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Anti-*N*-methyl-D-aspartate receptor encephalitis in children of Central South China: Clinical features, treatment, influencing factors, and outcomes

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ABSTRACT

Background and purpose: We analyzed the clinical manifestations of children with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in Central South China and the factors influencing the effectiveness of treatment.

Methods: A retrospective study of children (0–14 years old) with anti-NMDAR encephalitis in Central South China was carried out from March 2014 to November 2016. Demographics, clinical features, treatment, outcome, and the factors influencing the effectiveness of treatment were reviewed.

Results: Fifty-one patients with anti-NMDAR encephalitis were enrolled (age from 4 months to 14 years old; median age, 8 years; 30 females). Forty-five patients (88%) presented with psychiatric symptoms, 40 (78%) with dyskinesia and movement disorders, 39 (77%) with sleep disturbances, 34 (67%) with seizures, 30 (59%) with a decreased level of consciousness (Glasgow score < 15), 28 (55%) with speech disturbances, and twelve (24%) with autonomic instability. None presented with hypoventilation, and only one patient (female, 14 years old) had an ovarian teratoma. All patients received first-line immunotherapy, 25 patients both received firstline and second-line immunotherapy. Forty-four of the 51 patients achieved good outcomes (score on the modified Rankin Scale [mRS] of 0–2), while the other seven had poor outcomes (mRS score of 3–5).

Conclusions: This study investigated the clinical characteristics of children (aged 14 or younger) with anti-NMDAR encephalitis in Central South China. Patients with decreased consciousness, PICU stay and autonomic instability were more likely to have no or limited response to first-line immunotherapy and to require second-line or even more aggressive immunotherapy. Children with anti-NMDAR encephalitis in China have a much lower incidence of tumors, lower mortality rates, and a lower proportion of lethal autonomic instability than adults.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an IgG antibody-mediated diffuse encephalitis, in which the antibody specifically binds with the NR1 subunit of the NMDA receptor (Dalmau et al., 2011; Mikasova et al., 2012). In 2005, Vitaliani et al. (2005) were the first to report on four women with teratomas who presented with prominent psychiatric symptoms and memory loss. In 2007, Dalmau et al. (2007) found the specific anti-NMDA receptor in the cerebrospinal fluid of eight similar patients, and formally proposed the concept of anti-NMDAR encephalitis.

About 38% of patients with anti-NMDAR encephalitis (Titulaer et al., 2013) have an underlying tumor (ovarian or testicular teratoma). Paraneoplastic cases are less common in children than in adults. The younger the child, the less likely he or she is to have an underlying tumor (Armangue et al., 2013). The major clinical manifestations of this disease include psychiatric symptoms, behavioral symptoms, seizures, memory deficits, decreased consciousness, dyskinesia, autonomic instability, and hypoventilation (Brenton and Goodkin, 2016). The overall prognosis is good, with 80% of patients fully recovered or left with a slight disability if treatment is administered within two years of onset (Titulaer et al., 2013). The reported mortality rate is 8–10% (Dalmau et al., 2008; Lebas et al., 2010). Since its discovery, more and more cases of anti-NMDAR encephalitis have been reported in many

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countries, including China. And > 400 cases involving children have been reported.

Our study is now the largest to date on children with anti-NMDAR encephalitis in China. The purpose of our study is to provide a summary of the clinical features, series of symptoms, laboratory and neuroimaging findings, treatments, and outcomes in children with anti-NMDAR encephalitis.

2. Material and methods

This retrospective study examines patients aged 14 or younger with positive anti-NMDAR antibodies in their cerebrospinal fluid (CSF). These patients were admitted to Xiangya Hospital of Central South University between March 2014 and November 2016. All patients were also tested for anti-NMDAR antibodies in serum. All patients (with or without positive serum tests) were included, regardless of the severity of clinical symptoms, and patients with less than one month of follow-up duration were excluded.

The serum and CSF samples of each patient were sent to Oumeng Biotechnology Corporation, Beijing, China, or Xiangya Hospital of Central South University, China, for the antibodies against the NMDA receptor. All samples were evaluated for anti-NMDAR immunoglobulin G antibodies by indirect immunofluorescence using EU 90 cells transfected with the NMDAR1 subunit (NR1) of the NMDAR complex and immobilized on BIOCHIPs (Euroimmun AG, Lubek, Germany) (Fig. 1).

Symptoms were categorized into the following eight groups based on previously reported manifestations: psychiatric symptoms, seizures, speech disturbance, sleep disturbance, dyskinesia and movement disorders, loss of consciousness, memory deficit, and autonomic instability. Clinical data including age, gender, prodromal symptoms, clinical symptoms, brain magnetic resonance imaging (MRI), CSF examinations, electroencephalography (EEG), contrast-enhanced computed tomography screening for systemic neoplasms, and treatment were reviewed. First-line immunotherapy included intravenous (IV) methylprednisolone or intravenous immunoglobulins (IVIG), or a combination of these. The use of rituximab or cyclophosphamide was defined as second-line immunotherapy (Titulaer et al., 2013). Oral immunosuppressants (including azathioprine, mycophenolate mofetil and cyclosporine A) and/or intrathecal treatment with methotrexate and methylprednisolone were considered as third-line immunotherapy. The modified Rankin Scale (mRS) was used to evaluate the effectiveness of treatment and outcomes at 14 days and every three months after the end of first-line immunotherapy, and 1 month after every session of second-line immunotherapy. The patients were described as having a full recovery with a mRS score of 0; mild deficit with mRS scores of 1–2; severe deficit with mRS scores of 3–5; or dead with an mRS score of 6. Good and poor functional outcomes were defined as mRS scores of 0–2 and 3–6, respectively.

The treatment strategy was switched to second-line immunotherapy if there are no signs of clinical improvement at 14 days after first-line immunotherapy. Patients were subdivided into two subgroups: one group who accepted only first-line immunotherapy, and another group who accepted both first-line and second-line immunotherapy. The following five categorical variables were analyzed between the two groups: gender, clinical symptoms (including prodromal symptoms, fever within three weeks of onset, psychiatric symptoms, seizures, speech disturbances, sleep disturbances, dyskinesia and movement disorders, decreased consciousness, and autonomic instability), abnormal CSF results, abnormal EEG findings, and abnormal MRI findings. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables such as age, interval from symptom onset to definitive diagnosis, and interval from first-line immunotherapy to full recovery were analyzed with an independent *t*-test. Categorical variables were analyzed with Fisher's exact test, while ordinal variables were analyzed with Fisher Freeman Halton test. *P* values < 0.05 (two-sided) were considered significant.

3. Results

3.1. Clinical characteristics

Fifty-one patients were reviewed, and 37 patients were under 12 years old when onset. Antibodies were tested in both the serum and CSF of all patients. Beside CSF positive, 31 of the 51 children had positive serum tests. Table 1 and Fig. 2 summarize the demographic and clinical characteristics of those groups.

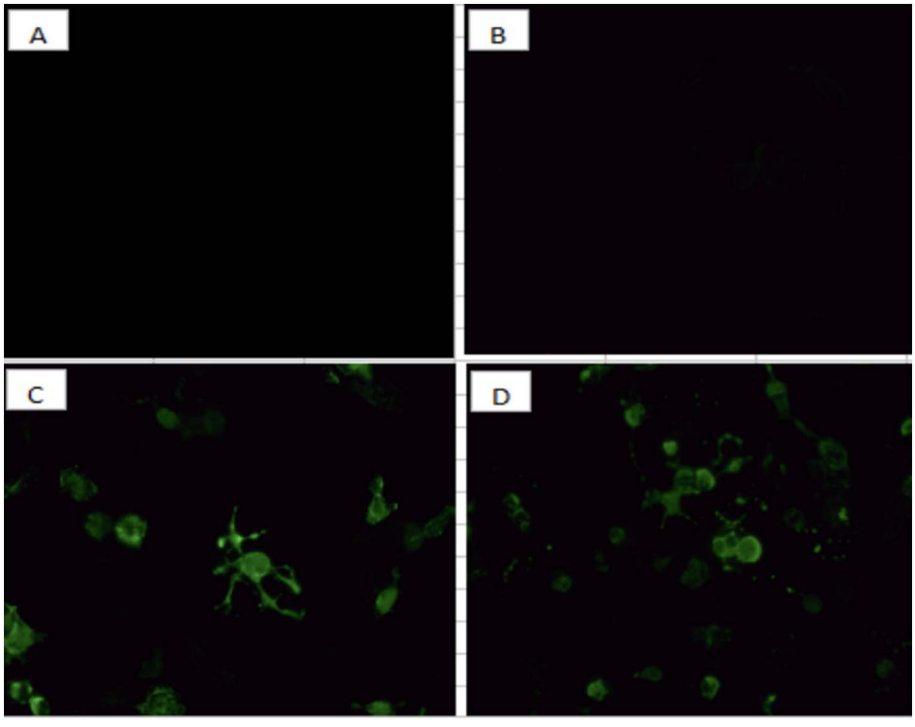

Fig. 1. The biological results of the anti-NMDAR antibodies in CSF Antibodies negative (A). Antibodies Positive + (B). Antibodied positive + + (C). Antibodied Positive + + + (D).

Table 1
Demographic and clinical characteristics of patients.

Item	All patients (%)	Age under 12 (%)
Number	51	37
Female:male	30:21	21:16
Median age, range (years)	8, 0.33–14	7, 0.33–11
Initial symptoms		
Psychiatric	26 (51%)	18 (49%)
Seizure	14 (27%)	10 (27%)
Others	11 (22%)	9 (24%)

In all of the 51 patients, thirty children were female (59%), and twenty-one of them were male (41%), ranging from 4 months to 14 years old (median age, 8 years). Twenty-six patients (51%) had prodromal symptoms such as headache, vomiting, viral-like symptoms, or falling down. Fifteen patients (29%) experienced a fever within three weeks before onset. The most common clinical manifestations were psychiatric symptoms (n = 45, 88%). Dyskinesia and movement disorders were experienced by 40 patients (78%). Thirty-nine cases (77%) displayed with sleep disturbances. Thirty-four patients (67%) had seizures. Thirty patients (59%) demonstrated a decreased level of consciousness. Twenty-eight patients (55%) developed speech disturbances. Twelve patients (24%) suffered from with autonomic instability, among which three with bradycardia, four with tachycardia, one with both tachycardia and low blood pressure, three with long-term fever, and one with abnormal erection. None of them presented with hypoventilation. Only one patient (female, 14 years old) had an accompanying tumor (teratoma). 26 out of 51 patients initially presented with psychiatric symptoms, while 14 initially presented with seizure. Forty-five patients (88%) developed at least three of the eight categories of symptoms.

It was the same trend in group of patients under 12 years old, which were shown in Table 1 and Fig. 2. 18 patients initially presented with psychiatric symptoms, and 10 initially presented with seizure.

3.2. Ancillary examination

Initial brain MRI, EEG, and CSF findings after onset are showed in Table 2. Eighteen out of 50 (36%) patients had abnormal brain MRIs, the abnormal findings included the following: fourteen with increased signal upon brain MRI T2-weighted or fluid-attenuated inversion recovery (two in frontal cortex, two in frontal lobe, two in basal ganglia, two in thalamus, one in temporal lobes, one in cerebellum, two in frontal cortex, cerebellum and temporal lobes, one in frontal lobe, thalamus, basal ganglia and caudex cerebri, one in frontal lobe, temporal lobe, parietal lobe and basal ganglia), two with encephalomalacia (one in frontal lobe, one in temporal lobe), one with increased signal upon T2-weighted and contrast enhancement in temporal lobe, insular lobe, occipital lobe and basal ganglia,

one with contrast enhancement in meninges. 44 out of 51 patients had abnormal EEGs. Thirty-six of these patients had diffuse background slow wave (delta or theta) activity and/or generalized or predominantly frontotemporal slow activity, three displayed with epileptic discharges, and five displayed with both slow activity and epileptic activity. Initial CSF examinations were available for 49 patients. Six patients had CSF pleocytosis only, seven had increased intracranial pressure (> 180 mm H_2O) only, two patients had both pleocytosis and intracranial pressure, four had both pleocytosis and increased protein concentration, and two patients had all three conditions.

Table 2
Results of ancillary examinations.

Examination	All patients
Brain MRI (information from 50 patients)	Numbers (%)
Total abnormal findings	18 (36%)
EEG (information from 51 patients)	
Total abnormal findings	44 (86.3%)
Slow activity	36
Epileptic activity	3
Slow activity and epileptic activity	5
CSF (information from 49 patients)	
Total abnormal findings	21 (42.9%)
Pleocytosis	14
Increased intracranial pressure	11
Increased protein concentration	5

3.3. Treatment and outcome

All of 51 patients received immunotherapy treatment. Table 3, Figs. 3 and 4 show the treatment and outcome. Three patients were treated exclusively with intravenous methylprednisolone (15–30 mg/kg per day for 5 days). Twenty-three patients were treated with both intravenous methylprednisolone and intravenous immunoglobulin (IVIG, 0.4 g/kg per day for 5 days). Twenty-four patients received a combination treatment of intravenous methylprednisolone, intravenous immunoglobulin, and a second-line therapy (seven with rituximab, eleven with cyclophosphamide, and six with both rituximab and cyclophosphamide). One patient whose second-line therapy failed took oral azathioprine as a third-line immunotherapy. Only one patient had a teratoma and underwent a tumor resection. The mean interval between onset and diagnosis was 30.4 days, ranging from 2 to 170 days. The mean follow-up period was 16.1 months, ranging from 1 to 47.8 months. The median mRS score before immunotherapy was 4, and was 3 at 14 days after initial immunotherapy. By the last follow-up, thirty-four patients (67%) had fully recovered. The mean time until full recovery was 4 months (ranging from 0.9–12 months). Ten patients (20%) had mild deficits, seven patients (14%) had severe deficits, only one patient relapsed, and there were no deaths. Deficits included speech disturbances (n = 8), movement disorders (n = 4), mood regulation disorders (n = 2), psychiatric symptoms (n = 1), memory deficits (n = 4), seizures (n = 3), and hypertonia (n = 1).

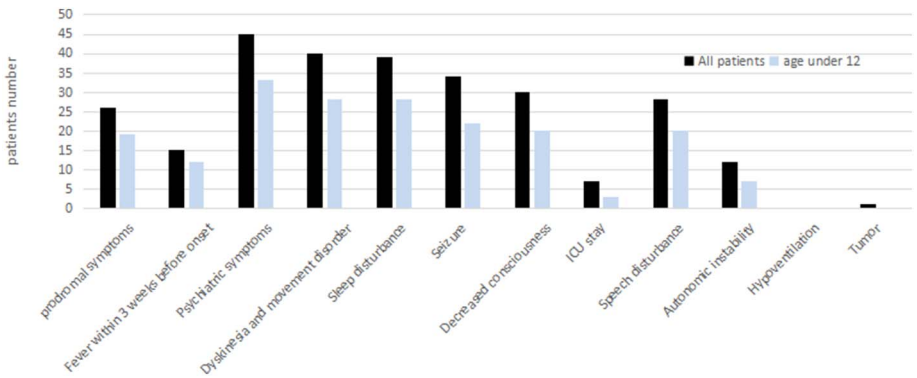

Fig. 2. Clinical features of this study.

Table 3
Treatment and outcome.

Item	All patients (%)	Age under 12 (%)
First-line immunotherapy	51 (100%)	37 (100%)
Intravenous immunoglobulin	48 (94%)	35 (95%)
Intravenous methylprednisolone*	51 (100%)	37 (100%)
Tumor resection	1	0
Second-line immunotherapy	25 (59%)	17 (46%)
Cyclophosphamide	18 (35%)	12 (32%)
Rituximab	14 (28%)	9 (24%)
Third-line immunotherapy	1 (2%)	1 (3%)
PICU stay	7 (14%)	3 (8%)
Median mRS before immunotherapy	4	4
Median mRS at 14 days after first-line immunotherapy	3	3
Mean interval between onset and diagnosis, range (days)	30.4, 2–170	35, 2–170
Mean interval between onset and treatment, range (days)	28.8, 5–171	33.2, 5–171
Mean follow-up duration, range (months)	16.1, 1–47.8	17.5, 1–47.8
Outcome		
Full recovery	34 (67%)	25 (68%)
Mild deficits	10 (20%)	9 (24%)
Severe deficits	7 (14%)	3 (8%)
Relapses	1 (2%)	1 (3%)
Death	0	0
Mean time until full recovery, range (months)	4, 0.9–12	4.3, 0.9–12

* Two patients were treated with oral prednisolone.

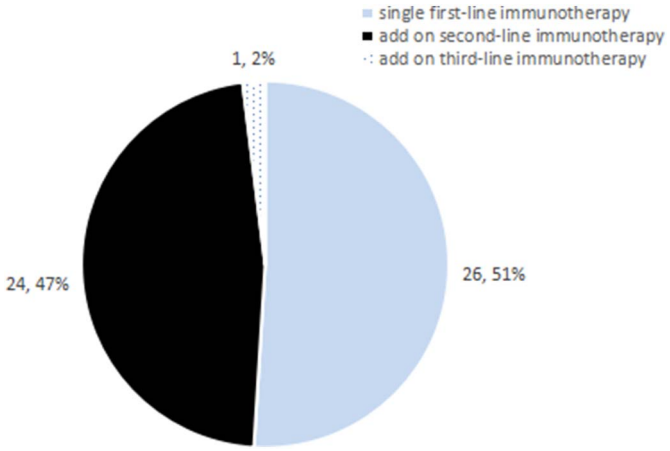

Fig. 3. Treatment of patients in this study.

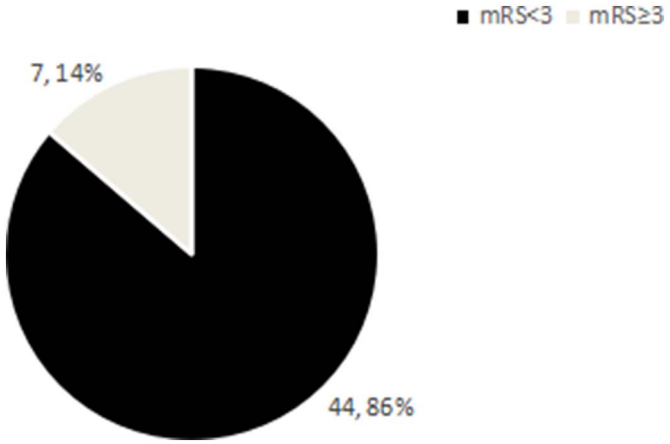

Fig. 4. Outcome of patients in this study.

It was almost the same situations in patients under 12 years old. By the last follow-up, twenty-five patients (68%) had fully recovered, nine patients (24%) had mild deficits, three patients (8%) had severe deficits, only one patient relapsed, and no deaths.

3.4. Comparison between patients who received only first-line immunotherapy and those who received both first-line and second-line immunotherapy

Table 4 compares the two groups. Twenty-two of the 25 patients who received both first-line and second-line immunotherapy displayed decreased consciousness, compared to only eight of the 26 patients in the first-line immunotherapy group ($p < 0.0005$, Table 4). Seven patients used to stay in PICU in both first-line and second-line immunotherapy group, and none in the first-line immunotherapy group ($p = 0.004$, Table 4). Ten patients suffered from autonomic instability in patients who received both first-line and second-line immunotherapy, compared to 3 out of 26 patients in the first-line immunotherapy group ($p = 0.027$, Table 4). The median initial mRS scores were 3 and 4, respectively, which is a significant difference ($p = 0.001$, Table 4). The mean age, interval between onset and diagnosis, gender frequency, and other symptoms (including prodromal symptoms, fever within three weeks before onset, psychiatric symptoms, seizures, speech disturbances, sleep disturbances, movement disorders, and the frequency of abnormal brain MRI findings, abnormal EEG findings, and abnormal CSF findings) were not significantly different between the two groups.

3.5. Comparison between the good outcome and poor outcome groups

Table 5 compares the good outcome and poor outcome groups. Five patients were used to stay in PICU in the poor outcome group, and 2 in the good outcome group ($p < 0.0005$, Table 5). The mean age, the mean interval between onset and diagnosis, gender frequency, the median initial mRS and other symptoms (including prodromal symptoms, fever within three weeks before onset, psychiatric symptoms, seizures, speech disturbances, sleep disturbances, movement disorders, autonomic instability, and the frequency of abnormal brain MRI findings, abnormal EEG findings, and abnormal CSF findings) were not significantly different between the two groups.

3.6. Comparison between patients initially presenting with psychiatric symptoms and those initially presenting with seizure

Table 6 shows the comparison between patients initially presenting with psychiatric symptoms and those initially presenting with seizure. The mean age, the mean interval between onset and diagnosis, gender frequency, frequency of PICU stay and other symptoms (including prodromal symptoms, fever within three weeks before onset, psychiatric symptoms, seizures, speech disturbances, sleep disturbances, movement disorders, autonomic instability, and the frequency of abnormal brain MRI findings, abnormal EEG findings, and abnormal CSF findings) were not significantly different between the two groups.

3.7. A special case

The youngest patient at the time of presentation was 0.33 years old (4 months). He initially presented with fever and seizures, then developed involuntary movement and mental regression including not chasing light or objects, no eye contact, and no communication with others. He was definitively diagnosed with anti-NMDAR encephalitis 55 days after onset, with positive anti-NMDAR antibodies (++) in both CSF and serum. He was treated with methylprednisolone and intravenous immunoglobulin, but had no response to this first-line therapy. Treatment was shifted to rituximab (once a week, for four weeks), cyclophosphamide (once a month, for seven months), and

Table 4
Comparison between patients (all patients) who only received first-line immunotherapy and those who received both first-line and second-line immunotherapy.

Item	Only first-line immunotherapy	Both first-line and second-line immunotherapy	*P* value
n	26	25	
Speech disturbance	14	14	1.00[a]
Seizure	17	17	1.00[a]
Dyskinesia and movement disorder	20	20	1.00[a]
Abnormal EEG findings	22	22	1.00[a]
Mean interval between onset and diagnosis (days)	31.4	29.4	0.81[b]
Mean age (years)	8.42	8.76	0.72[b]
Mean interval between onset and treatment (days)	30.4	27.1	0.69[b]
Psychiatric symptoms	22	23	0.67[a]
Prodromal symptoms	12	14	0.59[a]
Abnormal brain MRI findings	8	10	0.58[a]
Fever within 3 weeks before onset	6	9	0.37[a]
Sleep disturbance	16	19	0.21[a]
Abnormal CSF findings	9	12	0.22[a]
Female:male	18:8	12:13	0.11[a]
PICU stay	0	7	0.004[a]
Autonomic instability	3	10	0.027[a]
Decreased consciousness	8	22	< 0.0005[a]
Median initial mRS	3	4	0.001[c]

[a] *p* value obtained by Fisher's exact test.
[b] *p* value obtained by independent *t*-test.
[c] *p* value obtained by Fisher Freeman Halton test.

Table 5
Comparison between good outcome group and poor outcome group.

Item	Good outcome	Poor outcome	*P* value*
Patient number	44	7	–
Psychiatric symptoms	39	6	1.00[a]
Dyskinesia and movement disorder	34	6	1.00[a]
Sleep disturbance	33	6	1.00[a]
Seizure	29	5	1.00[a]
Autonomic instability	11	2	1.00[a]
Abnormal CSF findings	18	3	1.00[a]
Abnormal brain MRI findings	15	3	1.00[a]
Mean age (years)	8.55	8.83	0.83[b]
Median initial mRS	3.5	4.5	0.50[c]
Mean interval between onset and diagnosis (days)	29.2	37.4	0.47[b]
Mean interval between onset and treatment (days)	27.5	37.1	0.42[b]
Prodromal symptoms	21	5	0.42[a]
Abnormal EEG findings	37	7	0.38[a]
Decreased consciousness	24	6	0.22[a]
Fever within 3 weeks before onset	11	4	0.19[a]
Speech disturbance	22	6	0.09[a]
Female:male	28:16	2:5	0.09[a]
PICU stay	2	5	< 0.0005[a]

[a] p value obtained by Fisher's exact test.
[b] p value obtained by independent *t*-test.
[c] p value obtained by Fisher Freeman Halton test.
* Because of multiple comparisons, the level of significance was adjusted to $p < 0.003$ by Bonferroni correction: aadjusted = a/c, where a is the overall experiment-wise alpha (0.05) and c is the number of comparisons made (18).

Table 6
Comparison between patients initially presenting with psychiatric symptoms and those initially presenting with seizure.

Item	Psychiatric symptoms as initial sign	Seizure as initial sign	*P* value
Patient number	26	14	–
Mean age (years)	8.5	9.1	0.613
Female:male	14:12	8:6	0.554
Prodromal symptoms	14	7	0.539
Fever within 3 weeks before onset	8	4	0.591
Dyskinesia and movement disorder	21	9	0.220
Sleep disturbance	20	12	0.412
Decreased consciousness	16	9	0.571
Speech disturbance	16	7	0.571
Autonomic instability	5	6	0.111
Abnormal CSF findings	12	4	0.171
Abnormal brain MRI findings	8	7	0.221
Abnormal EEG findings	22	13	0.418
Mean interval between onset and diagnosis (days)	30.5	31.5	0.924
Mean interval between onset and treatment (days)	28.9	32	0.761
Median initial mRS	3.5	4.0	0.219
PICU stay	6	1	0.208

intravenous immunoglobulin (1–2 g/kg per month, for six months) as second-line immunotherapy, after those therapies he chased light or objects, but antibodies were also positive (++) in both CSF and serum. He was then treated with oral azathioprine (10 mg/d) as third-line immunotherapy in 10 months after onset. When one year and four months after onset, and he had already been taking oral azathioprine for more than five months, he was able to sit on a seat steadily with assistance, smile, and have a little eye-contact with his parents but unable to speak (mRS score of 5). We carried out intrathecal treatment with methotrexate and dexamethasone for him then. After three rounds of intrathecal treatment, he was able to sit on a seat steadily by himself, and stand up with assistance, but still had involuntary body movement (mRS of 4). Four times of brain MRIs showed no specific change but enlargement of the extracerebral gap. Several EEG examinations showed slow activity and/or epileptic activity.

4. Discussion

Our study is the largest of its kind in China, focusing on children with anti-NMDAR encephalitis. There was no gender difference in this sample, which is similar to a previous report on adult-onset anti-NMDAR encephalitis in Korea (Lim et al., 2014). Only one of our 51 patients (1.9%) had a neoplasm, which is similar to the research in France (one death) (Zekeridou et al., 2015), while is a much lower incidence than previously reported in America (38%) (Titulaer et al., 2013), Korea (9%) (Lim et al., 2014), and China (8%) (Wang et al., 2016). Previous reports shown that the prevalence of tumors in anti-NMDAR encephalitis is associated with age, gender, and race (Dalmau et al., 2008; Florance et al., 2009). The prevalence of teratomas in

females over 18 years old was 56%, but only 31% in females under 18 years old, and only 9% in females under 14 years old (Dalmau et al., 2011). In short, the younger the age, the lower the incidence of teratomas. There was only one female patient with tumor, which was similar to previous studies. Given the low rate of tumors in younger patients, routine radiologic screening for systemic neoplasms in children under 12 years old needs more supporting evidence (Frawley et al., 2012; Li and Zhao, 2015). Previous researchers have found that suggesting that race, human leukocyte antigen, or other genetic factors may contribute to susceptibility to anti-NMDAR encephalitis (Kayser et al., 2013; Titulaer et al., 2013; Verhelst et al., 2011).

The most common clinical features of children with anti-NMDAR encephalitis in our study were psychiatric symptoms, speech disturbances, seizures, sleep disturbances, loss of consciousness, and movement disorders. Younger children typically initially present seizures, abnormal movements and focal neurologic symptoms, whereas adolescents more often present with psychiatric symptoms, but the progression of symptoms evolves toward a similar course (Brenton and Goodkin, 2016). Most patients (78.4%) initially presented with psychiatric symptoms and seizures, which aligns with previous findings (Armangue et al., 2013; Haberlandt et al., 2017). Twelve out of 51 children were too young (under six years old) to make an objective judgment about memory deficit. This is unfortunate, as memory deficit is an independent factor associated with poor outcome (Wang et al., 2016). In our study, twelve patients (23.5%) demonstrated autonomic instability (presenting with tachycardia, bradycardia, hypotension, hyperthermia, and abnormal erection). Other studies on anti-NMDAR encephalitis that include adult patients report higher incidences of autonomic instability. Titulaer et al. (2013)) reported that 37%–48% of patients displayed autonomic symptoms. In a study by Florance et al. (2009)), 86% of patients displayed autonomic instability (predominantly tachycardia, hyperthermia, and hypertension). Fifteen out of 40 patients (37.5%), and 14 out of 51 patients (28%) displayed autonomic symptoms in Korea (Lim et al., 2014) and China (Wang et al., 2016), respectively. These results indicate that children with anti-NMDAR encephalitis develop fewer autonomic symptoms than adults. There were no cases with hypoventilation and no patient needed respiratory support in our study, compared to 23% in Philadelphia (32 of 73 patients aged 18 or younger) (Florance et al., 2009), 28% in Korea (all adult patients) (Lim et al., 2014), and 25.5% in southwest China (10 of 51 patients under 14 years old at the time of presentation) (Wang et al., 2016), but most of those conditions were occurred in adults. The mortality rate in these studies was 8–10%, and the most common causes of death were sepsis, sudden cardiac arrest, acute respiratory distress, refractory status epilepticus, and disease progression (associated with autonomic symptoms or lack of treatment). There was no death in our study, which was in line with previous studies, as the death rate in young children was also lower (2.7%) in the largest pediatric study to date (Titulaer et al., 2013). Lower death rate is perhaps associated with the lower proportion of autonomic instability and hypoventilation. However, further studies with larger samples are required to confirm this hypothesis. Previous literatures demonstrated that the first sign is different according the age and the sex of the patients, more neurological symptoms in children and more psychiatric in adults (Titulaer et al., 2013), autonomic dysfunction was more frequent in females than in males (Zekeridou et al., 2015), female patients more frequently initially present with psychiatric disorder but male patients more frequently initially present with seizure (Wang et al., 2016). There were no such differences in our study.

The youngest patient in our study was 0.33 years old (4 months), compared with 0.7 years (Titulaer et al., 2013), neonates (Jagota et al., 2014; Hilderink et al., 2015), and 2 months old (Armangue et al., 2012) in previous reports. The anti-ANMDR antibodies of the patient remained positive (++) in CSF in the last follow-up (one year and six months). He had received six rounds of intrathecal treatment, and made some improvements gradually, including walking by assistance, turning over and siting on, grabbing toys steadily and pronouncing “Mum and Dad”. Lack of specific initial symptoms in such a young patient led to misdiagnosis at the first time of admission. And it's a challenge when second-line immunotherapy fails, because there is no clear treatment strategy at that point. Long term follow-up and further research are necessary. In addition, studies show that it takes a long time to recover from anti-NMDAR encephalitis. 75–81% of patients have a good outcome (mRS of 0–2) (Houtrow et al., 2012; Titulaer et al., 2013) within two years of onset, while some patients take a longer time to recover (Iizuka et al., 2010). The duration of disease with this patient was less than two years, so it was difficult to determine whether to perform more intensive immunosuppressive therapy or maintain the current treatment and wait for natural improvement.

In previous studies, the predictors of good outcome were early treatment and lack of ICU admission (Titulaer et al., 2013), while the predictors of poor outcome were younger age, decreased consciousness and memory deficit (Titulaer et al., 2013; Lim et al., 2014). In our study, PICU stay was a predictor of poor outcome, which was agreed with previous research, while younger age and decreased consciousness didn't predict a poor outcome in our study, but larger-scale studies are needed, considering the data bias due to the small number of cases. The frequency of decreased consciousness, PICU stay and autonomic instability were significantly different between patients who only received first-line immunotherapy and those who received both first-line and second-line immunotherapy. This result suggested that patients with decreased consciousness, PICU stay or autonomic instability are more likely to have no or limited response to first-line immunotherapy and to require second-line immunotherapy, which echoes previous findings. In our study, more than half of the children (60%) achieved full recovery by the last follow-up. Four of the 19 patients with second-line immunotherapy achieved full recovery. Ten of these patients were left with a mild deficit, while five had a severe deficit, which aligns with previous studies (Armangue et al., 2012).

Relapses were defined as new onset of symptoms, or worsening of symptoms after at least 2 months of improvement or stabilization. Our study had a relatively short follow-up period (16.1 months on average, ranging from 1 to 47.8 months) and only one patient experienced relapse, whom was an 11-year-old female. This patient fully recovered in 26 days after receiving intravenous ethylprednisolone and IVIG, but along with seizure, psychiatric symptoms, movement disorder and memory deficit again five months after treatment. Titulaer et al. followed their anti-NMDAR encephalitis patients for a median duration of 24 months and 7.8% of patients in that study experienced one or more clinical relapses. During the first 24 months, three patients relapsed in France (Zekeridou et al., 2015). We could not evaluate the probability of relapse in our study due to our comparatively short follow-up period.

In conclusion, our study demonstrates that patients with decreased consciousness, autonomic instability and PICU stay are more likely to need intensive immunosuppressive therapy. Children with anti-NMDAR encephalitis in Central South China have a lower incidence of tumors, a better prognosis, and a lower mortality rate than adults. But there are several challenges to treating anti-NMDAR encephalitis. For example, when there is no significant improvement with active immunotherapy within two years of onset, do we wait for natural improvement or pursue aggressive immunotherapy? The answer to this and other questions lies in further research.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

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