

## Case Report

# A case of anti-NMDAR encephalitis presented hypotensive shock during plasma exchange

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## Abstract

We are reporting on a case of pediatric anti-NMDAR encephalitis with autonomic instability. The patient showed little response to first-line treatment of steroid and IVIG. We initiated plasma exchange, also a first-line treatment. This worsened his autonomic instability, resulting in hypotensive shock. He responded well to rituximab and cyclophosphamide, second-line therapies.

Anti-NMDAR encephalitis is often accompanied by autonomic instability. Our and other reported cases, raise the question of plasma exchange as a first-line therapy for pediatric NMDAR encephalitis, which is frequently accompanied by autonomic instability. Plasma exchange should be performed cautiously in such patients.

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**Keywords:** Anti-NMDAR encephalitis; Plasmapheresis; Autonomic instability; Rituximab; Cyclophosphamide

## 1. Introduction

Encephalitis associated with N-methyl-D-aspartate receptor (NMDAR) antibodies is caused by autoimmune mechanisms associated with antibodies [1,2]. Anti-NMDAR encephalitis has been increasingly reported since 2007, and is the second most frequent cause of pediatric encephalitis after acute demyelinating encephalomyelitis [1,3]. More than one-third of anti-NMDAR encephalitis cases present flu-like prodromal symptoms (headache, vomiting, fever) followed by altered consciousness, seizures, cognitive dysfunction,

movement disorder, autonomic instability and central hypoventilation [1,4].

Current first-line treatment strategies recommend the initiation of steroids, intravenous immunoglobulins (IVIG) and plasma exchange, which is effective in up to 48% of cases. In cases refractory to first-line treatments, the administration of rituximab, cyclophosphamide, or both is recommended as second-line treatment [1]. However, there are few reports on their use for pediatric anti-NMDAR encephalitis. Here, we report on a child with anti-NMDAR encephalitis. The patient did not respond to steroid and IVIG treatments, and exhibited hypotensive shock during plasma exchange. He responded well to rituximab and cyclophosphamide.

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## 2. Case report

The patient (11-year-old male; no past or family medical history) initially presented with high-grade fever and delirium-like psychiatric symptoms (shouting, agitation, abnormal behavior). Laboratory tests on admission were normal (white blood cell count: 6700/ $\mu$ l; C-reactive protein: 0.02 mg/dl). Cerebrospinal fluid (CSF) revealed an elevated cell count (116/ $\text{mm}^3$ ; polycyte 2  $\text{mm}^3$ , monocyte 114  $\text{mm}^3$ ), elevated protein levels (64 mg/dl) and normal glucose (80 mg/dl). The CSF culture was negative. Serum viral antibodies for the human immunodeficiency virus and varicella zoster virus were negative. Herpes simplex virus (HSV)-DNA was negative in the CSF by PCR. Interictal electroencephalogram (EEG) showed laterality, 2–4 Hz slow waves on the right side and mostly low voltage on the left side (Fig. 1). Brain magnetic resonance imaging showed no abnormalities (Fig. 2). Tumor screening for thoraco-abdominal computed tomography and tumor markers was negative (AFP 1 ng/ml, HCG- $\beta$  < 0.1 ng/ml).

We suspected anti-NMDA encephalitis and initiated corticosteroids (1000 mg/day for 3 days, 3 cycles) from day 5 to 26 and IVIG (0.4 g/kg for 5 days) from day 13 to 17, with no effectiveness. On day 21 post-admission, the patient developed generalized convulsions, uncontrollable with phenytoin and midazolam. Interictal EEG focal spikes were observed mainly in the frontal and anterior temporal lobe (Fig. 1). In addition, he exhibited central apnea, and autonomic instability such as urinary incontinence, hypersalivation, episodic bradycardia and intermittent hypo- and

hypertension. These autonomic symptoms continued for two weeks, but did not lead to hypotensive shock. An ELISA analyses of anti-NMDA glutamate receptor antibodies revealed that serum and CSF were positive for anti-glutamate receptor  $\epsilon 2$  and  $\delta 2$  antibodies on admission (serum: 1.192 (normal:  $0.52 \pm 0.23$ ); CSF: 0.935 ( $0.22 \pm 0.08$ )). In addition, a cell-based assay using GluR $\zeta 1$  N/R+ GluR $\epsilon 2$  N/R, expressed at the HEK293T cellular membrane, also proved the presence autoantibodies in serum and CSF [5].

Plasma exchange was initiated from day 35 for refractory convulsions and psychiatric symptoms. One hour after initiation of the second treatment, the patient developed a rapid decrease in blood pressure, which resulted in shock, consisting of bradycardia (50 beats/min) and hypotension (50/30 mmHg) within 5 min. The procedure was stopped; he was treated with intravenous epinephrine (0.5 mg) and hydrocortisone (100 mg). In addition, administration of normal saline and 25% albumin bolus followed by continuous infusions of noradrenaline were required to control blood pressure. Anaphylaxis was not suspected as he was devoid of urticaria and wheezing. His neurological status was not improved with plasma exchange, which was discontinued. On day 42 we started weekly administration of rituximab (375 mg/ $\text{m}^2$ /week for 4 weeks) and cyclophosphamide (750 mg/ $\text{m}^2$ /month for 6 months), the recommended second-line treatment, due to lack of improvement with first-line treatments [1,6,7]. Within days of initiating second-line treatment, the patient's clinical symptoms, including convulsions, autonomic instability and central apnea, markedly

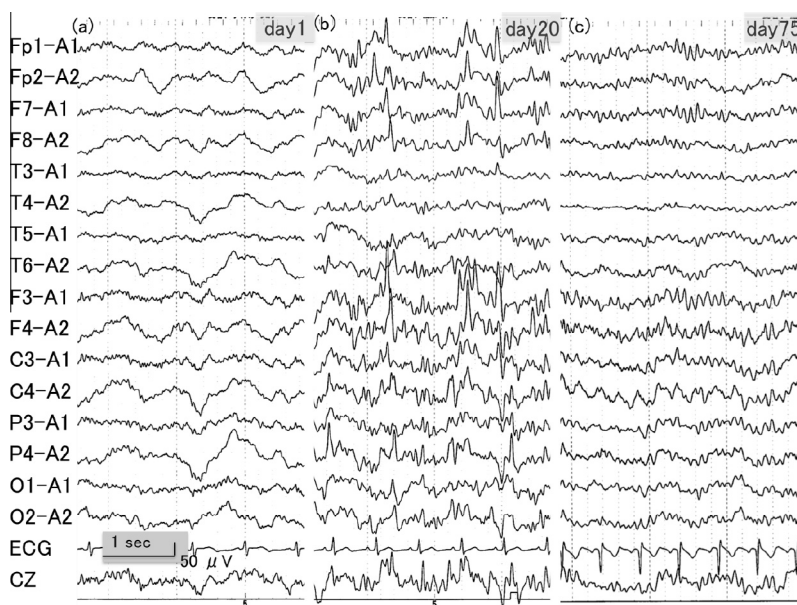


Fig. 1. Interictal electroencephalogram. (a) 2–4 Hz slow waves on the right side and mostly low voltage on the left side were seen before first-line treatment. (b) Focal spikes were observed mainly in the frontal and anterior temporal lobe. (c) After second-line treatment was introduced, abnormal findings were improved.

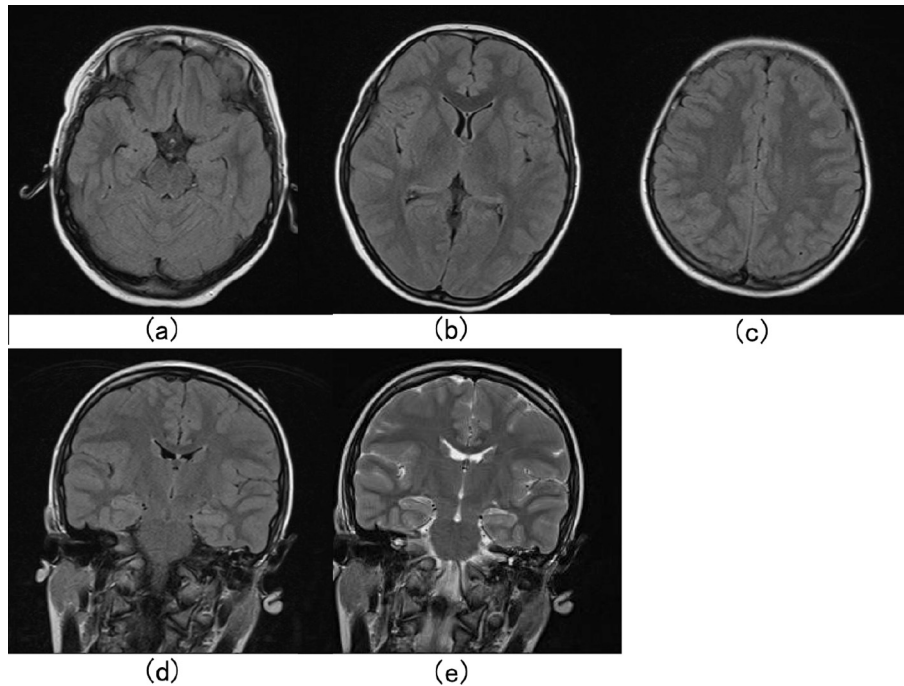


Fig. 2. Brain magnetic resonance imaging. (a)–(d) Fluid-attenuated inversion recovery (FLAIR), (e) T2-weighted image.

improved. Artificial ventilation was discontinued on day 46. Subsequently, disturbances of consciousness and involuntary movement gradually disappeared in conjunction with decreased levels of serum and CSF antibodies, anti-glutamate receptor  $\epsilon 2$  and  $\delta 2$  antibodies; serum and CSF on day 222 were decreased to 0.516 and 0.231, respectively. He regained the ability to perform daily activities and was discharged on day 252.

### 3. Discussion

The patient presented with a typical clinical course for anti-NMDAR encephalitis, including initial psychiatric symptoms, repetitive generalized convulsions, central apnea and autonomic instability [1,4]. Diagnosis was made based on positive serology for anti-NMDA antibodies in the serum and CSF. Firstly, we initiated first-line treatment, including steroid and IVIG, but this was not effective. Therefore plasma exchange, which is also considered a first-line therapy, was started, but had to be stopped due to severe complications resulting in shock status. Therefore, we initiated the second-line treatment, including rituximab and cyclophosphamide, without side effects. He started improving shortly after.

We implemented plasma exchange, common complications of which include hypotension, symptomatic hypocalcemia, allergic reactions and catheter-related infection, although there are limited reports on the risks of side effects in children (Table 1) [8–12]. Michon and colleagues reported that pediatric plasma exchange and plasma apheresis are associated with higher

complication rates compared to adults (55% vs 4.3–28%), and frequent side effects were hypotension (14%) and hypotension requiring fluid bolus (4.8%) [8]. A previous report showed that in 56 procedures with 9 patients with anti-NMDAR encephalitis, 11% of the complications involved hypotension requiring either fluid bolus or vasopressor treatment [9].

In anti-NMDAR encephalitis, autonomic instability is reportedly associated with hypotension [1]. Here, autonomic instability resulted in hypotension during plasma exchange. It is reported that autonomic symptoms are found in about 50% of pediatric anti-NMDAR encephalitis patients, similar to adult patients [4]. Although plasma exchange is a first-line treatment [1], there are few reports on pediatric patients with anti-NMDAR encephalitis that have undergone it [9,13,14]. Compared to adults, plasma exchange is more limited in children due to small vascular size, lack of cooperation, and difficult vascular access [1,8]. Arman-gue et al. reported on 20 pediatric cases that received first-line immunotherapy, of which only 1 patient received plasma exchange [13].

Rituximab and cyclophosphamide, second-line treatments, also have side effects, including infusion reaction, infection, dermatitis, hemorrhagic cystitis and myelosuppression. However, they are not related to autonomic instability. Similar second-line-treatment protocols have been used for non-Hodgkin's lymphoma and dermatomyositis and opsoclonus-myoclonus syndrome in children [6,7]. Moreover, in anti-NMDAR encephalitis, 65% of patients who do not respond to

Table 1

Complication rates for plasma exchange and plasma apheresis related hypotension.

Author, year	Number of patients	Number of procedures	Complication rate per procedure (%)	Hypotension requiring fluid bolus (%)
Michon et al. (2007) [8]	186 (0–18 years)	1632	55	4.8
Pham et al. (2011) [9]	9 (3–30 years) anti-NMDAR encephalitis	56	20	11
Shemin et al. (2007) [10]	174 (9–87 years)	1727	36	1.3
Kara et al. (2013) [11]	14 (20 months ~ 16 years)	50	8	0
Kaya et al. (2013) [12]	115 (5–85 years)	771	2.7	0.5

nd: no data.

first-line treatments do respond to second-line treatments, indicating the efficacy of rituximab and cyclophosphamide [1,4].

Here, we reported on an 11-year-old male with first-line-refractory anti-NMDAR encephalitis. The patient may have responded to plasma exchange, but it could not be continued because of severe complications. He improved well after treatment with rituximab and cyclophosphamide without side effects. This case and the literature suggest that plasma exchange should be applied cautiously for pediatric NMDAR encephalitis with autonomic instability. Considering the efficacy of rituximab and cyclophosphamide, one option would be to first attempt rituximab/cyclophosphamide therapy without plasma exchange in pediatric patients with anti-NMDA antibody encephalitis refractory to methylprednisolone and/or IVIG.

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