CASE REPORT

Successful use of delayed therapeutic plasma exchange in seronegative pediatric autoimmune encephalitis

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Summary

Introduction: We present a 5-year-old girl with severe seronegative autoimmune encephalitis (AE) who was treated with therapeutic plasma exchange (TPE) after unsuccessful treatment with corticosteroids and intravenous immunoglobulins (IVIG).

Case report: We performed 6 TPEs every other day in the Intensive Care Unit (ICU) using a Spectra Optia apheresis system and a central venous catheter for vascular access. We used a 5% albumin for substitution and acid-citrate dextrose-A (ACD-A) solution for anticoagulation. The exchange set was primed with allogenic compatible red blood cells because the patient weighed < 20kg. Before each TPE, we checked the patient's blood count and coagulation status. A slow intravenous infusion of calcium gluconate (30mg/kg/h) was administered to maintain ionized calcium levels above 1 mmol/L. The mean inlet flow rate was 22.5 ± 4.1 ml/min, and the processed total blood volume was 2794.5 ± 106.0 ml. On average, 1243.2 ± 49.2 ml (1.55 ± 0.05) total plasma volume was exchanged, with 288.8 ± 13.8 ml of ACD used. The mean procedure duration time was 137.2 ± 9.2 min. After the third procedure, significant clinical improvement was observed in the girl. She smiled purposefully, followed with her gaze, and focused on the audiovisual content adapted for her age. Two weeks after the last TPE, the girl was discharged in good clinical condition from the hospital. Three years after the treatment, the patient was in good general condition with normal neurological status and without sequelae.

Conclusion: This case highlights the therapeutic effectiveness of TPE, even when initiated late, in pediatric patients with severe AE.

Keywords: therapeutic plasma exchange, autoimmune encephalitis, pediatrics

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INTRODUCTION

Autoimmune encephalitides (AE) are disorders characterized by various clinical manifestations – seizures, psychiatric and behavioral symptoms, movement disorders, and autonomic disturbances. It results from the immune response and the creation of antibodies to neuron antigens. According to the latest literature data, the incidence of AE is 1.54 children/million with a female predominance (1-3). Some forms of AE are more prevalent in children and young adults, like anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and acute disseminated encephalomyelitis (ADEM)(4). The presence of antibodies against neuronal cell-surface proteins, receptors, and ion channels characterizes these forms of AE. The clinical presentation of AE can be very diverse. One of the most common symptoms is various types of epileptic seizures, including epileptic status. In the subacute phase of the disease, which can last from a few days to a few weeks, fluctuations in the state of consciousness are noticeable (from a gradual decrease in the level of consciousness up to coma) and cognitive functions. Abnormal movements such as ataxia, dystonia, and myoclonus can also be one of the leading symptoms. Based on the severity of symptoms, first-line therapies include intravenous steroids, intravenous immunoglobulins (IVIG), and/or therapeutic plasma exchange (TPE). Rituximab or cyclophosphamide is the second-line treatment in refractory cases (1). TPE's role in treating AE is well-established and recommended. For NMDAR encephalitis, TPE is the first option (5). The efficacy of TPE relates to the reduction of titers in circulating autoantibodies and the consequent immunomodulatory effect (6).

This work aimed to show that delayed treatment with TPE could also be effective in a severe seronegative form of AE in a 5-year-old child.

The publication of this case report was reviewed and approved by the Ethics Committee of the Mother and Child Health Care Institute of Serbia "Dr.Vukan Čupić", Belgrade, approval number 8/87/25 (date July 22, 2025). The patient's parents gave written informed consent to publish the details of the patient's medical case and any accompanying images.

CASE REPORT

A female patient, a 5-year-old, was admitted to the Institute with severe encephalopathy preceded by fever. The illness began two weeks before her admission, characterized by an elevated body temperature of up to 38.3°C and general weakness. The girl was admitted to the regional health center for rehydration. A few hours after her admission, she experienced an episode of agitation when she bent forward from a supine to a sitting position with clenched fists. A similar episode occurred a few hours later. Following this, the girl exhibited blurred consciousness, a staggered gait, and instability, without any verbal communication. During this episode, her gaze was fixed to the left. Intravenous hydration was initiated, along with antiedematous treatment (20% mannitol at 0.25 mg/kg and dexamethasone at 0.4 mg/kg), and antimicrobial therapy (Ceftriaxone and Acyclovir). Due to the persistence of neurological deficits and only slight clinical improvement, the girl was transferred to the Institute for further care.

The mother recalls that her daughter received all vaccinations on schedule and developed normally until six months old, when she began experiencing episodes of cyanosis and a fixed gaze. Doctors recommended rectal diazepam for her febrile episodes. At eight months, during another fever, she had tonic-clonic convulsions. Initially treated with phenobarbital, she was switched to valproic acid (VPA) due to side effects. Remarkably, she remained seizure-free for three years on VPA. Although the medication was stopped six months before her current condition, she stayed seizure-free during that time.

After admission to our Institute, the patient's clinical condition indicated encephalitis, and appropriate empiric therapy was applied. We treated her initially with triple antimicrobial therapy (ceftriaxone, erythromycin, acyclovir) for 21 days, antiedematous (mannitol), and anti-inflammatory (dexamethasone) therapy for six days. Severe coma persisted despite normal cytological and biochemical findings in the cerebrospinal fluid (CF), and therefore, an immune-mediated etiology of encephalitis was suspected. On the second day of hospitalization, we started with a five-day methylprednisolone pulse therapy, followed by oral prednisone 2mg/kg. The microbiological (Herpes simplex virus, Coxsackievirus B1-B5, West Nile Virus, Mycoplasma pneumoniae, Borrelia burgdorferi) and immunological (IgA, IgM, IgG, C3, C4, antiphospholipid, anticardiolipin, ANA, pANCA, cANCA, anti-dsDNA antibodies) analyses of serum and CF were negative. The specific antibodies for AE and anti-NMDAR were also negative. An additional metabolic examination was performed, which included screening of urine, plasma amino acids, and organic acids in the urine. All test results were normal. The endocranium MRI was normal. In the second week of hospitalization, due to a lack of clinical improvement, we started with intravenous immunoglobulin (IVIG) therapy (2mg/kg/48h). Despite the applied therapy, the girl's condition continued to deteriorate. Generalized hypotonia of the musculature and right-sided hemiparesis with greater hand involvement were observed. There were also many involuntary movements. Therapy with haloperidol (1mg/daily) and lorazepam (1mg/daily) was started, which gradually led to improvement in behavior and reduction of involuntary movements. After four weeks of hospitalization, the patient received another pulse dose of methylprednisolone (500mg/m2). Despite the applied immunomodulatory

and immunosuppressive therapy, there was no clinical improvement, so the team of physicians decided to start the treatment with TPEs.

We started with TPE treatments in the ninth week of hospitalization, which was seven weeks after IVIG. The patient weighed 16 kg and was 110 cm tall, with 1280 ml of total blood volume, 742.4 ml of plasma volume, and hematocrit (Hct) 0.42 L/L. We performed 6 TPEs every other day in the ICU using a Spectra Optia apheresis system with continuous centrifugation and a central venous catheter for vascular access. We used a 5% albumin solution for substitution and acid-citrate dextrose-A (ACD-A) solution for anticoagulation. The exchange set was primed with allogenic compatible red blood cells because the patient weighed less than 20 kg. Before each TPE, we checked the patient's blood count and coagulation status. A slow intravenous infusion of calcium gluconate (30mg/kg/h) was administered to maintain ionized calcium levels above 1 mmol/L. **Table 1** shows the characteristics of the procedures performed.

Table 1. Therapeutic plasma exchange (TPE) procedures characteristics

Procedure characteristics	Mean ± SD
IF rate (ml/min)	22.5 ± 4.1
TBV processed (ml)	2794.5 ± 106.0
PV exchanged (ml)	1243.2 ± 49.2
Total PV exchanged (L)	1.56 ± 0.05
Acid citrate dextrose used (ml)	288.8 ± 13.8
Procedure duration time (min)	137.2 ± 9.2
Ionized calcium before TPE (mmol/L)	0.90 ± 0.22
Ionized calcium after TPE (mmol/L)	1.0 ± 0.08
Hematocrit value before TPE (L/L)	0.38 ± 0.02
Hematocrit value after TPE (L/L)	0.41 ± 0.02

IF – inlet flow; TBV – total blood volume; PV – plasma volume; Mean – arithmetic mean; SD – standard deviation; TPE - therapeutic plasma exchange

There were no side effects during the procedures. After the third procedure, significant clinical improvement was observed in the girl. She smiled purposefully, followed with her gaze, and focused on the audiovisual content adapted for her age. After conducting six TPE procedures, the immunosuppressive drug azathioprine was introduced into the treatment plan. In addition to the drug therapy mentioned earlier, daily physical therapy and cognitive stimulation were conducted in collaboration with the girl's mother. Two weeks after the last TPE, the girl was discharged in good clinical condition from the hospital. She underwent physical therapy, resulting in significant clinical improvement. She communicated using complex sentences, and her motor skills were significantly better. During the most recent check-up, three years after undergoing treatment at our Institute, the patient was in good general condition with normal neurological status and without sequelae.

DISCUSSION

Various pediatric neurological disorders can be successfully treated with TPE. It primarily refers to pediatric immune-mediated diseases such as autoimmune encephalitis, acute and chronic polyneuropathy, acquired demyelinating diseases, paraneoplastic syndromes, and inflammatory vascular diseases of the CNS (7,8). With the advancement of technology, apheresis systems have become suitable for children with low body weight. Apheresis devices used nowadays (Spectra Optia, Amicus) have a smaller extracorporeal volume than older machines. The understanding of the TPE mechanism and the knowledge of the indications for its use by clinicians are also increasing. Thanks to these facts, we have expanded this immunomodulatory therapeutic approach to treat many pediatric neurological disorders.

The literature lacks consistent data on the use of TPE in treating pediatric AE, making it challenging to assess TPE's advantages compared to other immunomodulatory therapies.

Various responses to TPE in treating AE in children were demonstrated in previous studies. In their research, Atay et al. reported mild improvement in 5 out of 20 patients diagnosed with AE (7). The cross-sectional survey of Nikkhah et al. examined a cohort of 18 children with neuroimmunological diseases who underwent TPEs. The AE group, consisting of four patients, exhibited the most favorable outcomes in this study (9). In their research, Günay Ç et al. included ten pediatric patients with acute neurological conditions treated with TPEs. Two patients in this study demonstrated complete recovery after TPEs, and one had AE (10).

Our patient showed significant neurological improvement after three TPEs, even though they were applied late, in the ninth week of hospitalization. That leads us to think that some undetermined antibodies were present in her plasma, but we could not determine their specificity at the time. The list of potential antibodies involved in the pathogenesis of AE is constantly expanding and may still need to be completed. In addition, TPEs remove various other disease mediators from plasma, contributing to successful treatment with immunomodulatory effects on the CNS. Although the temporal association with TPE is clear, an immunomodulatory cumulative impact of prior corticosteroid and IVIG therapy cannot be excluded.

Our study needed to be improved in this regard because we didn't examine the presence of other antibodies that could be associated with AE. After all, they were not available to us at that time.

CONCLUSION

Even late treatment with TPEs can contribute to promising outcomes in treating pediatric patients with AE. TPE

acts as an immunomodulatory intervention, modifying immune components and removing antibodies. No adverse events related to TPE were observed. It is a safe and very effective procedure for autoimmune neurological disorders in children.

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Data Availability: Data could be obtained from the corresponding author upon request.

Ethical approval: The publication of this case report was reviewed and approved by the Ethics Committee of the Mother and Child Health Care Institute of Serbia "Dr.Vukan Čupić", Belgrade, approval number 8/87/25 (date July 22, 2025). The patient's parents gave written informed consent to publish the details of the patient's medical case and any accompanying images.

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USPEŠNA PRIMENA ODLOŽENE TERAPIJSKE IZMENE PLAZME KOD PEDIJATRIJSKOG SERONEGATIVNOG AUTOIMUNOG ENCEFALITISA

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Sažetak

Prikazujemo petogodišnju devojčicu sa teškim seronegativnim autoimunim encefalitisom koja je lečene terapijskim izmenama plazme (TIP), nakon neuspešne primene kortikosteroida i intravenskih imunoglobulina (IVIG). Sproveli smo ukupno 6 TIP svakog drugog dana u odeljenju intenzivne nege na Spectra Optia afereznom sistemu uz korišćenje centralnog venskog katetera za vaskularni pristup. Koristili smo 5% rastvor albumina za supstituciju i Acid Citrate Dextrose – A (ACD-A) rastvor za antikoagulaciju. Set za izmenu plazme je ispunjavan alogenim kompatibilnim eritrocitima jer je devojčica imala < 20kg. Pre svake TIP, kontrolisali smo krvnu slika i koagulacioni status. Vrednosti jonizovanog kalcijuma su održavani iznad 1mmol/L primenom spore intravenske infuzije kalcijum glukonata (30mg/kg/h). Srednja vrednost brzine utoka bila je 22.5 ± 4.1 ml/min, procesiranog ukupnog volumena krvi 2794.5 ± 106.0 ml. U proseku je izmenjeno 1243.2 ± 49.2 ml (1.55 ± 0.05) volumena plazme i upotrebljeno 288.8 ± 13.8 ml ACD-A. Procedure su u proseku trajale 137.2 ± 9.2 min. Nakon treće procedure, zapaženo je značajno kliničko poboljšanje. Devojčica se svrsishodno osmehivala, pratila pogledom i fokusirala na audiovizuelne sadržaje prilagođene njenom uzrastu. Otpuštena je iz bolnice dobrog opšteg stanja, dve nedelje nakon poslednje TIP. Na poslednjoj kontroli, tri godine nakon lečenja, devojčica je bila dobrog opšteg stanja, sa normalnim neurološkim statusom, bez sekvela. Ovaj prikaz slučaja ističe terapijsku efikasnost TIP kod pedijatrijskih pacijenata sa teškim AE čak i kada se započne kasnije.

Ključne reči: terapijska izmena plazme, autoimuni encephalitis, pedijatrija

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