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Anti-NMDAR Encephalitis of 11 Cases in China – Detailed Clinical, Laboratory and Imagiological Description

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Key Words
Anti-N-methyl-D-aspartate receptor encephalitis · Autoimmune encephalitis · China · Teratoma

Abstract
Background and Purpose: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a synaptic autoimmune disorder in which the auto-antibodies target NMDARs were first reported in 2007. Now, anti-NMDAR encephalitis is a widely recognized disease in the world. Our purpose was to analyze the clinical characteristics of anti-NMDAR encephalitis patients in West China Hospital in China and report the prognosis of the patients after accepting immunotherapy. ***Methods:*** Patients admitted to the West China Hospital who were diagnosed with anti-NMDAR encephalitis from 2013 to 2014 were retrospectively collected and their clinical features were analyzed. ***Results:*** We ultimately included 11 anti-NMDAR encephalitis patients. The median age of the 11 patients was 25 years, 46% patients were females, 27% patients were 15–18 years, and 73% patients were over 18 years. One of them was diagnosed with teratoma after discharging from hospital. The application of immunotherapy produced favorable outcomes in 67% patients included in our study. ***Conclusions:*** Anti-NMDAR encephalitis should be suspected in patients who developed a rapid change in behavior or psychosis, seizures, dyskinesia, and hypoventilation. Anti-NMDAR encephalitis is a kind of fatal but treatable disease. Timely diagnosis and treatment may yield favorable prognosis.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis belongs to a new category of immune-mediated disorders that can be fatal but it is also treatable; it can be diagnosed serologically [1]. The presence of NMDAR, which is the target antigen of anti-NMDAR encephalitis, was originally confirmed in 2007 [2]. Along with the progress of the anti-NMDAR antibody assay and the growing attention paid to the disease, researches about the disease began to develop rapidly. Anti-NMDAR encephalitis is a described disorder with clinical features; it is predominantly seen in young adults and children with or without teratomas [1, 3]. The patients of anti-NMDAR encephalitis usually have prominent psychiatric manifestations, followed by severe neurological features like seizures, movement abnormalities, autonomic instability, or hypoventilation, often requiring ICU-level care [1, 4]. Despite the serious disorder, patients often improve with immunotherapy in autoimmune anti-NMDAR encephalitis, or through the removal of the teratoma in paraneoplastic anti-NMDAR encephalitis [5].

A quick and accurate diagnosis of anti-NMDAR encephalitis is critical for the implementation of treatment strategies. However, the recovery process is slow, taking nearly 18 months, and the disease can relapse during this time [5, 6]. There were a few reports about patients with anti-NMDAR encephalitis in China [7, 8], but the characteristics of the disease in Chinese people have not been

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described uniformly. The aim of this study was to characterize the clinical presentation, laboratory findings, responses to immunotherapy, and prognosis of the patients with anti-NMDAR encephalitis.

Subjects and Methods

Patients

Patients diagnosed with anti-NMDAR encephalitis were retrospectively included after being admitted to the West China Hospital, Sichuan University, Chengdu, China, from January 1, 2013 to November 30, 2014. We used human embryonic kidney 293 cells expressing the NR1 subunit of NMDARs to test for the presence of NMDAR antibodies in serum and/or cerebrospinal fluid samples.

Baseline Data Collection and Categorization

We analyzed symptoms, laboratory examinations, CSF examinations, and imageological examinations of the patients included. Symptoms were categorized into 8 groups: psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, loss of consciousness, autonomic instability, and central hypoventilation [5, 9]. The immune therapy (corticosteroids, intravenous immunoglobulins, plasmapheresis or rituximab, and cyclophosphamide) and the prognosis of the patients were also observed and analyzed. The treatment effect and outcome were assessed by the modified Rankin scale (mRS). Favorable and poor functional outcomes were defined as mRS scores of 0–2 and 3–6, respectively.

Statistical Analysis

We described the characteristics of the clinical manifestations, and the frequencies of the clinical manifestations were described as percentages respectively. Fisher exact test for categorical variables was used to compare groups. Two-sided values of $p < 0.05$ were considered statistically significant, but we acknowledge the unlikelihood of positive p values with a small sample size. All statistical analyses were performed using SPSS version 20.0.

Results

From January 1, 2013 to November 30, 2014, 11 patients were tested positive of antibodies against NMDAR, and were eventually diagnosed as anti-NMDAR encephalitis. Five of the 11 patients were female (46%), with ages ranging from 15 to 39 years (median 25 years). The clinical features of these 11 patients are summarized in table 1. Three patients (27%) were 15–18 years and 8 (73%) patients were over 18 years.

Clinical Features

The characteristics of the clinical features are shown in table 1. The prodromal symptoms including fever, headache, upper respiratory symptoms, vomiting, and/or nausea before admission to the hospital were viewed in 8 (73%) of the 11 patients. Ten patients (91%) had psychiatric symptoms, with mood, behavioral, or personality changes: agitation, mood lability, and bizarre behavior, and 6 (55%) patients had visual or auditory hallucinations. Seizures were observed in 10 (91%) patients, and a fall in consciousness was developed in 10 (91%) patients as well. Seven (64%) patients had obvious speech problems including speech reduction, aphasia, or mutism. During the process of the disease, 5 (46%) patients developed movement abnormality with orofacial dyskinesia, and the percentage of patients with dystonic postures was 36 (4/11). Furthermore, 8 (73%) patients also had autonomic dysfunction with mild fever, cardiac dysrhythmias and unstable blood pressure, and 5 (46%) patients had central hypoventilation. Four patients required assistant respiration because of central hypoventilation. No differences in clinical manifestations were observed between male and female patients.

Auxiliary Examinations

Antibodies against NMDAR were tested both in serum and CSF of these 11 patients. All of the 11 patients were tested positive in CSF: 9 patients were positive and 2 patients were strongly positive. The proportion of testing negative in serum was 28% (3/11). Ten patients received brain MRI, and 2 patients (cases 4 and 11) had generalized or focal meningitis changes. The others did not show any changes of encephalitis in brain MRI. Seven patients received electroencephalography. Only 1 patient's electroencephalography result (case 10) was normal, and the EEG results of others were abnormal. All the patients received cerebrospinal fluid examinations. Cerebrospinal fluid studies revealed leukocyte counts of $10–220 \times 10^6$/l, glucose levels of 2.47–4.7 mmol/l, and total protein levels of 0.56–0.79 g/l (table 2).

All of the patients had negative results of viral assay in CSF. Four patients (cases 3, 5, 6 and 11) were positive in serological viral assay, all of whom were found with CMV, rubella virus, and single blister type I/II virus antibody IgG in serum. In addition, case 6 was found to have a single blister type I/II virus antibody IgM as well.

All the 11 patients had no tumors identified during hospitalization. Only 1 patient (case 3) was examined by abdominal computed tomography, and the others were examined using ultrasonography during hospitalization. When the patients were discharged from the hospital, all of them had a whole body examination done including abdominal CT or MRI. Teratoma was identified in 1 female patient (case 1), aged 15 years, and the tumor was immediately removed.

Table 1. Clinical features of the 11 patients with anti-NMDAR encephalitis in China

Case, n	Sex/age, years	Tumor	Prodromal symptoms	Neuropsychiatric symptoms	Movement abnormalities	Autonomic dysfunction and hypoventilation
1	F/15	Yes	Fever	Mood lability, hallucination, agitation, seizure	Orofacial dyskinesia	Hyperthermia, tachycardia, hypoventilation
2	M/34	No		Memory deficit, bizarre behavior seizure		Hypoventilation
3	F/39	No		Sleep disorder, hallucination		Hyperthermia, hypoventilation
4	M/25	No	Dizziness, headache	Hallucination, bizarre behavior talkative, seizure	Orofacial, dyskinesia and dyskinesia	Hyperthermia, hypoventilation
5	F/28	No	Fever, headache, vomiting	Hallucination, bizarre behavior talkative, seizure		Hyperthermia, hypoventilation
6	F/32	No	Dizziness, headache	Hallucination, seizure	Orofcial, dyskinesia and dyskinesia	
7	M/16	No	Headache upper, respiratory symptoms	Hallucination, seizure, talkative	Orofacial, dyskinesia and dyskinesia	Hyperthermia, tachycardia
8	M/27	No	Fever, headache			Hyperthermia
9	F/21	No	Fever	Talkative, agitation seizure		Hyperthermia
10	M/25	No		Talkative, agitation seizure	Orofacial, dyskinesia and dyskinesia	Hyperthermia
11	M/18	No	Fever	Talkative, agitation, mood lability, seizure		

Treatment and Outcomes

Of the 11 patients, 2 patients (cases 2 and 8) refused to accept any immunotherapy. The others received first-line immunotherapy consisting of corticosteroids and immunoglobulins, or cyclophosphamide as second-line immunotherapy for acute treatment during hospitalization. Nine patients accepted immunotherapy, and the time from onset to start immunotherapy (table 2) ranged from 1 to 28 days (median 13.1 days) after being admitted to hospital. Seven patients received combination therapy consisting of corticosteroids and immunoglobulins, and 2 patients (cases 4 and 10) received immunoglobulins only. One patient (case 9) accepted cyclophosphamide 800 mg after failing first-line immunotherapy (combination of corticosteroids and immunoglobulins).

After getting discharged from the hospital, 4 patients (cases 1, 4, 6 and 7) accepted antiepileptic treatment, 2 patients (cases 9 and 10) received antipsychiatric treatment following the doctor's advice, while 4 patients did not receive any treatment during the follow-up.

None of the patients were lost to follow-up. The follow-up period ranged from 8 to 16 months (table 2). The patients (cases 2 and 8) who refused to accept immunotherapy had different outcomes. Case 2 had a poor outcome (mRS 3) at 9 months follow-up, while case 8 had a good outcome (mRS 0) at 1 year follow-up. Of the 9 patients who received immunotherapy, 6 patients (67%) had a substantial recovery after immunotherapy. One patient (case 3) died because of multiple organ dysfunction syndrome (MODS) during hospitalization, case 5 committed suicide at 11 months follow-up, and the score of case 6 was 3 at 1 year follow-up. In addition, case 1 who was diagnosed with teratoma and had the teratoma removed immediately, finally had a neurological improvement (mRS 0) at follow-up of 9 months. Lastly, none of the 11 patients had a neurological relapse during follow-up.

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Table 2. Auxiliary examinations, treatment, and outcomes of the 11 patients with anti-NMDAR encephalitis in China

Case, n	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
CSF											
Glucose, mmol/l	Normal	Normal	Normal	↑	↑	↑	Normal	Normal	↓	Normal	Normal
Cl, mmol/l	Normal	Normal	↑	Normal	Normal	↑	Normal	↑	↑	Normal	Normal
Protein, g/l	Normal	↑	Normal	Normal	↑	Normal	Normal	↑	↑	Normal	Normal
Leukocytes, $\times 10^6$/l	↑	↑	↑	↑	Normal	↑	Normal	↑	↑	↑	↑
IgG synthesis, mg/day	Normal	↑	↑	Normal	Normal	Normal	Normal	↑	Normal	Normal	
Serum virology	–		CMV, rubella virus, and single blister type I/II virus antibody IgG ↑	–	CMV, rubella virus, single blister type I/II virus antibody IgG ↑	CMV, rubella virus single blister type I/II virus antibody IgG ↑, single blister type I/II virus antibody IgM ↑	–	–		–	CMV, rubella virus, single blister type I/II virus antibody IgG
CSF virology	–	–	–	–	–	–	–	–	–	–	–
NMDAR antibodies (serum)	++	++	++	–	–	–	++	++	++	+	++
NMDAR antibodies (CSF)	+++	++	++	+++	++	++	++	++	++	++	++
EEG		Marked abnormal	Mild abnormal			Moderate abnormal	Marked abnormal		Marked abnormal	Normal	Mild abnormal
MRI		Normal	–	Focal meningitis change	Normal	Normal	–	–	Normal	Normal	Generaized meningitis change
Time from onse to diagnosis, days	7		20	8	1	5	28		11	25	13
Treatment	Steroids, IVIG		Steroids, IVIG	IVIG	Steroids, IVIG	Steroids, IVIG	Steroids, IVIG		Steroids, IVIG, CTX	IVIG	Steroids, IVIG
mRS (follow-up time)	0 (9 months)	3 (9 months)	Dead (during hopitalization)	2 (10 months)	Suicide (11months)	3 (1 year)	1 (1 year)	0 (1 year)	1 (14 months)	1 (16 months)	2 (8 months)

Discussion

Anti-NMDAR encephalitis, which was once considered fatal-encephalitis, is now clinically recognizable, diagnosable by the presence of antibodies in CSF or serum, and treatable with the immunotherapy. Little information about clinical features of anti-NMDAR encephalitis in China is currently available. There were a few cases that reported about anti-NMDAR encephalitis in China [7, 8, 10–12], which have many limitations like a small number of cases, and lacking long time follow-up. Our research reported clinical symptoms, laboratory examinations, CSF examinations, imageological examinations, the response to the immune therapy and the long time prognosis of the 11 patients diagnosed with anti-NMDAR encephalitis.

According to previous studies [13–16], approximately 80% of patients with anti-NMDAR encephalitis were female. In addition, it predominantly affected young adults and children. However, the median age in the present study was higher than the one mentioned in previous reports [1–4, 13–16]. Furthermore, there was no predominance of female patients in the present study. This might be affected by a small number of cases.

In our research, 9 patients (81.9%) had the typical 5 stages [6]: prodromal phase, psychotic and/or seizure phase, unresponsive phase, hyperkinetic phase, and gradual recovery phase, except cases 8 and 11, and this finding is similar to that of the other earlier studies [6, 17]. Therefore, our study indicates that testing of antibodies against NMDAR in serum and CSF should be performed in young females, or children with any step of the typical 5 stages.

In the study, antibodies against NMDAR of the 11 patients were found positive in CSF. According to previous studies [18, 19], antibodies against NMDAR were intrathecal synthesis antibody. When we found antibodies against NMDAR in CSF, patients can certainly be diagnosed with anti-NMDAR encephalitis.

Approximately, 37–50% of encephalitis have unknown etiologies according to the previous studies [20, 21]. Since the development of systematic laboratory testing included PCR and antibody assays, some cases of unknown cause have been able to be reclassified as the infectious encephalitis, or as an autoimmune process. Previous studies [22, 23] indicated that approximately 4.4% of encephalitis with uncertain etiology were anti-NMDAR encephalitis, followed by enterovirus, herpes simplex virus type 1, varicella zoster virus, and West Nile virus. In this study, none of the patients found positive results in CSF viral assay, except that 4 patients were identified positive for CMV, rubella virus, and single blister type I/II virus antibody in serum. This can be explained by the possibility that some patients may have had viral infection before or during the disease.

None of the 11 patients was found to have tumors during hospitalization. Not all of them had enough examinations during hospitalization. One female patient (case 1), aged 15 years, was diagnosed with teratoma through a whole body examination, 1 month after getting discharged from the hospital. In a case series of 400 patients, an underlying teratoma was detected more often in female patients over 18 years [22]. Therefore, we suggest that female patients with anti-NMDAR encephalitis be screened for ovarian tumors. Periodic screening for ovarian teratomas for at least 2 years has been recommended even if the patients have recovered from encephalitis [17].

Management of anti-NMDAR encephalitis should initially focus on immunotherapy and the detection and removal of ovarian tumors [1–5]. In the Titulaer et al. [5], 81% of the patients with anti-NMDAR encephalitis who received immunotherapy and removal of tumors had good outcomes after a median follow-up of 24 months. In the research, 1 patient with tumors underwent tumor resection, and 9 patients received immunotherapy. At the end of follow-up ranging from 8 to 16 months, 67% patients had achieved a neurological recovery after immunotherapy or removal of tumors. In this study, the prognosis of the patients with immunotherapy tended to be favorable, in accordance with the results of the previous study [16].

In this study, 2 patients (18%) died during the follow-up. Case 3 died of MODS during hospitalization, though she had received immunotherapy. It may be associated with the time of starting immunotherapy (20 days) delayed. Case 5 committed suicide because of serious psychiatric disease at 11 months after anti-NMDAR encephalitis. Therefore, it is also important to assess the mental condition of these patients with anti-NMDAR encephalitis after discharging them from the hospital.

Conclusions

In our clinical work, anti-NMDAR encephalitis should be suspected in patients who developed a rapid change in behavior or psychosis, seizures, dyskinesia, and hypoven-

tilation for unknown reasons. At the same time, patients should be examined for the underlying tumor, especially for teratoma. As a neurologist, it is important to be familiar with the clinical presentations of the disease, especially in children and young adults.

Disclosure Statement

The authors have no conflicts of interest to declare.

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