Pediatric Anti-NMDAR Encephalitis in Southern China: Analysis of 107 Cases

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Abstract

Background: Research on pediatric anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is limited. We studied clinical features of children with anti-NMDAR encephalitis in southern China.

Methods: Pediatric anti-NMDAR encephalitis between 2014 and 2019 from one tertiary medical center was analyzed. The Modified Rankin Scale (mRS) score was adopted to evaluate outcomes.

Results: 107 children (M/F=50/57; mean onset age=6.3 y) with anti-NMDAR encephalitis were involved. Boys significantly showed earlier onset age, higher ratio of fever, longer hospital day, more courses of steroid treatment, higher mRS score after treatment. 48.6% of patients had prodromal events with infectious events most common. The most common symptom at onset and during whole course was seizures and psychiatric symptoms respectively. Initial median white cell count of cerebral spinal fluid (CSF) was 22.0x10^6/L. 12.1% of patients had positive herpes simplex virus DNA of CSF. All patients had CSF positive NMDAR antibodies, although 86.9% of patients had serologically positive. 9.3% of patients had overlapping other neuronal antibodies. Electroencephalograph showed abnormalities with slow wave (95.3%) and epileptic activity (41.5%). Delta brush was revealed in 3.8% of patients. 36.4% of patients had lesions in brain MRI, with local lesions most common. No tumor was found in all. 84.9% of patients responded well to the first line therapy (steroid plus immunoglobulin), while 12 patients accepted second-line therapy (Rituximab) with 91.7% of effective rate. 12.1% of patients relapsed. 2 male patients died. The median length of hospital stay was 28 days. The mRS score was significantly improved after treatment. 51.0% of patients had a full recovery. 76.6% of patients had mild neurological disability (mRS≤2). Male, speech disorder, initial score of mRS and administration of second-line therapy were independent risk factors associated with the outcome.

Conclusions: Of pediatric anti-NMDAR encephalitis in southern China: the mean onset age was about 6-year-old, earlier in boys; boys remained slower to recover and with a worse prognosis; the most common respective symptom at onset and during whole course was seizures and psychiatric symptoms; combination with tumor was rare; most patients respond well to the immunotherapy; relapse and fatality rate were relatively low; most patients had a good prognosis.

Background

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder associated with autoantibodies binding with NR1 subunit of NMDAR receptor[1]. Since it was first described in 2007, plenty of cases have been reported during these years[2, 3]. Anti-NMDAR encephalitis is the most common form of autoimmune encephalitis. It was more frequent than viral encephalitis with identified viral etiology in children and adolescents reported in the California Encephalitis Project[4].

The common clinical manifestations of anti-NMDAR encephalitis include psychiatric symptoms, behavioral dysfunction, seizures, movement disorder, speech disorder, cognitive impairment, decreased consciousness, autonomic dysfunction or central hypoventilation[5]. Majority of these manifestations
resemble those in NMDAR hypofunction caused by NMDAR antagonists. NMDAR hypofunction caused by antibody mediated NMDAR internalized is a popular hypothesis for the mechanism of anti-NMDAR encephalitis\[1, 6\]. But this hypothesis is insufficient to explain some core symptoms like seizures\[1, 6\]. Besides, the clinical features of anti-NMDAR encephalitis vary in different ages, ethnicities and regions. Reginal studies of anti-NMDAR encephalitis may promote the research on its mechanism and enrich the clinical phenotypes. However, the regional studies of local spectrum especially focusing on the pediatric population with large sample size is still considered limited.

As our hospital is the reginal tertiary center for children's medicine in south China, we reported 107 pediatric anti-NMDAR encephalitis patients from southern China, focusing on the clinical features of pediatric anti-NMDAR encephalitis including demographics features, prodromal events, clinical manifestations, laboratory investigations, neuroelectrophysiological and neuroimaging examinations, treatments, therapy outcomes and prognosis.

**Methods**

**Patients**

This was a retrospective study of children diagnosed with anti-NMDAR encephalitis from October, 2014 to October, 2019 in the department of neurology of Guangzhou Women and Children’s Medical Center. This study was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (2019052419364384).

**Data Collection**

Clinical information including demographics features (age; gender), prodromal events, clinical manifestations, laboratory test results, electroencephalograph (EEG), brain magnetic resonance imaging (MRI), treatment outcomes, and follow-up were reviewed. Cerebrospinal fluid (CSF) pleocytosis was defined as white cell count ≥5/ml\[7\].

**Disease Severity Evaluation**

Neurological disability was assessed by modified Rankin Scale (mRS)\[8, 7, 9\] at the time before immunotherapy defined as initial mRS, after immunotherapy and when discharged and at the end of follow-up. No obvious or mild neurological disability was defined as mRS score ≤ 2. Severe neurological disability was defined as mRS score ≥ 4 and ≤ 6. A poor response was defined as no improvement in the mRS score or as mRS score ≥ 4 for 4 weeks. Clinical improvement was defined as a decrease in mRS score ≥ 1 compared with the previous visit. Long-term good prognosis was defined as mRS score ≤ 2 and poor prognosis was defined as mRS score > 2.
Inclusion Criteria

Patients aged younger than 18 years old, diagnosed with anti-NMDAR encephalitis according to diagnostic criteria proposed by Graus et al[5] and excluding primary schizophrenia and mental behavior abnormalities secondary to intracranial infection, drugs, poisoning, brain trauma, genetic and metabolic diseases and psychological diseases. Relapse was defined as the new onset or worsening of symptoms occurring after at least two months of improvement or stabilization[10].

Antibodies Test

NMDAR IgG, and gamma-aminobutyric acid type B IgG in both serum and cerebrospinal fluid (CSF) were determined by cell-based assay (EUROIMMUN, Lübeck, Germany). CSF glial fibrillary acidic protein (GFAP) IgG and myelin oligodendrocyte glycoprotein (MOG) IgG and aquaporin-4 (AQP4) IgG in serum were determined by cell-based assay. These assay methods have been reported in detail in our previous study[11].

Treatment

Immunotherapy: In total, 106 patients received the first line therapy of IVMP combination with IVIG, while only 1 referral patient who just transferred to our center died of central hypoventilation and shock on the 7th days after onset didn't receive immunotherapy. 90 patients (84.9%, 90/106) had good response to first line therapy. 38.9% (39/106) of patients achieved remission after treatment with one course of IVMP and IVIG. 38.9% (39/106) of patients achieved remission after treatment with 1 course of IVMP and 2 courses of IVIG. 9.4% (10/106) of patients achieved remission after treatment with 2 courses of IVMP and IVIG. 1.9% (2/106) of patients achieved remission after treatment with 1 course of IVMP and 3 courses of IVIG. 15.1% (16/106) of patients didn't response to the first line therapy, among which 1 case died and 3 cases with poor compliance refused to the RTX therapy and lost to follow up. A total of 12 cases received RTX treatment, among which 10 cases had poor response to first-line immunotherapy and improved after RTX treatment without relapse. Other 2 out of 12 cases had poor response to first-line treatment at relapse and improved after RTX treatment. Only one patient with critical illness and rapid progression treated with plasma exchange.

Antiepileptic treatment: 39.3% (42/107) of patients were treated with antiepileptic drug (AED). 71.4% (30/42) of patients needed one AED to control seizures, 21.4% (9/42) of patients needed two AEDs to control seizures, 4.8% (2/42) of patients treated with 3 AEDs and got seizures partially controlled and 2.4% (1/42) of patients with spasm onset had no response to 3 AEDs and got seizures partially controlled after treatment with adreno-cortico-tropic-hormone. AEDs that have been used included Valproate (47.6%, 20/42), Levetiracetam (40.5%, 17/42), Oxcarbazepine (28.6%, 12/42), Nitrazepam (16.7%, 7/42), Topiramate (4.8%, 2/42), Lamotrigine (2.4%, 1/42) and Lacosamide (2.4%, 1/42).
Supportive treatment: 4.7% (5/107) of patients were treated with tracheal intubation and mechanical ventilation. 37.4% (40/107) of patients received anti-infection treatment including intravenous acyclovir (19.6%, 21/107) and oral azithromycin (14.0%, 15/107). 46.7% (43/107) patients received oral nitrazepam or chloral hydrate to improve sleep in acute stage.

Results

Demographics

A total of 107 children (male: female = 50:57) with NMDAR encephalitis from south of China were involved, mean onset age of which was 6.3 ± 3.1 years old. Among included patients the mean onset age of the boys was 5.6 ± 2.8 years old, which was significantly younger than that of the girls (6.9 ± 3.3 years, \( P = 0.032 \), Table 1). 18.9% (20/107) of patients had a history of preexisting other diseases including sleep disorder (n = 1), tic disorder (n = 2), attention deficit hyperactivity disorder (n = 1); febrile convulsion (n = 2); intracranial infection (n = 1) which had been cured; intellectual disability (n = 1); mild hydrocephalus (n = 1) which had been cured; low birth weight premature infants (n = 4, born within 32–36 weeks, birth weight from 2.2 to 2.3 kg); fetal macrosomia (n = 1, birth weight was 4.25 kg); neonatal asphyxia (n = 3); allergy (n = 2); short stature with ptosis for unknown reason (n = 1).
| Clinical features | NO. of patients (percentage) |  |  |
|-------------------|-----------------------------|---|---|
|                   | Total n = 107               | Male n = 50 | Female n = 57 |
| Age (mean ± SD, year) | 6.3 ± 3.1                   | 5.6 ± 2.8 | 6.9 ± 3.3 | 2.177 | 0.032<sup>a</sup> |
| Fever             | 51(47.7)                    | 29(58.0) | 22(38.6) | 4.020 | 0.045<sup>c</sup> |
| Consciousness disturbance | 37(34.6)              | 22(44.0) | 15(26.3) | 3.682 | 0.055<sup>c</sup> |
| Movement disorder | 82(76.6)                    | 38(76.0) | 44(77.2) | 0.021 | 0.884<sup>c</sup> |
| Limb paralysis    | 22(20.6)                    | 13(26.0) | 9(15.8)  | 1.700 | 0.192<sup>c</sup> |
| Ataxia            | 39(36.4)                    | 17(34.0) | 22(38.6) | 0.243 | 0.622<sup>c</sup> |
| Seizures          | 77(72.0)                    | 37(74.0) | 40(70.2) | 0.193 | 0.660<sup>c</sup> |
| Speech disorder   | 85(79.4)                    | 40(80.0) | 45(78.9) | 0.018 | 0.893<sup>c</sup> |
| Psychiatric symptoms | 98(91.6)                 | 45(90.0) | 53(93.0) | -     | 0.731<sup>d</sup> |
| Autonomic dysfunction | 36(33.6)               | 20(40.0) | 16(28.1) | 1.698 | 0.193<sup>c</sup> |
| Sleep disorder    | 82(76.6)                    | 37(78.0) | 45(78.9) | 0.364 | 0.546<sup>c</sup> |
| Memory disorder   | 33(30.8)                    | 12(24.0) | 21(36.8) | 2.059 | 0.151<sup>c</sup> |
| CSF detection     |                            |           |           |       |                   |
| Pleocytosis       | 59(55.1)                    | 25(50.0) | 34(60.0) | 1.003 | 0.317<sup>c</sup> |

CSF: cerebrospinal fluid; EEG: electroencephalogram-graph; IVIG: intravenous immunoglobulin; MRI: magnetic resonance image; RTX: rituximab.

*: 106 patients underwent EEG examination.

<sup>a</sup>: independent t’ test. <sup>b</sup>: Wilcoxon rank-sum test. <sup>c</sup>: Pearson Chi-Square. <sup>d</sup>: Fisher’s exact test.
| Clinical features | NO. of patients (percentage) | v/Z/χ² | P-value |
|-------------------|-----------------------------|--------|---------|
|                   | Total n = 107               |        |         |
|                   | Male n = 50                 |        |         |
|                   | Female n = 57               |        |         |
| Increase level of protein | 14(13.1) | 6(12.0) | 8(14.0) | 0.097 | 0.755<sup>c</sup> |
| EEG with epilepsy discharge | 44(41.5)* | 25(50.0) | 19(33.3) | 3.056 | 0.080 |
| MRI changes       | 39(36.4) | 17(34.0) | 22(38.6) | 0.243 | 0.622<sup>c</sup> |
| Initial mRS [Median, (IQR)] | 4(3–5) | 4(4–5) | 4(3–5) | 1.237 | 0.216<sup>b</sup> |
| mRS after treatment [Median, (IQR)] | 2(1–2) | 2(1–2) | 2(1–2) | 2.635 | 0.008<sup>b</sup> |
| Anti-NMDAR antibody titer in CSF [Median, (IQR)] | 32(10–32) | 32(10–100) | 32(3.2–32) | 1.257 | 0.209<sup>b</sup> |
| Duration from onset to diagnosis [Median (IQR), day] | 15(10–22) | 15(10–22) | 15(10–21) | 0.505 | 0.052<sup>b</sup> |
| Hospital day [Median (IQR), day] | 28(22–36) | 26(22–31) | 28(22–39) | 2.135 | 0.036<sup>a</sup> |
| Steroid course [Median, (IQR)] | 1(1–1) | 1(1–1) | 1(1–1) | 2.073 | 0.038<sup>b</sup> |
| RTX treatment | 12(11.2) | 5(10.0) | 7(12.3) | 0.139 | 0.709<sup>c</sup> |

CSF: cerebrospinal fluid; EEG: electroencephalogram-graph; IVIG: intravenous immunoglobulin; MRI: magnetic resonance image; RTX: rituximab.

*: 106 patients underwent EEG examination.

<sup>a</sup>: independent t’ test. <sup>b</sup>: Wilcoxon rank-sum test. <sup>c</sup>: Pearson Chi-Square. <sup>d</sup>: Fisher’s exact test.
Clinical Presentation

Prodromal events

48.6% (52/107) of patients had prodromal events. Among them, 73.1% (38/52) of patients had prodromal infectious events within 1 month before onset, among which 63.2% (24/38) were non-neurological infectious prodromal events including acute respiratory infection (n = 17), hand, foot and mouth disease (n = 3), acute gastroenteritis (n = 3), and acute mumps (n = 1), while 36.8% (14/38) was intracranial infections including herpes simplex virus (HSV) encephalitis (n = 13) and Japanese encephalitis (n = 1). 26.9% (14/52) of patients had non-infection events including vaccination (n = 5), trauma (n = 5), psychological stress (n = 3) and urticaria (n = 1) within 2 weeks before onset.

Neurological Symptoms

Initial neurological symptoms included: seizures (39.2%, 42/107), movement disorder (29.9%, 32/107), psychiatric symptoms (18.7%, 20/107), speech disorder (5.6%, 6/107), headache (4.7%, 5/107), sleep disorder (1.9%, 2/107). During the whole course, the psychiatric symptoms were the most common presentation followed by movement disorder and seizures respectively (Table 1). Meanwhile the ratio of speech disorder increased to 79.4% and autonomic dysfunction increase to 33.6% from initially less than 10% of both (Table 1).

Ancillary Test Results
Peripheral blood test results

All patients underwent blood routine test, blood gas and electrolyte examination, liver and renal function test, erythrocyte sedimentation rate and blood C-reactive protein (CRP) test when they were first admitted to our hospital. The results showed the median white blood cells count was $9.4 \times 10^9/L$ (IQR 7.3-12.7 $\times 10^9/L$), liver and renal function test was normal except 26 cases (24.3%, 26/107) showed increase creative kinase. The median creative kinase was 739.5 IU/L (IQR 514-1663.5 IU/L), while the median blood sodium was 137.0 mmol/L (IQR 135.0-139.4 mmol/L). The median erythrocyte sedimentation rate was 12.0 mm/h (IQR 2–22 mm/h). CRP increase was seen in 7 cases (6.5%, 7/107), in which the median CRP was 13.04 mg/L (IQR 10.26–26.28 mg/L). All patients underwent serum anti-NMDAR antibodies test in acute phase and it was positive in 93 cases (86.9%, 93/107).

Co-existing Autoantibodies And Associated Autoimmune Diseases

63 patients underwent anti-thyroid antibodies test, in which 39 cases (61.9%, 39/63) showed positive in thyroglobulin antibody and 36 cases (57.1%, 36/63) showed positive in thyroid peroxidase antibody. 7 patients showed positive in serum MOG IgG among whom 5 patients were complicated with central never system demyelination. The detail clinical feature of these 7 patients have been reported in our previous study[11]. 1 patient showed positive in serum AQP4 IgG but didn't show central never system demyelination. 1 patient showed CSF GFAP IgG positive and was complicated with noninfectious meningoencephalitis. 1 patient showed positive in serum anti gamma-aminobutyric acid type B receptor IgG.

Csf Test

All patients underwent CSF examination by performing lumbar puncture at acute phase. The median white cell count of CSF at the first lumbar puncture was $22.0 \times 10^6/L$ (IQR 12.0–57.0 $\times 10^6/L$) and majority of which was lymphocyte dominant. The median protein level in CSF was 0.28 g/L (IQR 0.21–0.43 g/L) and ranged from 0.10 g/L to 3.87 g/L. While the glucose and chloride level were normal. All patients underwent CSF anti-NMDAR antibodies test at acute phase and it was positive in all patients.

Etiological Examination

Blood pathogenic examination was positive in 48 patients out of 107 (44.9%, 48/107), in which herpes simplex virus (HSV) IgM positive was the most common (45.8%, 22/48) and mycoplasma pneumonia IgM positive (35.4%, 17/48) ranked the second. Influenza B virus IgM positive (6.25%, 3/48), cytomegalovirus IgM positive (4.2%, 2/48), Epstein-Barr virus capsid IgM positive (4.2%, 2/48) and enterovirus 71 IgM positive (4.2%, 2/48) were also found in a few patients. 14 cases of these patients
(29.2%, 14/48) showed positive in CSF pathogenic examination, in which HSV DNA positive was the most common (92.9%, 13/14). The remaining one had positive Japanese encephalitis IgM both in serum and CSF.

**Neuroelectrophysiological Examination**

Nearly all patients underwent EEG, visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) examination. 106 patients underwent 167 times EEG examination during acute stage phrase. 95.3% (101/106) of patients had slow wave and 41.5% (44/106) had epileptic activity in EEG. Among 167 times EEG examination, normal background was seen in 7.8% (13/167), epilepsy discharge was seen in 32.3% (54/167) including 16 episodes of clinical seizures (10 episodes of focal origin, 2 episodes of focal status epilepticus, and 2 episodes of generalized tonic-clonic status epilepticus), 4 episodes of electric seizures (2 out of 4 episodes with non-convulsive status epilepticus) and 34 episodes of interictal epileptiform discharges and Delta brush was seen in 3.8% (4/106). 13 cases (12.1%, 13/107) showed the bilateral latency of P100 wave of VEP was prolonged and 13 cases (12.1%, 13/107) showed the latency of III and V wave of BAEP in unilateral or bilateral was prolonged at acute phase. The abnormal outcomes either from VEP or from BAEP were restored in the following recovery period.

**Imaging Examination**

All patients underwent brain MRI examination in acute phase and non-specific changes was found. 36.4% (39/107) of patients had lesions in brain MRI. 43.6% (17/39) of patients had local lesions in brain MRI, while 30.8% (12/39) of patients had multiple lesions including 7 cases of multiple demyelination lesions in white matter. And 5 cases among these 7 cases had MOG antibody positive. Patients having MOG antibody positive were reported in our previous study[11]. 10.3% (4/39) of patients had patchiness lesions around lateral ventricle. 7.7% (3/39) of patients had bilateral ventricle enlargement. 7.7% (3/39) of patients had leptomeninges enhancement, among which one had GFAP antibody positive. All patients underwent tumor screening including Chest CT scan, abdominal and genital MRI scans. None patients had combined with tumor.

**Courses And Relapse**

The median time from onset to diagnosis was 15 days (IQR 10–22 days) and the median length of hospital stay was 28 days (IQR 22–36 days). 12.1% (13/107) of patients relapsed, among which 92.3% (12/13) had a good response to first-line treatment at the time of the first onset, 53.8% (7/13) relapsed at the 6th month of the disease course (2–4 weeks after tailing off prednisone), 23.1% (3/13) relapsed at the 8th month of the disease course when oral prednisone was reduced to 0.5 mg/kg/d, and 15.4% (2/13) relapsed at the 15th month of the disease course (9 months after stopping steroid treatment). 5 patients received one course of IVMP and IVIG, 5 patients received one course of IVMP and two courses of IVIG
and 2 patients received two courses of IVMP and IVIG among the 12 patients mentioned above. 7.7% (1/13) of patients had poor response to first-line treatment at the first onset, which was improved after RTX treatment, and relapsed 5 years later (3 years after stopping RTX treatment). 84.6% (11/13) of patients who relapsed were still effective to first-line treatment, and 15.4% (2/13) of patients, who relapsed were poorly responsive to first-line immunotherapy, received RTX treatment (including the one who received RTX in the first episode). All children did not relapse during follow-up. Interestingly, we found CSF anti-NMDAR antibody in 13 relapsed patients turned positive again (9 cases) or titer increased (4 cases) compared with that in stable period. The effect of changes in anti-NMDAR antibody needs further research.

Prognosis

1. 4.7% (5/107) of patients was lost of follow up, among which 1 case abandoned further treatment for no response to the first line therapy and the other 4 cases for poor compliance. And we got their information by telephone contact. All these 5 patients survived and had mRS > 2. 1.9% (2/107) of male patients died, among which 1 case died of central hypoventilation and shock and the other one didn’t respond to the first line therapy, then got secondary sepsis and died of multiple organ failure. In total, the fatality rate was 1.9% (2/107).

2. 76.6% (82/107) of patients had a mRS \( \leq 2 \) at the last follow up. Comparing with initial mRS of which the median was 4 (IQR 3–5), the mRS after treatment of which the median was 2 (IQR1-2) was significantly improved (Wilcoxon rank-sum test, \( P < 0.0001 \)). Changes of patients mRS score during the course was shown in Fig. 1. The ratio of poor prognosis in patients treated with RTX was higher than patients without RTX treatment (75.0% vs 16.8%, \( P < 0.0001 \), Table 2). The median length of follow up of 100 survival patients not containing 5 patients who were lost follow-up was 12 months (IQR 6–18 months). 51.0% (51/100) of patients had a full recovery. 49.0% (49/100) of patients had more than one item of neurological dysfunction. 19.0% (19/100) of patients had sequela with emotional problems which manifested as irritability. 10.0% (10/100) of patients had sequela with speech disturbance which manifested as verbal communication difficulties. 8.0% (8/100) of patients had sequela with sleep disorder which manifested as waking up frequently at night and night mare. 12.0% (12/100) of patients had sequela with poor memory and learning difficulties. 9.0% (9/100) of patients had sequela with attention deficit hyperactivity disorder. 9.0% (9/100) of patients had sequela with movement disorder. 6.0% (6/100) of patients had sequela with seizures. 6.0% (6/100) of patients had sequela with involuntary movement.
Table 2
Univariate analysis of factors associated with the outcomes of pediatric anti-NMDAR encephalitis

| Clinical characteristics | Total (n) | Good prognosis n = 82 | Poor prognosis n = 25 | t/Z/χ² | p-value |
|--------------------------|----------|-----------------------|----------------------|--------|---------|
| Age ≤ 3 years (n, %)     | 89       | 73(82.0)              | 16(18.0)             | -      | 0.011ᵇ |
| Male (n, %)              | 50       | 33(66.0)              | 17(34.0)             | 5.929  | 0.015ᵃ  |
| Prodromal event (n, %)   | 46       | 30(65.2)              | 16(51.6)             | 5.875  | 0.015ᵃ  |
| Fever (n, %)             | 51       | 36(70.6)              | 15(29.4)             | 1.990  | 0.158ᵃ  |
| Consciousness disturbance (n, %) | 37 | 24(64.9) | 13(35.1) | 4.376 | 0.036ᵃ |
| Movement disorder (n, %) | 82       | 60(73.2)              | 22(26.8)             | 2.353  | 0.125ᵃ  |
| Limb paralysis (n, %)    | 22       | 16(72.7)              | 6(27.3)              | 0.236  | 0.627ᵃ  |
| Ataxia (n, %)            | 39       | 30(76.9)              | 9(23.1)              | 0.003  | 0.958ᵃ  |
| Epilepsy (n, %)          | 77       | 60(77.9)              | 17(12.1)             | 0.254  | 0.614ᵃ  |
| Speech disorder (n, %)   | 85       | 61(71.8)              | 24(28.2)             | 5.487  | 0.019ᵃ  |
| Psychiatric symptom (n, %) | 98 | 74(75.5) | 24(24.5) | -      | 0.682 |
| Autonomic dysfunction (n, %) | 36 | 22(61.1) | 14(38.9) | 7.302  | 0.007ᵃ  |
| Sleep disorder (n, %)    | 82       | 61(74.4)              | 21(25.6)             | 0.988  | 0.320ᵃ  |

AED: antiepileptic drug; CSF: cerebrospinal fluid; EEG: electroencephalogram-graph; IVIG: intravenous immunoglobulin; MRI: magnetic resonance image; NMDAR: N-methyl-D-aspartate receptor; RTX: rituximab.

ᵃ: Pearson Chi-Square;ᵇ: Fisher's exact test
| Clinical characterstics | Total (n) | Good prognosis (n = 82) | Poor prognosis (n = 25) | \( t/Z/\chi^2 \) | \( p \)-value |
|--------------------------|-----------|-------------------------|------------------------|-----------------|-------------|
| Memory disorder (n, %)   | 33        | 24(72.7)                | 9(27.3)                | 0.407           | 0.523\(^a\) |
| CSF pleocytosis (n, %)   | 59        | 46(78.0)                | 13(22.0)               | 0.130           | 0.718\(^a\) |
| CSF protein increase (n, %) | 14    | 10(71.4)                | 4(28.6)                | -               | 0.735\(^b\) |
| CSF anti-NMDAR antibody titer \( \geq 100 \) (n, %) | 18       | 12(66.7)                | 6(33.3)                | -               | 0.357\(^b\) |
| Serum etiology positive (n, %) | 48    | 37(77.1)                | 11(22.9)               | 0.010           | 0.921\(^a\) |
| EEG with epilepsy charge (n, %) | 44    | 30(70.0)                | 14(30.0)               | 2.944           | 0.084\(^a\) |
| MRI changes (n, %)       | 39        | 25(64.1)                | 14(35.9)               | 5.383           | 0.020\(^a\) |
| Duration from onset to diagnosis (±14 days) (n, %) | 59       | 40(67.8)                | 19(32.2)               | 5.739           | 0.017\(^a\) |
| Hospital day (±30 days) (n, %) | 37   | 21(56.8)                | 16(43.2)               | 12.482          | 0.000\(^a\) |
| Relapse (n, %)           | 13        | 10(76.9)                | 3(42.9)                | -               | 1.000\(^b\) |
| Initial mRS(≥3) (n, %)   | 43        | 33(76.7)                | 10(23.3)               | 14.548          | 0.000\(^a\) |

AED: antiepileptic drug; CSF: cerebrospinal fluid; EEG: electroencephalogram-graph; IVIG: intravenous immunoglobulin; MRI: magnetic resonance image; NMDAR: N-methyl-D-aspartate receptor; RTX: rituximab.

\(^a\): Pearson Chi-Square; \(^b\): Fisher's exact test
Prognosis risk factors analysis was shown in Table 2 and Table 3. On univariate analysis, the factors associated with poor outcome were aged 3 years or younger, male, with prodromal event, consciousness disturbance, speech disorder, autonomic dysfunction, brain MRI changes, duration from onset to diagnosis longer than 14 days, initial mRS higher than 3 and RTX treatment (Table 2). On multivariate analysis, male, speech disorder, RTX treatment and initial mRS were independent risk factors associated with outcome (Table 3). While consciousness disturbance, anti-NMDAR antibody titer and relapse were not associated with outcome (Table 2).
Table 3
Multivariate analysis of factors associated with poor prognosis of pediatric anti-NMDAR encephalitis

| Variables                              | OR   | 95% CI          | P-value |
|----------------------------------------|------|-----------------|---------|
| Age ≤ 3 years                          | 6.157| 0.868–43.664    | 0.069   |
| Male                                   | 7.460| 1.390-40.000    | 0.019   |
| Prodromal event                        | 1.320| 0.218-8.000     | 0.716   |
| Consciousness disturbance              | 6.993| 0.834–58.823    | 0.073   |
| Speech disorder                        | 37.016| 1.390-985.928  | 0.031   |
| Autonomic dysfunction                  | 1.485| 0.304–7.264     | 0.625   |
| MRI change                             | 1.956| 0.384–9.963     | 0.419   |
| Duration from onset to diagnosis (≥14 days) | 1.175| 0.241–6.250     | 0.850   |
| RTX treatment                          | 13.214| 1.595-109.467  | 0.017   |
| Hospital day (≥30 days)                | 1.919| 0.390–9.434     | 0.423   |
| Initial mRS(≥3)                        | 13.522| 1.637-111.704  | 0.016   |

OR: odds ratio; CI: confidence intervals.

Clinical Comparisons Between Different Genders Of Patients

Besides onset age of boys was younger than girls mentioned above, we found differences of clinical features between them (summarized in Table 1). The ratio of fever in boys was higher than girls (58.0%, 29/50 vs 38.6%, 22/57, P = 0.045, Table 1). The median mRS after treatment of boys was 2 (IQR 1–2, ranging from 1 to 6, Table 1) which was higher than that of girls (2; IQR 1–2, ranging from 1 to 4, P = 0.036, Table 1). 82.0% (41/50) of boys needed 1 course of steroid treatment and 18.0% (9/50) needed 2 courses of steroid treatment. While for girls, 94.7% (54/57) of girls needed 1 course of steroid treatment and 5.3% (3/57) needed 2 courses of steroid treatment. Boys were more likely to need more course of steroid treatment (P = 0.037, Table 1). And the length of hospital day in boys was 28 days (IQR 22–39 days, ranging from 2 to 89 days) which was slightly longer than that of girls (26 days) (IQR 22–31 days, ranging from 12 to 59 days, P = 0.036, Table 1). However, there was no statistical difference of ratio of symptoms including consciousness disturbance, movement disorder, limb paralysis, ataxia, seizures, speech disorder, psychiatric symptoms, autonomic dysfunction, sleep disorder and memory disorder, laboratory findings including CSF pleocytosis, protein increase and anti-NDMAR titer, abnormal outcomes
of MRI, EEG with epilepsy discharge, initial mRS, RTX treatment, IVIG course and relapse between boys and girls (Table 1).

In total, boys presented different clinical features partially. Boys were more likely to occur onset at younger age and have fever, longer hospital day, higher mRS score after treatment and needed more course of steroid treatment compared with girls.

**Discussion**

Anti-NMDAR encephalitis is the most common type of autoimmune encephalitis[3]. Some clinical features are different between children and adult with anti-NMDAR encephalitis. And they may vary from regions and racial. Besides most published papers focused on adult patients. Our study focused on children with anti-NMDAR encephalitis and had relatively large cases in southern China to provide more practical information and guidance.

There were some differences in demographic data of patients comparing with the previous studies. According to previous studies, pediatric anti-NMDAR encephalitis in China and other countries was more common in children aged around 8–12 years[3, 12–16]. While in our study, the mean age at onset was 6.3 ± 3.1 years old which was slightly younger (See Additional file 1: Table S1). In addition, the onset age of boys in our study was younger than that of girls, which was different from the outcomes of UK and Thailand studies [13, 12]. These differences suggested that the demographics feature of age might range from regions and nations. The gender ratio in our study was 50:57 (male: female), which was similar to the outcomes of previous studies in Asia including studies from different regions of China in which the ratio of female ranged from 50–70% (See Additional file 1: Table S1)[17–19, 13, 15, 16, 14, 20]. While in studies from western country female was moderately predominate (higher than 70%)[10]. And the gender ratio was also various in different age, with the age increase, proportion of female patient increase[14, 20, 15]. One reason for the predominance of female is teratomas which are more common in female more than 14 years old[10]. Therefore, we presumed the dissimilarity of gender ratio in our patients was likely to racial, region and age differences.

Some common neurological and psychological symptoms are present in anti-NMDAR encephalitis. And symptoms presentation varied between children and adult. In our pediatric study, the proportion of seizures (39.2%, 42/107) among initial symptoms was similar to others’ studies, whereas the movement disorder (29.9%, 32/107) was more common than other studies and psychiatric symptoms (18.7%, 20/107) was less than other studies[17, 3, 10, 20, 16, 14, 15] (See Additional file 1: Table S1). The distribution of symptoms during whole course was similar to other studies[17, 3, 10, 20, 16, 14, 15].

The initial symptoms were various in the different age. Previous studies found that in adult and children older than 12 years old, psychiatric symptoms were the most common initial presentation[17, 10, 15, 14]. However, in children younger than 12 years old, the proportion of psychiatric symptoms at initial symptoms was nearly equal to that of seizures, but more common than that of movement disorder[10, 15, 21]. It remained unclear why there existed age differences on the initial symptoms of anti-NMDAR
encephalitis. In general speaking, the manifestation of anti-NMDAR encephalitis associated with NMDAR dysfunction in neurobiology. One hypothesis for explaining the anti-NMDAR clinical features is that psychiatric symptom which is more common in adults is caused by NMDAR hypofunction resulted from antibody mediated NMDAR internalized, while neurological symptoms like seizures and movement disorders as initial symptoms are caused by agonist effect of NMDAR, extrasynaptic NMDAR hyperfunction or neuronal network imbalance with impaired intraneuronal activity[6, 1]. Extrasynaptic NMDAR is more commonly in GluN1/2B, while synaptic NMDAR is more commonly in GluN1/2A[6]. And during development from juvenile to adult, NMDAR subunit switch from GluN2B to GluN2A[22]. In future, more researches about the NMDAR function network in physiology, disease during development need to do in order to elucidate the pathological mechanism of anti-NMDAR encephalitis.

The EEG abnormalities were not specific, and the proportion of EEG abnormalities was similar to other studies[23, 24, 8, 17]. Delta brush was relatively rare among the EEG examinations in current study, if compared to the EEG outcomes of Zhang et al study from north of China[16] (See Additional file 1: Table S1), which might be related to the time of EEG monitoring for patients. Though the MRI change of anti-NMDAR was non-specific, we found some abnormalities suggesting an association with other auto-antibodies, so called “antibody overlapping syndrome”. The outcomes of MRI scan in 7 cases in our previous studies showed the abnormal of multiple demyelination lesions, among which 5 cases having MOG antibody positive[11]. And among other 3 cases with MRI abnormalities of leptomeninges enhancement, one case had GFAP antibody positive.

Some patients with anti-NMDAR encephalitis have prodromal events. 48.6% of anti-NMDAR encephalitis patients in our study had prodromal events. 92.9% of these patients with prodromal events of intracranial infection was HSV encephalitis. Anti-NMDAR encephalitis is a major constitution of autoimmune encephalitis after HSV encephalitis and patients aged 4 years or younger are more likely to develop to autoimmune encephalitis after HSV encephalitis and develop movement disorder and worse condition, whereas older children develop behavioral and psychiatric manifestations predominated[9, 25, 15, 10]. The pathophysiology of anti-NMDAR encephalitis after HSV encephalitis is still unclear. In vitro model of the blood-brain barrier, HSV can reduce the cell-cell barrier resistance lead to a viability loss of the infected endothelial cells[26]. Blood-brain barrier disruption provides a convenient for entry of complement and other pro-inflammatory molecules. And complement may be involved in the pathological process of anti-NMDAR encephalitis and cause neuronal degeneration which is different from the other anti-NMDAR encephalitis[1, 27]. That's a hypothesis for why young children with anti-NMDAR encephalitis after HSV encephalitis are worse than others with classical encephalitis. Analysis of the prodromal events is helpful for further mechanism study of anti-NMDAR encephalitis.

The relapse rate of anti-NMDAR encephalitis ranges from 0.0–25%[15, 10, 20, 16, 14] (See Additional file 1: Table S1). And it was 12.1% in our study. The relapse rate may be associated with duration of follow-up. The fatality rate of anti-NMDAR encephalitis ranges from 0–12.5%[10, 28, 29, 20, 16, 14, 15] (See Additional file 1: Table S1). While it was 1.8% in current study, that was similar to studies from other region of China[20, 16, 14, 15], which ranged from 0.0–2.3% (See Additional file 1: Table S1), being
relatively low. A systematic review of reported cases which involved studies of pediatric and adult anti-NMDAR encephalitis showed that patients who died had an older onset age than patients who survived, and pediatric patients had a better outcome than the adult[17]. This might be an explanation for the lower fatality rate in our study and studies form other regions of China.

The ratio of patients with good prognosis in our study was 76.6% which similar to other study[30, 16, 10, 14, 12]. The predictors of poor outcome in previous study including decrease consciousness, speech disorder, longer hospital day, higher initial mRS, and treatment with RTX were consistent with the outcomes of our study[30, 16, 10, 14, 12, 31]. Byrne et al found the patients who recovered completely had shorter interval (15 days) between onset and initiation of treatment than that of those who did not recovered completely (21 days)[32]. Similarly, we found a longer duration (more than 14 days) served as a predictor of poor outcome, in consistent with the general value of “early treatment with good outcome”. Male, lesions in brain MRI and autonomic dysfunction served as predictors of poor outcome in our study, although previous study did not[30, 16, 10, 14, 12, 31]. We found patients aged 3 years or younger was a risk factor for outcome. The previous study involved both pediatric and adult anti-NMDAR encephalitis, found the younger age was a predictor of poor outcome[20], although the study only concentrating on pediatric patients did not found [16, 14, 12]. In our study, we found prodromal event was also associated with poor outcome that is rarely analyzed in previous studies. Prodromal events could play an important role in epigenetic change in patients. For now, epigenetic mechanisms for NMDAR receptor hypofunction in schizophrenia provided new insights into understanding of its neuropathophysiology and early interventions[22].

Besides boys occurred onset at younger age, we also found boys were more likely to have fever, longer hospital day, higher mRS score after treatment and needed more course of steroid treatment compared with girls. And male was an independent risk factor of poor outcome.

While no difference of initial mRS, level of CSF anti-NDMAR titer, ratio of abnormal MRI, initial mRS, RTX treatment and relapse between boys and girls was found. And these difference between boys and girls in our study might suggest though no difference of severity at initial onset, boys might more likely recover slower and have poor outcomes than girls. One study from UK which involved 31 pediatric patients with anti-NMDAR encephalitis also found partial phenotypes were different between girls and boys and boys were more likely to present predominant movement[13]. But in contrast to one study from Thailand which only involved 14 pediatric patients with anti-NMDAR encephalitis found that there was no difference of duration hospitalization between boys and girls and the ratio of fever in boys was tend to be higher than girls but this difference didn't have statistical significance and as a result, male was not a risk factor of poor outcome[12]. The difference of results between ours and other study might be caused by the sample size. And the sample size in our study was relatively large.

Conclusions
Of pediatric anti-NMDAR encephalitis in southern China: the mean onset age was about 6-year-old, earlier in boys; boys remained slower to recover and with a worse prognosis; the most common respective symptom at onset and during whole course was seizures and psychiatric symptoms; combination with tumor was rare; most patients respond well to the immunotherapy; relapse and fatality rate were relatively low; some independent risk factors associated with the outcomes; most patients had a good prognosis.

**Abbreviations**

AED: antiepileptic drug; AQP4:aquaporin-4; BAEP:brainstem auditory evoked potential; CSF:cerebrospinal fluid; CRP:C-reactive protein; GFAP:glial fibrillary acidic protein; IVIG:intravenous immunoglobulin; IVMP:intravenous methylprednisolone; mRS:Modified Rankin Scale; MOG:myelin oligodendrocyte glycoprotein; NMDAR:N-methyl-D-aspartate receptor; RTX: rituximab; HSV:serum herpes simplex virus; VEP:visual evoked potential.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (2019052419364384).

**Consent for publication**

Written and signed consents were obtained from the patients’ parent or legal guardian. The patients’ parent or legal guardian explicitly consent to publish their children personal details, clinical details and associated figures of themselves which could identify them.

**Availability of data and materials**

The datasets generated or analyzed during the current study are not publicly available due the data repository in our hospital is still under construction but are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**
WXC: conceived and designed, provided critical revision of the manuscript for important intellectual content, and study supervision; XJL: initiated and designed, performed the clinical investigation, and drafted the manuscript; CH: performed the clinical investigations and data collection, and drafted the manuscript; WLW: collected and analyzed the clinical data, and drafted the manuscript; HCL: performed the clinical investigation and provided critical revision of the manuscript for important intellectual content; KLZ, YNZ, HXZ, YT, YYG, BWP, SDY and HSL: performed clinical investigation and data collection; LFC, YRZ, and YTL: performed the follow-up investigation and data collection; XYW and SYN: performed the follow-up investigation and analyzed the EEG results. All authors were involved in revising the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Distribution of mRS scores at initial, after treatment and at last follow-up.

Supplementary Files

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