# Clinical diagnosis and treatment of pediatric anti-N-methyl-D-aspartate receptor encephalitis: A single center retrospective study

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**Abstract.** The aim of the present retrospective study was to investigate the diagnosis, treatment and prognosis of pediatric anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. A total of 23 pediatric patients with anti-NMDAR encephalitis were included in the present study. The clinical data, laboratory test results, imaging examination, treatment outcomes, and follow-up records were reviewed and analyzed. A total of 8 patients exhibited prodromal symptoms, including fever, cough, and vomiting. Clinical symptoms included epilepsy, convulsions, ataxia, coma, dyskinesia, personal behavior change and hallucinations. A total of 20 cases had the initial neurologic symptoms of dyskinesia or seizure, whereas 3 cases exhibited psychiatric symptoms of personal behavior change and hallucinations. Furthermore, pediatric patients >6 years old had more psychiatric symptoms than those ≤6 years. A total of 20 cases exhibited abnormal electroencephalography records, with 1 case of extreme δ brush. A total of 10 cases exhibited abnormal brain magnetic resonance imaging detection. Furthermore, the CSF protein contents for pediatric patients ≤6 years old was significantly higher than those >6 years. For treatment, 18 pediatric patients received the first-line treatment of methylprednisone and intravenous injection of immunoglobulin, and 6 cases were subjected to the second-line treatment of rituximab. A total of 2 patients underwent plasma exchange and/or cyclophosphamide treatment. In follow-up, 12 cases reported no convulsion, whereas 11 cases had moderate or severe neurological and psychiatric sequelae. The recovery rate for pediatric patients ≤6 years old was significantly higher than those >6 years. Anti-NMDAR encephalitis is commonly seen in pediatric patients, mainly with initial neurological symptoms. These patients could respond to immunotherapy, and younger pediatric patients typically have a better prognosis.

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*Key words:* autoimmune encephalitis, clinical treatment, extreme δ brush, pediatric patients

## Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was initially detailed by Dalmau *et al* (1) in 2007, who identified the anti-NMDAR antibody in the hippocampus and forehead of a young female suffering from paraneoplastic limbic encephalitis (PLE) accompanied by benign teratoma. At the initiating stage of disease development, adults with anti-NMDAR encephalitis are often characterized by mental symptoms, short-term memory loss and aphasia, whereas pediatric patients are accompanied by neurological symptoms, including epileptic seizure or status epilepticus, language reduction or silence, and movement disorders as the first symptoms (2), followed by the no-reaction period and the excessive exercise period (accompanied by involuntary movement and autonomic nervous instability) (3). Following the first case report in China in 2010 (4), there have been many case reports of adult and pediatric anti-NMDAR encephalitis (5), which has been regarded as the most common autoimmune encephalitis, ranking just after pediatric acute demyelinating encephalomyelitis (6).

Currently, etiological and epidemiological studies have demonstrated that the incidence of anti-NMDAR encephalitis is higher than other types of viral encephalitis (7-9). Diagnostic criteria for anti-NMDAR encephalitis include the generation of immunoglobulin G (IgG) antibodies against NMDAR (GLuN1 subunit) in the serum and cerebrospinal fluid (CSF) in pediatric patients, following excluding other possible causes (10,11). Prior to the diagnosis with serum and CSF antibody detection, treatments of suspected autoimmune encephalitis are typically administered on the experience of the physician (11), mainly including steroids and/or intravenous immunoglobulin (IVIG). According to the positive results from antibody detection, disease treatment regimen may include steroid therapy, combination therapy, and plasma exchange (12).

Although anti-NMDAR encephalitis has been demonstrated to be a curable autoimmune disease, there is still no standard for immunotherapy (13). Furthermore, the understanding of anti-NMDAR encephalitis is currently based on case reports and/or small-sample studies (14). In the present

retrospective study, the clinical manifestations, laboratory tests, imaging data, treatment methods, and follow-up of 23 pediatric patients with confirmed anti-NRDAR encephalitis were reviewed and analyzed.

## Patients and methods

*Study subjects*. The present study included 23 pediatric patients with anti-NMDAR encephalitis, who were diagnosed at the Department of Neurology at The Children's Hospital of Hunan (Changsha, China) from January 2015-February 2016. All patients exhibited one or more of the following clinical manifestations: i) Abnormal behavior (mental symptoms) or cognitive dysfunction; ii) language dysfunction (continuous mandatory language that cannot be interrupted, language reduction and silence); iii) seizure; iv) movement dysfunction, dyskinesia or muscle rigidity, and/or abnormal posture; v) declined consciousness; and vi) autonomic dysfunction or central hypoventilation. All 23 patients were positive for the anti-NMDAR (GluN1 subunit) IgG antibody detection (in serum and CSF samples, especially CSF) and other possible causes were excluded (1,11).

*Study methods*. Clinical data of these 23 patients with anti-NMDAR encephalitis were retrospectively analyzed, including sex, age, prodromal symptoms, major clinical manifestations, Glasgow Coma Scale (GCS) score (15), CSF outcome analysis, PCR detection of CSF Herpes simplex virus (HSV) and Epstein Barr virus (EBV), blood C-reactive protein (CRP) detection. All pediatric patients underwent abdominal and pelvic MRI examinations or abdominal and testicular US detection, immunotherapy regimen, clinical prognosis and follow-up, and Pediatric Cerebral Performance Category Scale (PCPC) scores in the follow-up period (16). These patients were divided into the preschool (≤6 years old) and school age (>6 years old) groups (17), with the follow-up periods lasting from 4 months-2 years.

*Disease treatment*. According to doctors' decisions, first-line treatments included methylprednisolone shock treatment (20 mg/kg/day, for three consecutive days, once a week for 2 weeks) and high-dose IVIG (400 mg/kg/day, for five days). No continuous improvement at 4 weeks following immunotherapy, together with the Pediatric Cerebral Performance Category (PCPC) score ≥4, indicated treatment failure. Treatment failure cases were subjected to second-line treatment, i.e., the CD20 monoclonal antibody (rituximab), 375 mg/m$^2$, once a week for 2-3 weeks (treatment could be repeated following 3 months when appropriate). In addition, the second-line treatment was also combined with plasma replacement or cyclophosphamide treatment (17). Follow-up was performed every 4 months (with the longest follow-up period lasting for 2 years), in which the patients were evaluated via the PCPC system and a score ≥3 indicated poor prognosis (16,18).

*Statistical analysis*. Data are presented as the mean ± standard deviation. SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Student's t-test was used for comparison of parametric data. Mann Whitney U test was used for comparison of non-parametric data. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Clinical characteristics of pediatric patients with anti-NMDAR encephalitis*. Clinical characteristics of pediatric patients with anti-NMDAR encephalitis were analyzed (Table I). In these pediatric patients with anti-NMDAR encephalitis, there were 13 females and 10 males, with a male to female ratio of 1:1.3; an age range of 2 years, 5 months-13 years, 7 months, with a mean age of 7.38±3.41 years; 9 cases belonged to the preschool group (≤6 years), whereas 14 cases were older than 6 years. Furthermore, in these pediatric patients, there were 22 cases positive for serum anti-NMDAR detection and 20 cases positive for CSF anti-NMDAR detection, with 19 cases positive for both the serum and CSF detections. The mean follow-up period was 0.95±0.57 years, ranging from 4 months-2 years.

*Clinical manifestations of pediatric anti-NMDAR encephalitis*. The pediatric patients with anti-NMDAR encephalitis exhibited a variety of clinical manifestations, with neurological symptoms as the main first symptom, and a number of pediatric patients exhibited prodromal symptoms (Table I). A total of 8 pediatric patients (34.78%) reported prodromal symptoms, including 5 cases (21.73%) of fever, 1 case (4.34%) of cough, and 3 cases (13.04%) of vomiting, in which 1 patient reported both fever and vomiting. Furthermore, 20 cases (86.95%) displayed initial neurological symptoms, including dyskinesia, convulsion, or seizure, whereas 3 cases (13.04%) reported first psychiatric symptoms, including personal behavior changes and hallucination. For the neurological symptoms, there were 13 cases (56.52%) of epilepsy, 20 cases (86.95%) of convulsions, 6 cases (26.08%) of ataxia, and 5 cases (21.73%) of coma, and 21 cases (91.30%) of dyskinesia. For the psychiatric symptoms, there were 12 cases (52.17%) of personal behavior change, and 7 cases (30.43%) of hallucination. For children older than 6 years, there were 7 cases suffering from hallucination, and 10 cases reporting personal behavior changes. These results suggest that, pediatric patients were accompanied with diverse clinical manifestations of anti-NMDAR encephalitis.

*Laboratory and imaging studies*. CSF examination, CRP test, GCS scoring, EEG, and MRI examination of these pediatric patients with anti-NMDAR encephalitis were analyzed (Table I). For CSF detection, the mean CSF protein content for pediatric patients ≤6 years (0.33±0.39 g/l) was significantly higher than those >6 years (0.23±0.11 g/l). However, no significant differences were observed in the CSF white cells, CSF glucose detection or blood CRP detection. Furthermore, the mean GCS scores for the pediatric patients ≤6 years and >6 years were 12.67±2.65 and 12.29±1.77, respectively. Furthermore, 20 pediatric patients (86.96%) reported EEG abnormalities, and EEG extreme δ brush was noted in 1 female child (Fig. 1). There were 10 cases (43.48%) reporting brain MRI abnormalities (Fig. 2). In addition, there were 3 pediatric patients positive for HSV-1, and 2 cases positive for EBV. No ovarian masses were detected.

*Disease severity and clinical prognosis*. The disease severity and clinical prognosis of these pediatric patients were then analyzed (Table II). Based on the first episode of anti-NMDAR encephalitis, 18 pediatric patients (78.26%) received the

Table I. Clinical characteristics of pediatric patients with anti-N-methyl-D-aspartate receptor encephalitis.

| Characteristics | ≤6 years old (n=9) | >6 years old (n=14) | P-value |
|---|---|---|---|
| Clinical manifestations | | | |
| Sex | | | |
| Male | 4 | 5 | 0.68[a] |
| Female | 5 | 9 | 0.68[a] |
| Serum anti-NMDAR detection positive | 9 | 13 | 0.42[a] |
| CSF anti-NMDAR detection positive | 8 | 12 | 0.82[a] |
| Prodromal symptoms | 2 | 6 | 0.32[a] |
| Fever | 2 | 3 | 0.96[a] |
| Cough | 0 | 1 | 0.42[a] |
| Vomiting | 0 | 3 | 0.15[a] |
| Neurological symptoms | | | |
| Convulsions | 8 | 12 | 0.82[a] |
| Epilepsy | 6 | 7 | 0.44[a] |
| Ataxia | 2 | 4 | 0.74[a] |
| Coma | 1 | 4 | 0.33[a] |
| Dyskinesia | 9 | 12 | 0.24[a] |
| Psychiatric symptoms | | | |
| Hallucination | 0 | 7 | 0.01[a] |
| Personal behavioral change | 2 | 10 | 0.02[a] |
| GCS, VEEG, MRI and laboratory test | | | |
| GCS scoring (mean ± SD) | 12.67±2.65 | 12.29±1.77 | 0.20[b] |
| VEEG abnormality | 8 | 12 | 0.82[a] |
| Extreme δ brush | 0 | 1 | 0.42[a] |
| MRI abnormality | 4 | 6 | 0.94[a] |
| Blood CRP, mg/l (mean ± SD) | 1.22±0.58 | 0.86±0.81 | 0.85[b] |
| CSF detection | | | |
| White cells, x$10^6$ (mean ± SD) | 15.56±21.81 | 22.29±25.49 | 0.40[b] |
| Protein, g/l (mean ± SD) | 0.33±0.39 | 0.23±0.11 | 0.02[b] |
| Glucose, mmol/l (mean ± SD) | 3.00±0.62 | 3.53±0.64 | 0.97[b] |
| HSV PCR | 0 | 3 | 0.15[a] |
| EBV PCR | 1 | 1 | 0.75[a] |

Data are presented as n unless other wise stated. [a]Calculated with Mann Whitney U test; [b]calculated with Student's t-test. Anti-NMDAR, Anti-N-methyl-D-aspartate receptor; CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; VEEG, video electroencephalo-graph; MRI, magnetic resonance imaging; SD, standard deviation; CRP, C-reactive protein; HSV, herpes simplex virus; PCR, polymerase chain reaction; EBV, Epstein Barr virus.

methylprednisolone treatment and intravenous IVIG treatment, whereas 3 pediatric patients received oxcarbazepine and 2 pediatric patients were treated with sodium valproate antiepileptic treatments. Furthermore, 6 pediatric patients (26.09%) received the second-line treatment with rituximab, in which 2 cases of treatment failure were subjected to plasma exchange and/or cyclophosphamide treatment. The second-line treatment included the rituximab treatment for 2-3 weeks, and cyclophosphamide treatment for 4-7 months. The treatment options for dyskinesia included diphenazine and piracetam, however no significantly satisfactory therapeutic effects were observed.

A total of 9 pediatric patients were treated in the intensive care unit, and 3 cases underwent the mechanical ventilation. During treatment, 11 pediatric patients had PCPC scores ≥4. In total, 19 cases (82.61%) reported a significantly improved condition. In these 19 cases, there were 12 cases (63.16%) of full recovery, 5 cases (26.31%) of mild disability, and 2 cases (10.52%) of moderate or severe disability (with a PCPC score of 3 or 4), for whom the symptoms were still improving following 4- and 9-month follow-up detection. No significant improvement was observed in the other 4 patients with disability (17.39%). For those fully recovered pediatric patients, 4 cases fully recovered at 3-5 months following symptom occurrence, and 8 cases fully recovered at 8-12 months following symptom occurrence. Furthermore, the recovery rate for patients ≤6 years was significantly higher than the patients >6 years. In those 19 cases with significantly improved conditions, the

Table II. Therapy and sequelae of pediatric patients with anti-N-methyl-D-aspartate receptor encephalitis.

| Therapy or sequelae | ≤6 years old (n=9) | >6 years old (n=14) | P-value |
|---|---|---|---|
| Disease treatment, severity, and prognosis | | | |
| Methylprednisone treatment | 8 | 10 | 0.33 |
| First-line antiepileptic drug treatment | 1 | 4 | 0.33 |
| Stilled used the antiepileptic drugs | 0 | 1 | 0.42 |
| IVIG treatment | 8 | 10 | 0.33 |
| Second-line treatment | 1 | 5 | 0.20 |
| ICU treatment | 2 | 7 | 0.19 |
| Recovery | 8 | 4 | 0.01 |
| Disability | 1 | 10 | 0.01 |
| Relapse | 1 | 2 | 0.82 |
| PCPC≥4 | 3 | 8 | 0.14 |

Data are presented as n. P-values calculated using Mann Whitney U test. IVIG, intravenous immunoglobulin; ICU, intensive care unit; PCPC, Pediatric Cerebral Performance Category Scale.

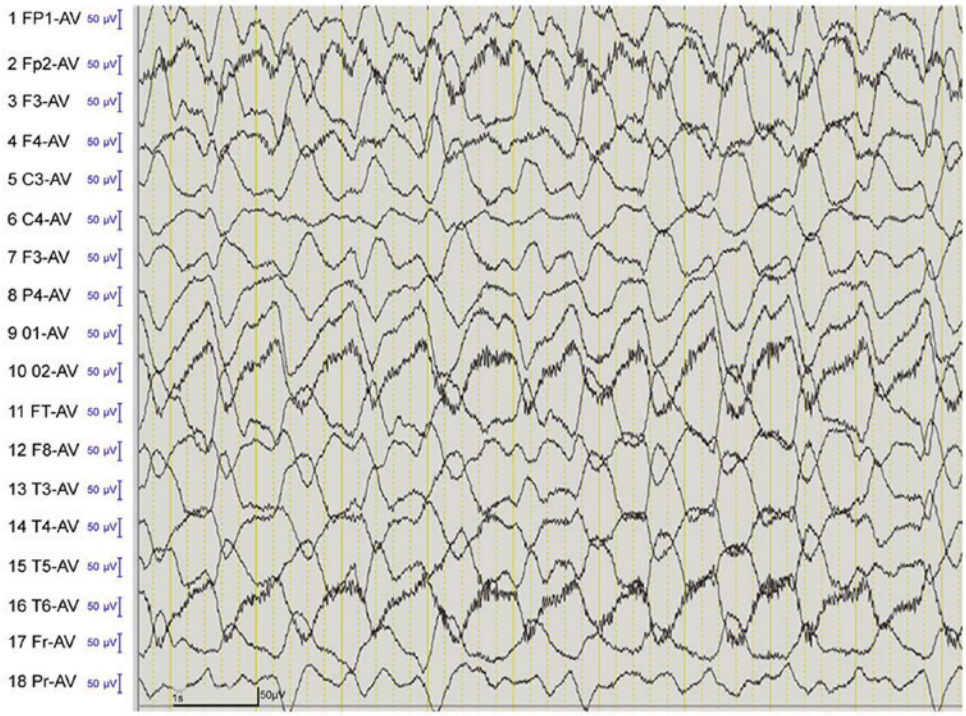


Figure 1. Electroencephalography pattern of a 10-year and 3-month old female child with anti-N-methyl-D-aspartate receptor encephalitis. Extreme δ brush consisted of almost completely continuous δ activities, with superimposed fast activities, typically in the β wave range of patients who were not under sedation or anesthesia. This pattern resembled the δ brush appearing in premature infants, but the extreme δ brush was mainly associated with frontal lobe symmetry and synchronization.

improved symptoms in 17 cases (89.47%) were associated with movement function, with ataxia as the last improved symptom in 1 case, whereas 3 cases reported disease recurrence.

## Discussion

In recent years, investigation of the autoantibodies in the neuronal cell membrane and synapses, and the corresponding autoimmune encephalitis, has become a major focus in the field of neuroimmunology (1). The related investigation of autoantibodies in in neuronal cell membranes and synapses has not only changed the pattern of encephalitis study, but also expanded the study scope to cover the mental illness, epilepsy, dyskinesia and cognitive dysfunction (1). Previous studies have demonstrated that there are more cases of anti-NMDAR encephalitis than other kinds of autoimmune encephalitis (11,19). In 2010, the first case report of anti-NMDAR encephalitis was published in China (4), and many cases of adult and pediatric patients have been reported since (5). However, there are significant differences in the

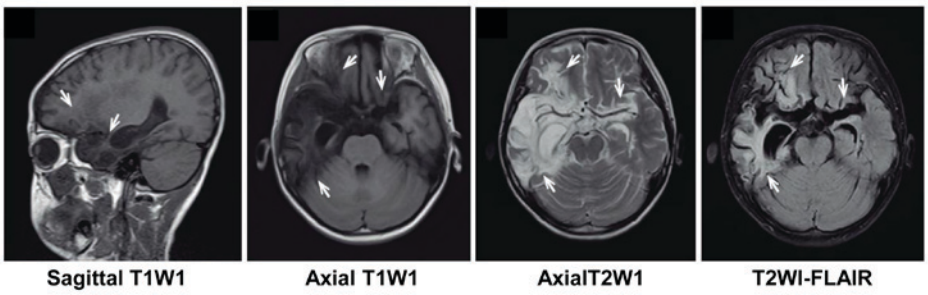


Figure 2. Magnetic resonance imaging detection of a representative pediatric patient (male, 13-year and 6-month old, admitted for convulsions for 1 week) with anti-N-methyl-D-aspartate receptor encephalitis. Multiple long T1 and long T2 signal shadows were noted in the bilateral frontal and temporal lobes, right thalamus and corpus callosum, which was obvious in the right front temporal lobe (as indicated by white arrows). Fluid-attenuated inversion recovery sequence mainly demonstrated high signals, within which low signals could be observed. Widened and deepened adjacent fissures were observed, as well as slightly enlarged bilateral lateral ventricle and third ventricle, with no obvious shift of the midline structure.

clinical symptoms between adult and pediatric patients. Although 60% of pediatric patients with anti-NMDAR encephalitis exhibit seizure, dyskinesia, and localized neurological symptoms, 70% of young patients have psychosis and other psychiatric symptoms (20). The present findings demonstrated that pediatric patients >6 years old were associated with the trend to have similar psychotic symptoms. Armangue *et al* (21) have previously compared the symptoms between children older than 12 years and younger than 12 years, and have demonstrated that patients over 12 years of age exhibited more psychiatric symptoms. Titulaer *et al* (22) have studied 568 patients covering various age ranges, and their results demonstrated that 95.6% of these patients exhibit ≥3 symptoms, whereas only 0.7% have a single symptom. Patients with systemic syndromes often gradually develop to have lower level of consciousness, autonomic nervous instability, and hypoventilation (22). In general, these findings suggest that the diagnosis of anti-NMDAR encephalitis should be carefully considered when a single symptom or symptoms do not match with anticipating symptoms. For these cases, CSF and serum antibodies need to be re-evaluated. However, clinical relapse may be unilateral with single symptoms, which are less severe than initial symptoms (21). In one case from the present study, isolated behavioral and linguistic disorders occurred twice independently over the past 2-year follow-up period.

The present findings demonstrated that the protein contents in CSF in pediatric patients ≤6 years were significantly increased compared with those >6 years, whereas no significant differences were observed in other CSF detection indicators. This might be due to the fact that the older pediatric patients develop awareness early, and they received less lumbar puncture (20). Findings in MRI and video EEG (VEEG) were similar to the reports in adults (23). In 1 pediatric patient, EEG detection exhibited extreme δ brush, which is a special EEG pattern exhibited in 30% of adult anti-NMDAR encephalitis patients (24). In the present study, 82.61% of pediatric patients had significant clinical improvement or complete recovery. In most cases, patients recovered at 8-12 months following symptom onset. Disease duration and hysteresis response to immunotherapy were partially caused by the antibodies in the central nervous system (CNS), which has been confirmed by the detection of antibody synthesis within the CNS sheath (25,26), as well as the findings concerning the long-term infiltration of plasma cells into the brain parenchyma and meninges (27). Rituximab is able to diminish B cells and prevent B cells from entering the CNS to developing into antibody-producing plasma cells (28). Cyclophosphamide can pass through the blood-brain barrier, and affect T and B cells, increasing anti-inflammatory factors and contributing to immunosuppression (29). In the present study, 6 pediatric patients received and responded to the rituximab treatment (combined with cyclophosphamide in 2 cases), without recurrence. Furthermore, no pediatric patients exhibited obvious side effects during treatment.

This was a retrospective study, with no uniform systematic treatment approach (e.g., the criteria, interval time, and therapeutic duration for the first- and second-line treatments). Therefore, further in-depth studies are required to address these issues. In addition, the sample size herein was relatively small, and expanded sample sizes may be needed to develop anti-NRDAR encephalitis treatment criteria and predict recurrence risk factors. In the present study, no tumors were detected in patients, suggesting that the majority of patients did not develop potential tumors. Previous studies have demonstrated that younger patients are less likely to would develop tumors (30-32). Furthermore, these findings suggest that the pathogenesis for pediatric patients might differ from adults (14). Certain patients (usually older than 12 years) do suffer from teratoma, similar to young adults, which may be detected following the recovery of encephalitis (31,32).

In the present study, 3 pediatric patients were detected positive for HSV infection, all older than 6 years, and within them, 1 case developed anti-NMDAR encephalitis at 4 weeks following HSV infection. The symptoms are similar to those of HSV infection, with unclear etiology. In these cases, negative detection results were obtained for the CSF and brain, and MRI did not indicate new necrotic hemorrhagic lesions, with no response to acyclovir treatment. Therefore, it was unlikely to be caused by virus activation. Abnormal movement may persist for several months or years, which do not respond to anti-epilepsy and dopamine receptor antagonists. Anti-NMDA receptors may be produced by the immune system in response to infection. In the present study, for the pediatric patients with biphasic symptoms, CSF was negative for HSV PCR detection and positive for NMDA receptor antibody detection, and the brain MRI demonstrated no other changes, with no response to acyclovir treatment. However, the rituximab and cyclophosphamide treatment lead to significant improvement. These findings suggest an association between

these two kinds of diseases. The results of the present study have indicated that certain pediatric patients with HSV infection may suffer from anti-NMDAR encephalitis. A previous study has suggested that NMDAR antibodies may be present in the serum or CSF in 11% of HSV-infected patients (33). The therapeutic effects for those pediatric patients ≤6 years were superior to those >6 years. This phenomenon might be caused by the fact that younger children may have an imperfect blood-brain barrier, through which, drugs may pass and enter into the CNS, thereby inhibiting immunity (29).

In conclusion, the present study investigated the common neurological symptoms of pediatric patients with anti-NMDAR encephalitis, and the majority of these patients responded to immunotherapy. Second-line immunotherapy (mainly including rituximab) was often effective and well-tolerated. Furthermore, extreme δ brush represents a notable feature of VEEG. These findings may contribute to the guidelines of disease treatment and relapse prediction of pediatric anti-NMDAR encephalitis.

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**Availability of data and materials**

The data analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

YS and XZ analyzed and interpreted data regarding anti-NMDAR encephalitis disease; YS and MF performed the statistical analysis; JT and HL participated in data collection and statistical analysis. YS was a major contributor in writing the manuscript. LT conceived the study and helped revise the manuscript. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Consent for publication was obtained from the patients' parents.

**Competing interests**

The authors declare that they have no competing interests.

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