ORIGINAL ARTICLE

Anti-NMDA receptor encephalitis: clinical characteristics, predictors of outcome and the knowledge gap in southwest China

W. Wang, J.-M. Li, F.-Y. Hu, R. Wang, Z. Hong, L. He and D. Zhou

Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

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Background and purpose: The aim was to analyse the clinical profiles and outcomes of patients with anti- *N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in China.

Methods: A retrospective study of anti-NMDAR encephalitis in China was performed between June 2011 and June 2014. The clinical characteristics and predictors of poor outcome were determined.

Results: A total of 51 patients with a definitive diagnosis of anti-NMDAR encephalitis were included in this study. Four of them were surgically confirmed to have a neoplasm. Thirty-two patients, amongst whom 24 were female, presented with psychiatric disorder as the initial symptom, whereas 14 patients, of whom nine were male, presented with seizure as the initial symptom ($P = 0.011$). Twenty-nine patients (56.86%) were initially misdiagnosed with psychosis, viral encephalitis or other diseases, and 58.8% of the patients experienced at least one type of complication. It typically took 3 weeks before these patients were admitted to our hospital and another 2 weeks before the correct diagnosis was made. Forty-one patients (80%) reached a good outcome; 10 patients (20%) had a poor outcome. Older age, extended hospital stay, memory deficits, decreased consciousness, central hypoventilation, complications and abnormal cerebrospinal fluid results were associated with poor outcome ($P < 0.05$).

Conclusions: Female patients more frequently initially present with psychiatric disorder but male patients more frequently initially present with seizure. Patients with anti-NMDAR encephalitis in China have a lower incidence of neoplasm. Nevertheless, this study reveals several challenges in treating anti-NMDAR encephalitis in China that may contribute to poor outcome.

Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder in which high levels of intrathecally synthesized antibodies are directed against the NR1 subunit of the NMDA receptor; this disorder results in a mortality rate of 8%–10% [1]. A previous study found that approximately 90% of patients with this severe disorder are women, and the clinical symptoms typically include psychiatric symptoms, seizures, memory problems, decreased consciousness, dyskinesia, autonomic instability and hypoventilation [1]. Recently, a French group found that adult female patients infrequently exhibited seizures as the first symptom; instead, these patients presented with a clinical pattern of generalized seizures and rapidly developing behavioural and psychiatric symptoms [2].

To date, more than 600 cases of anti-NMDAR encephalitis have been reported in the USA, Japan, Korea and European countries [3–7], and previous reports have indicated differences between countries and races [8]. However, very few cases have been reported in China, and the clinical characteristics of Chinese anti-NMDAR encephalitis patients are

Correspondence: Jin-Mei Li and Dong Zhou, 37th Guoxuexiang Road, Chengdu 610041, China (tel.: +86 28 85423038; fax: +86 28 85423550; e-mails: 27298177@qq.com; zhoudong66@yahoo.de).

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unclear. Additionally, the suboptimal management of anti-NMDAR encephalitis patients in China is associated with barriers such as delays in diagnosis and transportation to specialized centres, as well as economic affordability. Therefore, this retrospective study was conducted to analyse the clinical profile of patients with anti-NMDAR encephalitis in southwest China. Patients who initially presented with seizure were compared with those who initially presented with a psychiatric disturbance; the predictors of poor outcome amongst patients with anti-NMDAR encephalitis were explored and knowledge gaps in southwest China were identified.

Methods

Patients

The presence of NMDAR antibodies was tested for in serum or cerebrospinal fluid (CSF) samples from patients who presented with psychiatric symptoms, seizures or focal neurological signs at the West China Hospital of Sichuan University, a large tertiary care centre in China, between June 2011 and June 2014. All patients who tested positive for anti-NMDAR antibodies in CSF or/and serum were included in this study. Clinical information was obtained by the authors or referring physicians during the disease course. Brain magnetic resonance imaging (MRI), CSF examinations, electroencephalography (EEG), laboratory findings and radiological screening for a systemic neoplasm were reviewed. All patients with a definitive diagnosis of anti-NMDAR encephalitis were included in this study, and patients lacking key clinical data or suspected of virus encephalitis or other infectious encephalitis were excluded. All patients with a definitive diagnosis of anti-NMDAR encephalitis also received contrast-enhanced computed tomography scans of chest, abdomen and pelvis to search for potential tumours.

The symptoms were categorized into eight groups based on the previously reported manifestations of this disorder [1]: psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, decreased consciousness, autonomic instability, and central hypoventilation. To gain a better understanding of the disorder, the frequencies of mechanical ventilation, tracheotomy and complications were assessed. The cognitive symptoms were assessed using the Mini-Mental State Examination (MMSE) [1,9,10]. As for the assessment of memory deficits, the results of the MMSE, medical history and clinical characteristics of the patients (provided by their families) and physical examinations were combined to reach a conclusion. The effect and outcome of treatment were assessed using the modified Rankin Scale (mRS) at 4 weeks and every 3 months after the initiation of immunotherapy. The patients were described as experiencing a full recovery if they returned to their jobs (mRS 0); a mild deficit if they returned to most activities of daily living and remained stable for at least 2 months (mRS 1–2); a severe deficit for all other cases except death (mRS 3–5); or dead (mRS 6) [5,11]. The outcome of patients with full recovery or mild deficit was considered to be 'good'; and the outcome of patients with severe deficit or death was considered to be 'poor'. The Zung Depression Scale (ZDS) [12] and the Zung Anxiety Scale (ZAS) [13] were also used to assess the outcome of the psychological situation of the patients with anti-NMDAR encephalitis [14,15]. A diagnosis of anti-NMDAR encephalitis was considered to be definitive when (i) encephalitic signs such as psychiatric symptoms, seizures or focal neurological signs were shown; and (ii) anti-NMDAR antibodies were detected in CSF or/and serum [16,17]. The time from first symptom to definitive diagnosis was defined as the time to diagnosis. Relapse was defined as the onset or worsening of symptoms at least 2 months after improvement. This study was approved by the Research Ethics Committee of Sichuan University. Written informed consent was obtained from each subject.

Antibodies study

The serum and CSF samples of each patient were obtained simultaneously and were sent to Oumeng Biotechnology Corporation, Beijing, China, or Peking Union Medical College Hospital, China, for examining the antibodies against the NMDA receptor. All specimens (serum and CSF) 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, Lübeck, Germany) as previous described [18]. The dilution starting point is 1:10 for serum and 1:1 (undiluted) for CSF. Samples were classified as positive or negative based on the intensity of surface immunofluorescence of transfected cells compared to non-transfected cells. Antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptors 1 and 2, contactin-associated protein 2 (CASPR2), leucine-rich glioma-inactivated protein 1 (LGI1) and γ-amino-butyric acid receptors (GABAR B1/B2) were also examined by indirect immunofluorescence using specific transfected cells.

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Subgroup analysis

It was found that a considerable portion of patients with anti-NMDAR encephalitis initially visited a psychiatric clinic due to prominent psychiatric symptoms and that some of these patients were misdiagnosed with psychosis. Therefore, patients initially presenting with seizure or psychiatric symptoms were subdivided into the seizure and psychiatric symptom subgroups, respectively. The differences in the frequency of the following 10 characteristics were analysed between the two groups: gender, patients below 14 years old (including 14 years old), mean length of hospital stay, symptoms (including prodromal symptoms, fever within 3 weeks of onset, memory deficits, speech disturbances, dyskinesia, decreased consciousness and autonomic instability), central hypoventilation, mechanical ventilation, tracheotomy, abnormal MRI results, positive tumour presentation and prognosis (mean mRS).

Statistical analyses

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). A univariate analysis was performed in which age, length of hospital stay, interval from symptom onset to hospitalization and interval from hospitalization to definitive diagnosis were analysed as continuous variables. Gender, symptom presentation, prodromal symptoms, appearance of fever within 3 weeks, psychiatric symptoms, seizures, memory deficits, speech disturbances, dyskinesia, decreased consciousness, autonomic instability, central hypoventilation, mechanical ventilation, tracheotomy, complications, abnormal MRI results, abnormal CSF results, and tumour were analysed as categorical variables. The independent *t* test or one-way analysis of variance (ANOVA) was used for continuous variables, and the chi-squared test or Fisher's exact test was used for categorical variables. The predictive factors of poor outcome were determined using a logistic regression model. When counts of zero cells were recorded, odds ratios were calculated using Haldane's modification, which adds 0.5 to all counts to accommodate possible zero counts [19]. *P* values <0.05 (two-sided) were considered to be significant.

Results

Clinical characteristics

Fifty-one patients with a definitive diagnosis of anti-NMDAR encephalitis were included in this study. The tests for other autoimmune antibodies such as antibodies against AMPA receptors 1/2, CASPR2, LGI1 and GABAR B1/B2 were negative. The demographic and clinical characteristics are summarized in Table 1. Thirty-two patients were female (63%), and their mean age was 21.6 years, ranging from 9 to 39 years. Ten patients (eight females, two males) were

Table 1 Clinical profile of patients with anti-NMDAR encephalitis in southwest China

Item	Patients (%)
Number	51 (100%)
Female	32 (63%)
Median age, range (years)	21.6, 9–39
Prodromal symptoms	31 (61%)
Fever within 3 weeks	25 (49%)
Initial symptoms	–
Psychiatric	32 (63%)
Seizure	14 (28%)
Other[a]	5 (10%)
Psychiatric symptoms	46 (90%)
Memory deficits	16 (31%)
Speech disturbances	23 (45%)
Seizure[b]	43 (84%)
Dyskinesias and movement disorders	29 (57%)
Autonomic instability	14 (28%)
Decreased consciousness	29 (57%)
Central hypoventilation	14 (28%)
Mechanical ventilation	13 (26%)
Tracheotomy	10 (20%)
Complications[c]	30 (59%)
Abnormal MRI findings (information available for 50 patients)	20 (40%)
Abnormal EEG findings (information available for 49 patients)	42 (86%)
Abnormal CSF findings	32 (63%)
Tumour	4 (8%)
Immunotherapy	45
Outcome	–
Fully recovered	21
Mild deficits	20
Severe deficits	5
Death	5
Sequelae	–
Psychiatric symptoms	5
Seizure	2
Memory deficits	9
Speech disturbances	7
Dyskinesias and movement disorders	2
Median length of hospital stay, range (days)	38, 4–113
Interval between onset and hospitalization, range (days)	20, 1–90
Interval to definitive diagnosis (days)	15, 3–83

[a]One patient with memory deficits, two patients with speech disturbances, one patient with headache and one patient with ataxia; [b]16 patients experienced generalized tonic-clonic seizure alone, one patient experienced complex partial seizure alone, five patients experienced status epilepticus alone, one patient experienced unclassified seizure and 20 patients experienced multiple seizure types; [c]14 patients had lung infection alone, one patient had a urinary infection alone and 15 patients had multiple types of complications.

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under 14 years old (including 14) at the time of presentation.

Thirty-one patients (61%) exhibited prodromal symptoms such as headache or non-specific viral-like illness up to 2 weeks prior to hospital admission. Twenty-five patients (49%) had a fever within 3 weeks of onset. Thirty-two patients (63%) presented with psychiatric symptoms, including anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts, and visual or auditory hallucinations as the initial symptom. Fourteen patients (28%) presented with prominent seizures as the initial symptom.

During the disease course, 46 patients (90%) developed psychiatric symptoms. Forty-three patients (84%) experienced seizures, of whom 16 exhibited generalized tonic-clonic seizures and 20 exhibited two or more types of seizures, including generalized tonic-clonic seizures, complex partial seizure and status epilepticus. Sixteen patients (31%) demonstrated memory disturbance, 23 patients (45%) developed speech disturbance, 29 patients (57%) displayed dyskinesia or some other movement disorder, 14 patients (28%) exhibited autonomic instability, 29 patients (57%) developed decreased consciousness, 14 patients (28%) presented with hypoventilation, 13 patients (26%) required ventilation support and 10 patients (20%) underwent tracheotomy. Notably, one patient exhibited isolated ataxia but did not have any seizures or psychiatric symptoms, and one patient had a decade-long history of schizophrenia. Four out of 51 patients (8%) were surgically confirmed to have a neoplasm, including two women with mature teratoma of the ovary, one man with renal carcinoma and one man with mixed types of germ cell tumour (choriocarcinoma and teratoma) in the lung. Nineteen patients did not accomplish the MMSE because they could not cooperate, such as experiencing severe psychiatric symptoms or coma when they were admitted to our hospital. Amongst the 32 patients who completed the examination, two were illiterate, seven had a primary school education background and 23 had a junior high school education or above. The mean score of these patients was 22 (range 9–27).

General hospitalization status

The median length of hospital stay of the patients with anti-NMDAR encephalitis was 38 (4–113) days. It typically took 3 weeks (average 20 days; range 1–90 days) before these patients were admitted to our hospital (from the onset of the prodromal symptoms), and approximately two additional weeks (15 days; range 3–83 days) were required to make the correct diagnosis. Thirty patients (59%) experienced at least one type of complication, including lung infection, urinary infection, haemorrhage of the digestive tract and abnormal hepatic function. Twenty-nine patients were initially misdiagnosed with psychosis such as schizophrenia or post-traumatic stress disorder (nine patients), viral encephalitis or viral meningoencephalitis (17 patients), cerebral infarction (one patient), seizure (one patient) or involuntary movement disorder (one patient). The misdiagnosis could be made at the first visit to a physician or at the time of the hospitalization to our hospital. The misdiagnosis rate was 56.86%. The total number of patients diagnosed in every half-year and the relevant rates of the correct diagnosis are shown in Fig. 1, which reveals that the total number of patients diagnosed with anti-NMDAR encephalitis and the relevant rates of the correct diagnosis were increasing as time went on.

Ancillary examination (neuroimaging, EEG and laboratory findings)

The initial brain MRI, EEG and CSF results are presented in Table 1. Thirty out of 50 patients (60%) whose information was available had normal brain MRIs. Abnormal brain MRI findings included the following: seven patients with increased signal on T2-weighted or fluid-attenuated inversion recovery images of the medial temporal lobe; two with contrast enhancement of the cerebral cortex; one with contrast

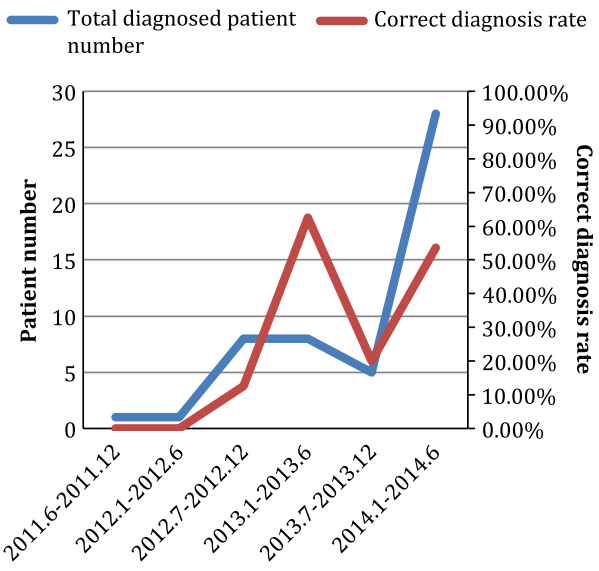

Figure 1 The number of patients diagnosed as anti-NMDAR encephalitis from June 2011 to June 2014 at West China Hospital. The blue line represents the total number of patients with anti-NMDAR encephalitis during each period. The red line represents the correct diagnosis rate during each period.

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enhancement of the cortex and cerebellum; one with contrast enhancement of the temporal lobes and basal ganglia; three with multifocal cortical and subcortical changes; four with multifocal white-matter changes; and two with cortical atrophy.

The EEG findings were abnormal in 42 out of 49 patients (86%) whose EEG information was available, including 30 patients (71%) with bilateral or unilateral generalized slow waves without epileptiform discharges and 12 patients (27%) with epileptiform discharges. Additionally, 32 patients (63%) displayed abnormal CSF findings, including 28 patients (55%) with pleocytosis and 13 patients (26%) with increased protein concentrations.

Treatment and outcome

Forty-five patients received immunotherapy (Table 1), amongst whom 24 patients were treated with intravenous immunoglobulin (IVIg, 0.4 g/kg per day for 5 days) once or several times, four patients were treated with intravenous methylprednisolone (1 g/day for 5 days) alone, 13 patients received a combination treatment of IVIg and intravenous methylprednisolone, one patient received a combination treatment of IVIg and plasma exchange, one patient received a combination treatment of IVIg, intravenous methylprednisolone and plasma exchange, and two patients received IVIg, intravenous methylprednisolone and a second-line therapy (one with cyclophosphamide, one with rituximab). Four patients underwent tumour resection.

The median follow-up duration was 12 months (5–41 months). The mRS at 4 weeks after the initial immunotherapy was 3.18. At the last follow-up (shown in Fig. 2), twenty-one patients (41%) had achieved full recovery; 20 patients (39%) had mild deficits; five patients (10%) had severe deficits; and five patients (10%) died, amongst whom four died due to disease progression and one died due to a complication. The sequelae included memory deficits (nine patients), speech disturbances (seven patients), psychiatric symptoms (five patients), seizure (two patients) and movement disorders (two patients). One patient relapsed during the course of this study. Two patients were lost to follow-up. Because some patients were lost to follow-up or too sick to do the scales (dead or with severe deficits, including experiencing severe psychiatric symptoms or coma), only 39 out of 51 patients were able to accomplish the ZDS and the ZAS. Amongst these patients, 31 (79%) were found to suffer from depression and/or anxiety to different degrees. The mean score for ZDS of the patients was 43 (range 29–69); the mean score for ZAS of the patients was 40 (range 22–52).

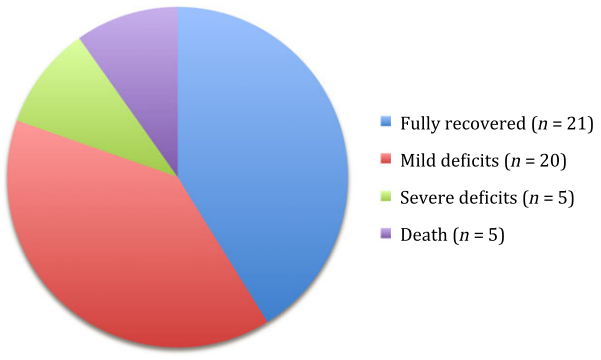

Figure 2 The outcome at the last follow-up. Twenty-one patients (41%) achieved full recovery (mRS 0); 20 patients (39%) had mild deficits (mRS 1–2); five patients (10%) had severe deficits (mRS 3–5); and five patients (10%) died (mRS 6).

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

The results of the comparison between patients initially presenting with seizure and those initially presenting with psychiatric symptoms are summarized in Table 2. Thirty-two patients, amongst whom 24 were female, presented with psychiatric disorder as the first symptom, whereas 14 patients, of whom nine were male, presented with seizure as the first symptom ($P = 0.011$, Table 2). Fourteen patients in the psychiatric symptom group but only one patient in the seizure group presented with memory deficits ($P = 0.018$, Table 2). The number of patients below 14 years old (including 14 years old), the frequency of other symptoms, such as prodromal symptoms, fever within 3 weeks of disease onset, speech disturbance, dyskinesia, decreased consciousness, autonomic instability and central hypoventilation, the frequency of mechanical ventilation, tracheotomy, abnormal MRI results, and positive tumour findings, the mean mRS and the mean length of hospital stay were not significantly different between the two groups.

Predictors of poor outcome for patients with anti-NMDAR encephalitis

In the present study, during the 12 months (5–41 months) follow-up survey, 41 patients had a good outcome (mRS 0–2) but 10 patients had a poor outcome (mRS 3–6). The mean age of the good outcome group was 20.5 (9–38) years, whilst the mean age of the poor outcome group was 26.0 (15–39) years ($P = 0.041$). The median length of hospital stay of the

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Table 2 Comparison between patients initially presenting with seizure and those initially presenting with psychiatric symptoms

	Psychiatric disorder as initial symptom	Seizure as initial symptom	*P* value
Patient number	32	14	–
Female:male	24:8	5:9	0.011
Patient ≤14 years old	4	4	0.222
Mean hospital stay (days)	42	38	0.657
Symptoms			
Prodromal symptoms	23	7	0.189
Fever within 3 weeks of onset	17	6	0.522
Memory deficits	14	1	0.018
Speech disturbances	15	5	0.482
Dyskinesia	22	7	0.225
Decreased consciousness	21	7	0.318
Autonomic instability	10	4	0.856
Central hypoventilation	10	4	0.856
Mechanical ventilation	10	3	0.724
Tracheotomy	6	4	0.465
Abnormal MRI findings	11	8	0.149
Tumour	4	0	0.298
Prognosis (mean mRS)	1.6	1.3	0.577

good and poor outcome groups was 33 (4–112) days and 56 (23–113) days, respectively ($P = 0.016$). The interval between the onset of the disease and hospitalization of the good and poor outcome groups was 22 (1–90) days and 13 (3–30) days, respectively ($P = 0.142$). The interval from hospitalization to definitive diagnosis of the good and poor outcome groups was 14 (3–69) days and 21 (4–83) days, respectively ($P = 0.125$). The predictors of poor outcome for patients with anti-NMDAR encephalitis are presented in Fig. 3. Older age, long hospital stay, memory deficits, decreased consciousness, central hypoventilation, complications and abnormal CSF results were more likely to have a poor outcome ($P = 0.041$, 0.016, 0.031, 0.019, 0.011, 0.027 and 0.049, respectively). All of the significant factors identified based on univariate analysis were included in a multivariate logistic regression model, which identified memory deficits as an independent factor associated with poor outcome ($P = 0.026$, odds ratio 9.739, 95% confidence interval 1.305–72.665).

Discussion

This study presents several novel findings regarding patients with anti-NMDAR encephalitis in China. Previous large-scale studies have suggested that the prevalence of tumours in anti-NMDAR patients is 38% and that 94% of these tumours are ovarian teratomas [3]. In the present study, only four out of 51 patients (8%) were confirmed to have a neoplasm. The prevalence of tumours was also lower in the Korean population than in western study populations [5], and previous studies have found that black women are more likely to have an underlying ovarian teratoma than patients from other ethnic groups [8], suggesting that a race-specific factor, perhaps involving the human leucocyte antigen or other genetic factors, may be involved in the susceptibility for anti-NMDAR encephalitis [7].

It was found that a considerable portion of patients with anti-NMDAR encephalitis initially visit a psychiatric clinic due to prominent psychiatric symptoms and that some of these patients are misdiagnosed with psychosis. Our patients were therefore divided into two groups and the clinical characteristics of patients initially presenting with seizure were compared with those of patients initially presenting with psychiatric

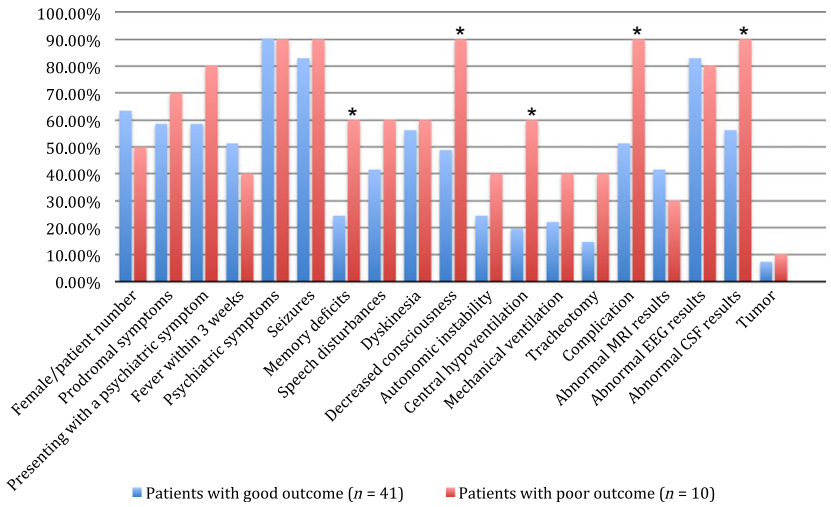

Figure 3 Predictors of poor outcome for patients with anti-NMDAR encephalitis. The blue bar represents the clinical characteristics of the patients with good outcome. The red bar represents the clinical characteristics of the patients with poor outcome. *$P < 0.05$.

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symptoms. It was found that a higher proportion of female patients presented with psychiatric disorder as the first symptom, whereas a higher proportion of male patients presented with seizure as the first symptom ($P = 0.011$, Table 2). Moreover, more patients who initially presented with psychiatric disorder exhibited memory deficits than those who initially presented with seizure ($P = 0.018$, Table 2). Previous studies suggested that children are more likely to present with seizures and adults with psychosis [3]. In the present study, there is no significant difference in the number of patients below 14 years old (including 14 years old) between the two groups. Our results were consistent with those of previous studies conducted from a different perspective. A recent study of 13 male patients also found that the initial symptom presented by male patients is different from that by female patients [2]. The difference in presentation of the first symptom between genders suggests a potential role of sexual hormones in the progression of autoimmune disorders and in epileptic pathogenesis [20]. However, the mechanism involved may be complex; oestrogen generally acts as a proconvulsant in animal studies, whereas progesterone generally exerts an anticonvulsant effect [21]. Androgens have also been shown to worsen seizures and to exert a proconvulsant effect [22]. Additionally, this could also be due to the bias in when men and women seek care: men may not seek medical care until seizures develop whilst women may pay more attention to their psychiatric symptoms. Nevertheless, the presence of psychiatric symptoms did not significantly affect patient outcome (Fig. 3).

The present study reveals several challenges in treating anti-NMDAR encephalitis in China that may contribute to poor outcome. It typically takes an average of 3 weeks (20 days; range 1–90 days) for patients to be admitted to our hospital and another 2 weeks (15 days; range 3–83 days) before the correct diagnosis is made. The misdiagnosis rate is as high as 56.86%. According to our data, 59% of patients experience at least one type of complication. Notably, the average length of hospital stay for our patients is much shorter than that for developed countries [1,7]; due to the financial burden, many patients were discharged before they fully recovered. They may go back to their home or be transferred to a primary care centre to continue recovery. Additionally, in the present study only two patients received second-line immunotherapy, which indicates that the neurologists in China should improve their knowledge for treating anti-NMDAR encephalitis.

Moreover, the prognosis in the present study was better than that of previous studies; in this study, 20% patients had a bad outcome (including severe deficits and death) compared with previously reported bad outcomes of 25% in America and 33% in Korea, no matter whether the follow-up time was longer or shorter than the present study [1,5]. Previous studies suggested that some patients with anti-NMDAR encephalitis continued to improve after 24 months [3]. Therefore the frequency of good outcome and level of recovery may be underestimated in our study, as some of our patients had a short follow-up. Meanwhile, for these patients, regular cancer screening should be conducted to find out whether they will develop tumours in the future.

It is worth mentioning that one of our patients had a decade-long history of schizophrenia diagnosed by psychiatrists. Previous studies have reported that several types of serum NMDAR antibodies were present in 9.9% of acutely ill patients who were initially diagnosed with schizophrenia [23], but the antibody subtype profile of these patients differed from those of non-schizophrenic anti-NMDAR encephalitis patients and the frequency of antibody positivity in these patients was similar to that observed in the controls [24–26]. Previous studies also showed that some patients with NMDAR antibodies could present with psychotic symptoms but lack any clinical sign of encephalitis throughout the course of the disease episode [27]. Therefore, even though the patient's schizophrenic symptoms had been completely under control for more than 10 years via treatment with antipsychotic drugs, it is difficult to determine whether the previous schizophrenic symptoms of this patient are separate from the anti-NMDAR encephalitis or not. Nevertheless, this case is a reminder that although a patient may have been diagnosed with schizophrenia for many years, autoimmune encephalitis should still be taken into consideration, especially when neurological symptoms show.

It is widely accepted that patients significantly benefit from awareness and knowledge of anti-NMDAR encephalitis [7,28,29]. Therefore, extending awareness of this disorder (amongst not only neurologists but also psychiatrists and primary care physicians) and reducing the interval to diagnosis and the rate of complications associated with treatment are essential and practical measures to further improve the prognosis of the disorder in China and other developing countries. Encouragingly, the number of patients diagnosed and the correct diagnosis rate are increasing over time (Fig. 1). Although a knowledge gap exists in southwest China compared with developed countries, the prognosis of patients with anti-NMDAR encephalitis in this region has improved, suggesting that the prognosis of anti-NMDAR encephalitis in China is

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predominantly related to race and the natural history of the disorder.

In conclusion, this study suggests that female patients more frequently initially present with psychiatric disorder but that male patients more frequently initially present with seizure. Patients with anti-NMDAR encephalitis in China have a lower incidence of neoplasm and a better prognosis than those in other countries examined. Nevertheless, this study reveals several challenges in treating anti-NMDAR encephalitis in China that may contribute to poor outcome. Extending the awareness of this disorder and reducing the interval to diagnosis and the rate of complications are essential and practical measures to further improve the prognosis of the disorder. However, this study contains several limitations, such as the small sample size and possible selection and recall bias. Therefore, these findings should be cautiously interpreted and should be verified by future studies of larger populations.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

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