Variables	Data
Basic information	
Age (months)	30 (19, 46)
Gender (male)	13 (44.8)
Season onset (winter)	18 (62.1)
Underlying disease	11 (3.4)
From disturbance of consciousness to admission to PICU (hours)	24 (10, 60)
Symptoms	
Fever	29 (100)
Convulsion	29 (100)
Disturbance of consciousness	29 (100)
Cough	16 (55.2)
Vomiting	13 (44.8)
Shock	18 (27.6)
Diarrhea	17 (24.1)

Data are presented as *n* (%) or median (lower quartile, upper quartile).

Table 2 shows that there are no significant differences between the two groups for GCS and ANE-SS when patients were admitted to the PICU. Most patients had elevated CRP (58.6%, 17/29) and PCT (82.8%, 24/29) levels on admission. Although the median CRP and PCT levels were higher in the PLEX group than in the non-PLEX group, the differences were not significant. Most patients had elevated alanine aminotransferase (ALT; 62.1%, 18/29) and aspartate aminotransaminase (AST; 75.9%, 22/29) levels on admission. The median ALT and AST levels were higher in the PLEX group than in the non-PLEX group, and a significant difference was found in AST between the two groups (355.1 *vs*. 74.0, $P = 0.039$). The routine CSF results were similar in both groups. The most common pathogen was the influenza virus (77.8%, 14/18). Cranial imaging results showed that bilateral thalami were involved in all patients, and most of them had lesions in the cerebral periventricular white matter (58.6%, 17/29) and internal capsule (51.7%, 15/29). The brainstem was involved in 14 patients (48.3%, 14/29).

Laboratory examination results 3 days after treatment were collected in 18 patients (62.1%, 18/29), seven in the PLEX group and eleven in the non-PLEX group.

The pre- and post-treatment indicators in the two groups were compared, and the results are shown in Table 3. In the PLEX group, CRP and PCT levels were significantly lower after comparing with before treatment (CRP: 13.1 *vs*. 8.0, $P = 0.043$; PCT: 9.8 *vs*. 1.5, $P = 0.028$). ALT and AST levels were also significantly lower after comparing with before treatment in the PLEX group (ALT: 133.4 *vs*. 31.9, $P = 0.028$; AST: 282.4 *vs*. 50.5, $P = 0.046$). In the non-PLEX group, only the CRP level was significantly lower after comparing with before treatment (19.0 *vs*. 5.3, $P = 0.038$).

Most patients (75.9%, 22/29) required invasive mechanical ventilation. The median duration of mechanical ventilation was longer in the PLEX group than the non-PLEX group, but the difference was not significant (Table 4). Most patients received steroids (96.6%, 28/29), IVIG (96.6%, 28/29), and antiviral therapy (93.1%, 27/29). The period from disturbance of consciousness to the first cycle of PLEX ranged from 6 h to 78 h, with a median of 32 h. The first cycle of PLEX was performed in eight patients (80%, 8/10) within 24 h after the patients were admitted to the PICU, but two patients received PLEX from 48 h to 72 h after admission due to a poor response to immunomodulation therapy.

Nine patients (31.0%, 9/29) died a short time after admission. All the dead patients were in the non-PLEX group, and a significant difference was found between the PLEX group and non-PLEX group at discharge [0 *vs*. 47.4% (9/19), $P = 0.011$] (Table 4). Considering the economic and prognostic factors, eight patients (27.6%, 8/29) chose palliative treatment. The follow-up period ranged from 2 months to 60 months, and the median period was 27 months. Three patients were lost to follow-up, and thirteen patients (50.0%, 13/26) died at the last follow-up,

TABLE 2 Laboratory findings of children with acute necrotizing encephalopathy in the two study groups

Variables	Plasma exchange group ($n = 10$)	Non-plasma exchange group ($n = 19$)	*P*
Severity of illness on admission			
GCS	6 (6, 8)	6 (3, 7)	0.310
ANE-SS	2 (1, 3)	2 (0, 5)	0.926
Laboratory findings on admission			
Serum CRP (mg/L)	16.1 (7.8, 26.1)	11.0 (8.0, 37.0)	0.817
Serum PCT (ng/mL)	12.6 (6.9, 51.9)	5.5 (0.2, 44.0)	0.281
WBC ($\times 10^9$/L)	6.7 (3.3, 9.4)	5.5 (3.5, 7.1)	0.680
PLT < 100 ($\times 10^9$/L)	4 (40.0)	4 (21.1)	0.390
ALT (U/L)	139.0 (60.0, 976.5)	31.9 (13.0, 180.0)	0.060
AST (U/L)	355.1 (135.7, 1414.4)	74.0 (31.7, 408.0)	0.039
Blood ammonia (mmol/L)	34.0 (18.5, 41.1)	46.0 (31.5, 56.7)	0.125
CSF routine			
Cell counts ($\times 10^6$/L)	2.0 (0, 4.8)	2.0 (1.0, 2.0)	0.962
Protein (mg/L)	919.0 (332.8, 4434.8)	538.0 (187.0, 3652.0)	0.582
Glucose (mmol/L)	4.3 (3.8, 5.0)	4.2 (3.7, 5.8)	0.927
Chlorides (mmol/L)	128.6 (121.9, 131.8)	123.1 (117.9, 125.4)	0.072
Pathogen			
Positive	6 (60.0)	12 (63.2)	1.000
Influenza virus	4 (40.0)	10 (52.6)	0.700
Cranial imaging			
Bilateral thalamus	10 (100)	19 (100)	NA
Cerebral periventricular white matter	7 (70.0)	10 (52.6)	0.449
Internal capsule	4 (40.0)	11 (57.9)	0.450
Brainstem	5 (50.0)	9 (47.4)	1.000
Cerebellar medulla	4 (40.0)	5 (26.3)	0.675

Data are presented as *n* (%) or median (lower quartile, upper quartile). GCS, Glasgow coma scale score; ANE-SS, acute necrotizing encephalopathy severity score; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CSF, cerebrospinal fluid; NA, Not applicable.

TABLE 3 Changes in the variables pre- and post-treatment in children with acute necrotizing encephalopathy

Variables	Plasma exchange group ($n = 7$)			Non-plasma exchange group ($n = 11$)		
	Pre-treatment	Post-treatment	*P*	Pre-treatment	Post-treatment	*P*
CRP (mg/L)	13.1 (8.0, 26.3)	8.0 (3.1, 8.0)	0.043	19.0 (8.0, 38.0)	5.3 (2.0, 8.0)	0.038
PCT (ng/mL)	999.8 (5.5, 100.0)	91.5 (0.9, 44.3)	0.028	993.5 (0.2, 76.4)	991.7 (0.4, 13.7)	0.208
WBC ($\times 10^9$/L)	996.1 (3.4, 7.8)	94.0 (3.1, 6.1)	0.753	995.5 (3.5, 12.4)	996.9 (4.4, 8.2)	0.721
PLT ($\times 10^9$/L)	121.0 (47.0, 146.0)	74.0 (32.0, 117.0)	0.345	202.0 (101.0, 386.0)	218.0 (164.0, 270.0)	0.689
ALT (U/L)	133.4 (63.9, 1631.5)	31.9 (27.4, 94.6)	0.028	918.7 (12.8, 1564.6)	974.0 (18.2, 315.8)	0.139
AST (U/L)	282.4 (137.2, 1721.3)	50.5 (40.8, 61.4)	0.046	970.6 (29.2, 1660.0)	959.1 (45.0, 179.3)	0.139

Data are presented as median (lower quartile, upper quartile). CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransaminase.

TABLE 4 Treatments and outcomes in children with acute necrotizing encephalopathy in the two study groups

Variables	Plasma exchange group (n = 10)	Non-plasma exchange group (n = 19)	P
Treatments			
Mechanical ventilation	9 (90.0)	13 (68.4)	0.367
Duration of mechanical ventilation (hours)	110.0 (42.5, 236.3)	38.0 (0, 99.0)	0.106
Antiviral therapy	10 (100)	17 (89.5)	0.532
Steroids	10 (100)	18 (94.7)	1.000
Intravenous immunoglobulin	10 (100)	18 (94.7)	1.000
Outcomes			
Duration of PICU stay (days)	10.1 (2.8, 19.1)	3.9 (2.0, 13.0)	0.191
Length of stay (days)	16.9 (3.5, 23.1)	8.0 (2.0, 19.0)	0.278
Died at discharge	0	9 (47.4)	0.011
Died at the last follow-up*	3 (33.3)	10 (58.8)	0.411

Data are presented as n (%) or median (lower quartile, upper quartile).*Three patients were lost to follow-up, including one patient in the plasma exchange group and two patients in the non-plasma exchange group.

comprising three patients (33.3%, 3/9) in the PLEX group and ten (58.8%, 10/17) in the non-PLEX group, but there was no significant difference between the two groups (P = 0.411) (Table 4). The two patients who received PLEX due to a poor response to immunomodulation therapy were alive at the last follow-up. On the basis of the PCPC and POPC, three patients (10.3%, 3/29) fully recovered, including one patient (10.0%, 1/10) in the PLEX group and two patients (10.5%, 2/19) in the non-PLEX group.

DISCUSSION

ANE is a rare and rapidly progressive encephalopathy with high mortality and disability rate. Song et al[11] reported 30 children with ANE, and among them, 13 patients (43.3%) died and only three patients (10.0%) recovered. Okumura et al[10] reported 34 patients with ANEC, and ten of them (29.4%) died, but four critically ill patients had been excluded. Bashiri et al[9] reported 12 patients with ANEC, among whom early death occurred in 25%, and the others were left with neurological sequelae. In this study, nine patients (31.0%) with ANEC died at discharge, which increased to thirteen (50.0%) at the last follow-up, and three patients (10.3%) recovered. The outcomes varied in different studies, which may be related to the sample size, severity of the illness, and the length of the follow-up period. However, no standardized treatment schedule has been established for this catastrophic disease. It is necessary for pediatricians to find effective treatments to improve the prognosis of ANEC patients.

PLEX could be used to remove inflammatory factors from plasma, which is theoretically effective for ANEC. In this study, only eight patients had cytokine levels that were tested twice, and the testing time was different due to the retrospective nature of the study. Thus, we chose serum CRP and PCT as indicators of the inflammatory response. In children with confirmed influenza with neurological complications, the sensitivity and specificity of PCT > 4.25 ng/mL to predict ANE were 73.3% and 100.0%, respectively.[11] Moreover, various proinflammatory cytokines had pronounced stimulatory effects on PCT expression, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α,[18] and elevated IL-6 and TNF-α were both found in serum and CSF of patients with ANE.[3,19] In this study, CRP, PCT, ALT, and AST levels were significantly lower after PLEX, which indicated that PLEX could eliminate harmful substances from plasma in critical patients.[20]

PLEX has been reported to treat ANEC, especially for patients with poor response to immunomodulation therapy. A patient with COVID-19 related ANE was treated with PLEX and survived at discharge, but required rehabilitation therapy after discharge.[15] Among 13 patients with ANEC, three patients underwent five cycles of PLEX after a poor or no response to the initial immunomodulation treatment, and they were alive at discharge.[16] Aksoy et al[21] reported on nine children with ANE, and the six patients who received immunomodulation therapy and PLEX survived. Two of whom received PLEX when there was no clinical improvement with immunomodulation therapy. All the six patients who survived were left with mild to severe motor impairment, and the other three patients who received immunomodulation therapy died. Overall, PLEX may be a good method for treating ANEC, but there is not enough evidence to support its efficacy in ANEC patients. To increase the sample size, this multicenter study was conducted. Most patients received PLEX within 24 h after they were admitted to PICU, and two patients received PLEX due to a poor response to immunomodulation therapy. All of these patients were alive at discharge. Moreover, more patients died in the non-PLEX group than in the PLEX group at the last follow-up, which indicated that PLEX may improve the prognosis of ANEC.

Most patients with ANE had elevated liver enzymes, which is consistent with other studies.[1,9] In this study, the AST level was significantly higher in the PLEX group than in the non-PLEX group on admission, which may suggest that clinically, PLEX is used selectively in children with higher liver enzyme levels. In the PLEX

group, ALT, and AST levels were significantly lower after PLEX. Therefore, the efficacy of PLEX for eliminating harmful substances in plasma can be observed. In addition to PLEX, most patients with ANE also received steroids and IVIG for immunomodulation in this study. The positive effects of steroid treatment may inhibit the inflammatory storm via suppressing cytokine levels and proinflammatory gene expression.[22,23] IVIG may reduce the proliferation of T-cell and suppress the expression of various pro-inflammatory cytokines.[24] The CRP level was significantly lower after treatment than before treatment in the non-PLEX group, which may be related to the immunomodulation treatment.

There are some limitations to this retrospective study. First, it is a non-randomized controlled trial, and the patients' condition and the technical limitations may affect the application of PLEX. The sample size was still small because ANEC occurrence is rare. Second, laboratory examinations 3 days after treatment were not performed for all patients. Third, the change in cytokine levels pre- and post-PLEX were not investigated in this study. Finally, although the use of drugs was similar in both groups, the effect of combination medication could not be ruled out. It is necessary to increase the sample size and perform a prospective study on the treatment of ANEC in the future.

PLEX may reduce serum CRP and PCT levels and improve liver function in the short term. PLEX may improve the prognosis of ANEC, and further studies are needed to confirm the efficacy of PLEX for treating ANEC.

ACKNOWLEDGMENTS

We would like to thank all the families and individuals who participated in this study, and appreciate all the staffs in the PICU from the four centers.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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How to cite this article: Li K, Zhang T, Liu G, Jin P, Wang Y, Wang L, et al. Plasma exchange therapy for acute necrotizing encephalopathy of childhood. Pediatr Investig. 2021;5:99-105. https://doi.org/10.1002/ped4.12280