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ORIGINAL COMMUNICATION

Brain magnetic resonance-imaging findings of anti-*N*-methyl-D-aspartate receptor encephalitis: a cohort follow-up study in Chinese patients

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Abstract

The aim of this report was to assess routine clinical brain magnetic resonance imaging (MRI) and its relation to clinical characteristics and disease prognosis. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis patients were consecutively recruited from West China Hospital between October 1, 2011 and April 1, 2016. Brain MRI findings of 106 patients were analysed, and outcomes were assessed at 4, 8, and 12 months after discharge from the hospital using the modified Rankin scale (mRS). An MRI of the brain was normal in 52/106 (49.1%) patients and abnormal or atypical in 54/106 (50.9%) patients. The initial MRI was abnormal with T2 or fluid-attenuated inversion recovery (FLAIR) hyper-intensity signals in 20/106 (18.9%) patients. There were no statistically significant differences between the MRI findings and clinical presentations (seizure, hypoventilation, loss of consciousness, and tumour) ($P > 0.05$). Patients with normal MRIs were younger than patients with abnormal MRIs ($P < 0.05$). The mean mRS score at the 4-month follow-up was significantly higher in patients with abnormal MRIs than in patients with normal MRIs ($P < 0.05$). Brain MRI abnormalities are typically mild or unrelated to clinical symptoms, which is a clinico-radiological paradox of this type of immune encephalitis. Abnormal MRIs did not affect prognosis evaluated by mRS.

Keywords Magnetic resonance imaging · Anti-NMDAR encephalitis · Modified Rankin scale · Prognosis

Introduction

Anti-NMDAR encephalitis is a severe but treatable antibody-mediated disorder that results in psychiatric, memory, and seizure symptoms. Having been formally recognized in 2007, this disease may include abnormal movements, disorders of consciousness, and hypoventilation and is associated with teratomas with further progression [1, 2]. Graus

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et al. proposed a clinical approach to the diagnosis of anti-NMDAR encephalitis that focuses on the clinical manifestations and laboratory tests such as electroencephalograms (EEG) and cerebrospinal fluid (CSF) analysis. Diagnoses can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies after reasonable exclusion of other disorders [3].

MRI remains one of the most important examinations for central nervous system disease diagnosis. The previous studies such as Irani et al. reported the initial brain MRI abnormalities in only 23% of patients [4]. Dalmau et al. reported brain MRI abnormalities in 50% [2], and Titulaer et al. reported MRI abnormalities in 33% [5]. However, as far as we know, there are no studies on brain MRI characteristics of Chinese patients with anti-NMDAR encephalitis, and information regarding the use of MRI for disease prognosis is still lacking.

With the purpose of obtaining estimates of the outcome associated with NMDAR encephalitis in western China, a study named Outcome of NMDAR Encephalitis Study in Western China (ONE-WC study) on continuously enrolled patients with NMDAR encephalitis collecting prospective observational data was initiated in October 2011. Our previous report showed that anti-NMDAR encephalitis patients in west China have some unique characteristics, such as a lower tumour incidence [6]. The present report is one part of ONE-WC study. In the cohort, further, we summarize the findings of routine brain MRI investigations, and discuss the contributions of these observations to the understanding of the usage of MRI in diagnosing anti-NMDAR encephalitis in West China. Moreover, we evaluated the relations of these observations to clinical features and disease outcome.

Methods

Participants

ONE-WC study included patients who had suffered from anti-NMDAR encephalitis and admitted to the Department of Neurology, West China Hospital.

Participants of this study recruited between October 2011 and April 2016. Patients included in the study tested positive for NMDAR antibodies and met the following inclusion criteria: (1) patients with encephalitic signs of psychiatric symptoms (agitation, paranoid thoughts, irritability, or hallucinations), seizures, or focal neurological signs and (2) detection of anti-NMDA receptor antibodies in CSF.

Exclusion criteria were as follows: (1) patients with human immunodeficiency virus (HIV) infection, brain abscess, prion diseases, cerebral malaria, brain tumour, or a diagnosis of a non-infectious central nervous system disease, such as acute demyelinating encephalomyelitis (ADEM); (2) patients with central nervous system infection with viral, bacteria, fungi, parasites, or mycobacterium tuberculosis (TB); or (3) patients with encephalopathy secondary to sepsis or systemic inflammatory response syndrome; (4) patients diagnosed with epilepsy, cerebral trauma, and/or other nervous system disease prior to the onset of encephalitis; and (5) patients with positive serum and/or CSF laboratory test for other auto-immune encephalitis: a-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptor antibody encephalitis, contactin-associated protein 2 (CASPR2) antibody encephalitis, leucinerich glioma-inactivated protein 1 (LGI1) antibody encephalitis and gamma-amino butyric acid receptors (GABAR) B1/B2 receptor antibody encephalitis, voltage-gated potassium channel (VGKC) complex antibody encephalitis, and glutamate decarboxylase (GAD) antibody encephalitis.

This study was approved by the Research Ethics Committee of the Medical School of Sichuan University. Written informed consent from each patient was obtained before enrollment in the study.

Determination of antibodies to NMDAR and clinical examinations

CSF examinations of patients were performed within 1 week of disease onset, and determination of antibodies against NMDAR was performed using indirect immunofluorescence (IIF) as previously reported [6]. Patient serum and CSF samples were obtained simultaneously and were maintained and transferred on ice to the laboratory. All specimens (serum and CSF) were evaluated for anti-NMDAR IgG antibodies by indirect immunofluorescence (IIF) using EU 90 cells transfected with the The NMDAR1 subunit (NR1) of the NMDAR complex and immobilized on BIOCHIPs (euroimmunAG, Germany) as previously described [6, 7]. Slides were incubated with undiluted CSF samples or serum samples at a starting dilution of 1:10, and analysis was performed according to the manufacturer's guidelines. Following incubation of samples with transfected or untransfected cell lines, slides were washed and stained with fluorescein-labeled anti-human IgG antibodies and visualized using a fluorescence microscope. Samples were classified as positive or negative based on the intensity of surface immunofluorescence of transfected cells compared to non-transfected cells, according to the manufacturer's suggested recommendations for reading and interpretation.

Intracranial pressure was evaluated by a cerebrospinal fluid pressure gauge, and a pressure > 180 mmH_2O was considered to be increased. Integrated CSF analyses included total cell count, total protein content, albumin, and IgG content in both CSF and serum. Abnormally elevated cell counts were defined as total white cell counts > 5/ml and CSF protein > 500 mg/L. The detection of organism-specific nucleic

acids in CSF by polymerase chain reaction (PCR) was used for rapid diagnosis of central nervous system (CNS) infections, such as nucleic acid testing for herpes simplex virus (HSV), varicella zoster virus (VZV), and enteroviruses. In addition, cultures for bacteria, tuberculosis, and fungal infections of the CSF were all performed.

MRI data were obtained by experienced technician within 1 week of disease onset and at different timepoints during the course of the disease. MRI studies were performed using a Germany Siemens-Trio Erlangen 3.0 T MRI (12-channel coil). Regular MRI series including axial T2-weighted image (T2WI), T1-weighted image (T1WI), and fluid-attenuated inversion recovery image (Flair). Contrast-enhanced studies were obtained using intravenous gadopentetate dimeglumine. Extensive investigations for tumours were done, which included thoraco-abdominal CT, pelvic CT scan, positron emission tomography (PET), or transvaginal ultrasound.

Evaluation of prognosis

Clinical outcome was evaluated in each patient recruited from the day of admission to the hospital with 4-month follow-up intervals. Clinical outcome was evaluated using the modified Rankin Scale (mRS) [8]. Patients were considered to have a good outcome when their mRS score was ≤ 2. Status of patients in the acute stage was obtained from hospital medical records and face-to-face interviews. Clinical outcome was collected by telephone interview and/or follow-up clinic visits.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 21.0, SPSS Inc., Chicago, IL, USA). The clinical and demographic features of patients were analysed using Student's *t* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. All tests were two-tailed, with clinical significance defined as values of $P < 0.05$.

Results

Demographics and clinical characteristics

A total of 112 patients with anti-NMDAR encephalitis (63 females and 49 males) provided data for the study. Demographic details, clinical characteristics, and laboratory tests of anti-NMDAR encephalitis patients are presented in Table 1.

The first symptom is headache, fever, dizziness, psychiatric symptoms, sub-acute memory disturbance, and seizures. Patients often presented with involuntary movements; Orofacial dyskinesias were the most common type. Hypoventilation requiring respiratory support occurs as the patient becomes comatose. All patients had undergone extensive whole body/pelvic imaging, and there were seven female patients with an underlying ovarian teratoma, one male patient diagnosed with renal carcinoma, and another male patient with choriocarcinoma. No other tumours were found in any other patient. Participants in our study presented the novel feature of a low paraneoplastic rate 9/112 (8%), as we have previously reported. Ten patients died: two died of multiple organ failure, six died after withdrawal of medical support, one committed suicide, and one died of tumour progression.

In our cohort, 107 patients received intensive immunotherapies (e.g., steroids, intravenous immunoglobulins, rituximab, cyclophosphamide, and tumour resection). One hundred and seven patients received immunotherapy (Table 1), amongst which 54 patients were treated with intravenous immunoglobulin (IVIg, 0.4 g/kg per day for 5 days) once or several times, 12 patients were treated with intravenous methylprednisolone (1 g/day for 5 days) alone, and 38 patients received a combination treatment of IVIg and intravenous corticosteroid. In addition, there is one patient received a combination treatment of IVIg, corticosteroid, and plasma exchange. Two patients received IVIg, intravenous corticosteroid and a second-line therapy (one with cyclophosphamide and one with rituximab). Seven patients underwent tumour resection.

MRI characteristics

In this study, the initial MRIs within 1 month of disease onset from 106 patients were available, all of which received intensive immunotherapies. The MRI of the brain was normal in 52/106 (49.1%) patients and abnormal or atypical in 54/106 (50.9%) patients. The initial MRI was abnormal with T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensity signals in 20/54 (37.0%) patients. T2 or FLAIR signal hyper-intensity was seen in the hippocampi, cerebellar, or cerebral cortex and insular regions, basal ganglia, and brainstem. Frequently, progressions to hippocampal or whole-brain atrophy were found in two patients. Other atypical MRI findings were found, including meninges enhancement, enlarged temporal horns of the lateral ventricles, pituitary lesions, non-specific periventricular white matter lesions, and non-specific cortical lesions (Please see Fig. 1).

Twenty-eight patients received repeated cranial MRI examinations, and 17 of these were normal. One repeat MRI brain scan showed gradually evolving brain atrophy. There were three patients still exhibiting extensive or multi-focal T2/FLAIR hyper-intense lesions, and two had non-specific

Table 1 Clinical features in 112 NMDAR-antibody positive patients

Characteristic/symptoms	Patients	
	n	%
Age (medium, range)	26.4 ± 11.5 (9–72)	
Sex		
Male	49	43.7%
Female	63	56.3%
Symptom presentation		
Fever	71	63.4%
Headache	44	39.3%
Dizziness	14	12.5%
Psychiatric symptoms	109	97.3%
Seizures	91	81.3%
Dyskinesias and movement disorders	58	51.8%
Disorders of consciousness	73	65.2%
Central hypoventilation	23	20.5%
Tumor	9	8.0%
CSF: total with abnormal findings	70	62.5%
Elevated total white cells	65	58.0%
Elevated total protein	22	19.6%
Elevated intracranial pressure	31	27.7%
First line therapy(corticosteroid, intravenous immunoglobulin)	107	95.5%
Corticosteroid only	12	10.7%
Intravenous immunoglobulin only	54	48.2%
Both corticosteroid and intravenous immunoglobulin	38	33.9%
Second-line therapy	3	2.7%
Corticosteroid, intravenous immunoglobulin and rituximab	1	0.9%
Corticosteroid, intravenous immunoglobulin and cyclophosphamide	1	0.9%
Corticosteroid, intravenous immunoglobulin and plasma exchange	1	0.9%
Tumor resection	7	6%

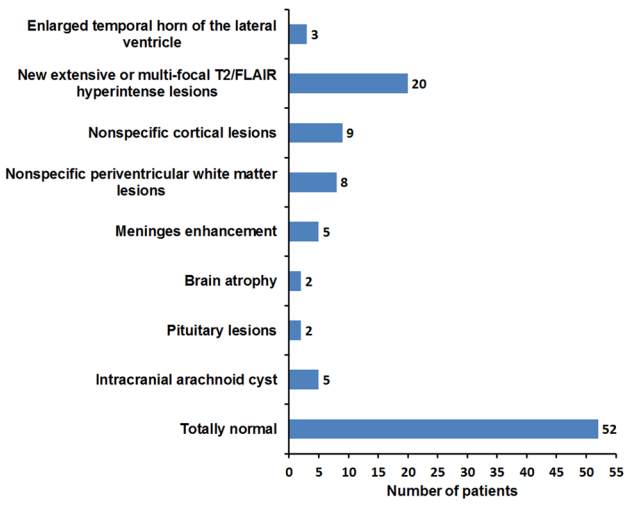

Fig. 1 Brain MRI findings of 106 patients with anti-NMDAR encephalitis

cortical lesions. While the clinical diagnoses were challenging, lesions resolved after treatment in four patients.

The MRI of the three patients received a combination treatment of IVIg, corticosteroid, and the second-line treatments were normal.

Correlation of MRI results with clinical characteristics in the acute stage

We investigated the correlation of MRI between three clinical presentations (seizures, disturbance of consciousness, and hypoventilation) and the frequency of tumour association. In the nine patients with tumours, two of them had normal MRIs, and seven had abnormal MRIs. There were 19 patients with hypoventilation, and 6 had normal MRIs. In 85 patients who had seizures, 40 patients had normal MRIs. In 68 patients who had disturbance of consciousness, 32 patients had normal MRIs. Relationships of these clinical presentations with MRI findings are shown in Fig. 2. Patients with normal MRIs were younger than patients with abnormal MRIs ($P < 0.05$). There were no statistically significant

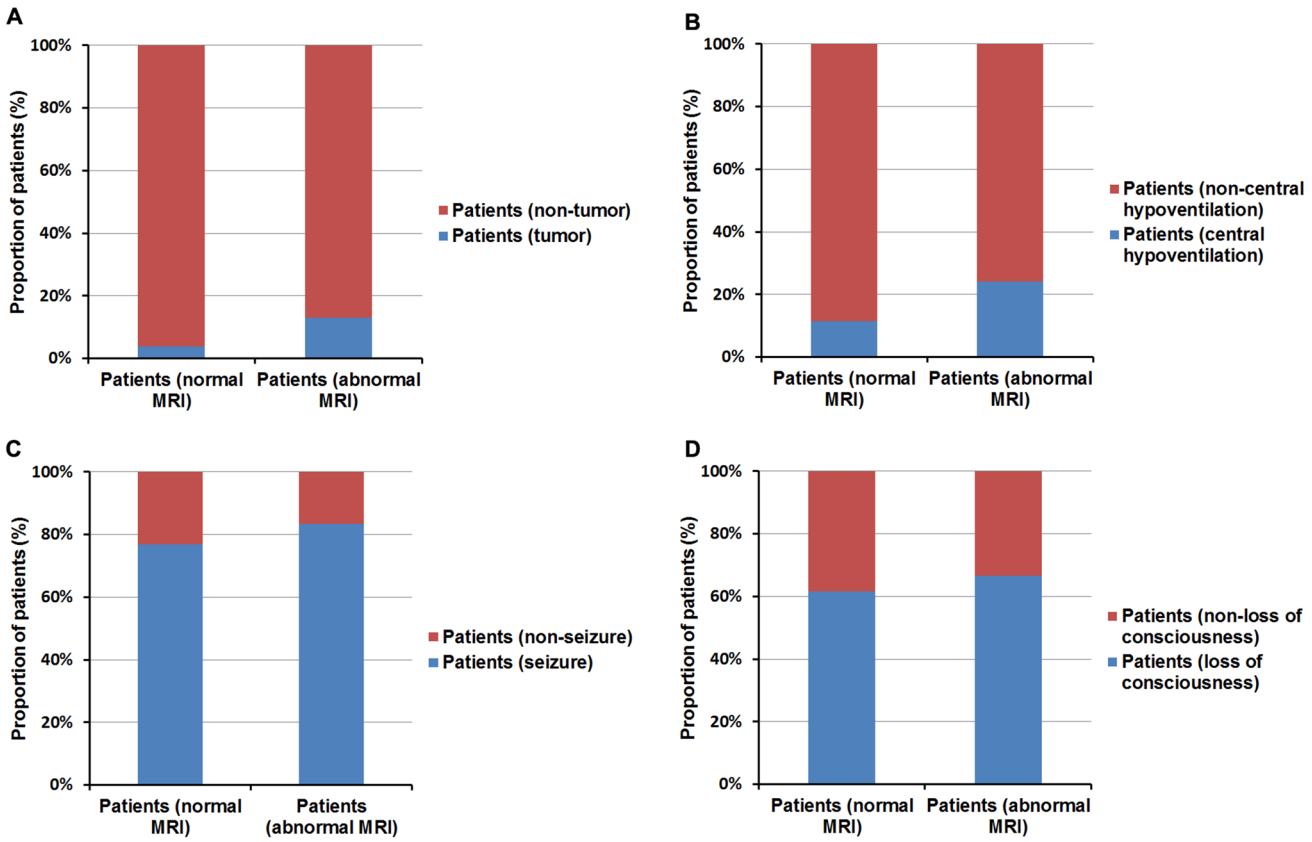

Fig. 2 Correlations of brain MRI findings and clinical characteristics: **a** tumour, **b** central hypoventilation, **c** seizure, **d** loss of consciousness

differences in MRI findings (normal or abnormal) between patients with or without tumours ($P > 0.05$), patients experiencing seizures or not ($P > 0.05$), patients experiencing hypoventilation or not ($P > 0.05$), or patients experiencing loss of consciousness or not ($P > 0.05$).

Correlation of MRI results with prognosis

Ninety-two of the 106 inpatients were followed for at least 4 months, during which nine were lost to follow-up, and five died. Sixty out of 92 patients (65.2%) had improved outcomes (mRS 0–2). After 8 months of follow-up, 75 out of 87 patients (86.2%) had improved outcomes (mRS 0–2), and 1 died. After 12 months of follow-up, 81/86 patients (94.2%) had mRS scores of 0–2, and three patients died. The improved prognosis of the disease was time-dependent, as a longer follow-up period was associated with better disease outcomes. (Please see Fig. 3). The mean baseline mRS score of the 106 patients was 3.37, and 2.07 at the 4-month follow-up, 1.34 at the 8-month follow-up, and 0.93 at the 12-month follow-up. Nine patients died, and three of them had normal MRIs. The comparison of mean mRS scores (at baseline, 4-, 8-, and 12-month follow-ups) between patients with normal and abnormal MRI findings is presented in Table 2 and Fig. 3. The mean mRS score at the 4-month follow-up was significantly higher in patients with abnormal MRIs than in patients with normal MRIs ($P < 0.05$), which was not independent of other factors, because patients with normal MRIs were younger than patients with abnormal MRIs ($P < 0.05$).

Fourteen patients had memory deficits, but only four patients had T2/FLAIR hyper-intense lesions in temporal lobes or hippocampus.

Discussion

In the 106 patients with anti-NMDA-receptor encephalitis in our study, the presence of brain MRI findings was identified. Our results suggest that MRI findings did not relate to patients' clinical presentations. Abnormal MRIs did not affect the prognosis of patients evaluated by mRS.

A review summarized abnormalities of MRIs in 23–50% of patients who are typically discrete and non-specific [9]. The MRI findings in this study are in accordance with the established literature. In our study, the MRI findings of the brain were normal in 52/106 (49.1%) patients and abnormal or atypical in 54/106 (50.9%) cases. The previous studies in China reported that MRI abnormalities 20 (60.6%)

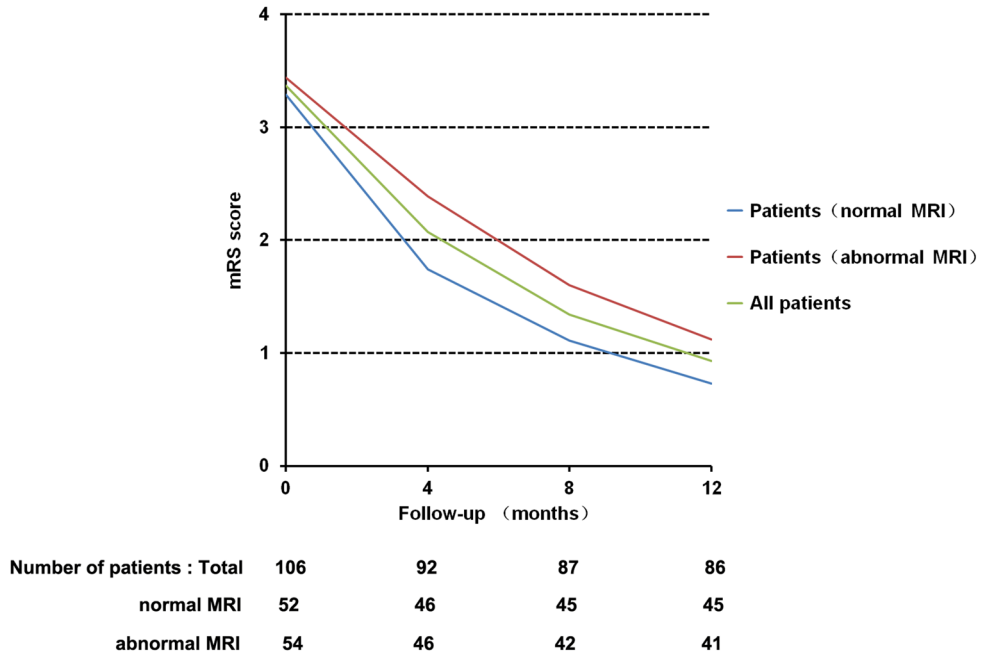

Fig. 3 Comparison of mean mRS scores at baseline, 4-, 8-, and 12-month follow-ups for patients with normal and abnormal MRI findings. Curves for the mRS score of patients with normal MRIs (blue line), patients with abnormal MRIs (green line) or all 106 patients

Table 2 Comparison of mean mRS score between patients with normal and abnormal MRI findings

Follow-up (months)	All patients (number)	Patients with normal MRI findings		Patients with abnormal MRI findings		*P* value
		Number of patients	Mean mRS score	Number of patients	Mean mRS score	
0	106	52	3.29	54	3.44	0.459
4	92	46	1.74	46	2.39	0.028
8	87	45	1.11	42	1.6	0.064
12	86	45	0.73	41	1.12	0.186

patients and 13 patients (39.4%) were normal [10]. Dalmau et al. reported abnormal MRI findings in 55% of patients [2]. In another large cohort study, only 35% of the patients had abnormal brain MRIs at disease onset [5]. Irani et al. found that brain imaging was normal in 39/44 (89%) in the initial MRIs and remained normal in 34/44 (77%) in subsequent MRIs [4]. Just as a recent review addressed, this clinical–radiological paradox constitutes one of the main challenges in NMDAR encephalitis neuroimaging [9].

Of the 106 patients in our study, 20 patients had T2 or FLAIR signal hyper-intensity in the hippocampi, cerebellum or cerebral cortex, insular regions, basal ganglia, and brainstem. Progressions to hippocampal or whole-brain atrophy were found in two patients. Other atypical MRI findings included meninges enhancement, enlarged temporal horns of the lateral ventricles, pituitary lesions, non-specific periventricular white matter lesions, and non-specific cortical lesions. These were in accordance with the previous studies [1, 4, 9, 11–13]. In a clinical–radiological comparison between herpetic encephalitis and limbic encephalitis of auto-immune aetiologies (including anti-NMDA receptor encephalitis), MRIs were abnormal in all cases of the former, but in only 60% of the latter [14]. Regardless of whether the MRI findings were normal or not, patients presented with a similar typical clinical syndrome: following a prodromal phase with low-grade fever and headache, patients develop psychiatric symptoms. With further progression, the disease may include abnormal movements, epileptic seizures, and disorders of consciousness. A few case reports and a study reported that anti-NMDAR encephalitis associated with acute demyelinating encephalomyelitis (ADEM), myelitis, or neuro-myelitis optica (NMO). These cases showed T2/FLAIR multi-focal, infratentorial, or extensive abnormalities, suggesting involvement of the white matter [15–18]. Those MRI features of demyelination occurred as episodes separate from anti-NMDAR encephalitis or occurred simultaneously with typical anti-NMDAR encephalitis.

Fourteen patients had memory deficits, but only four patients had T2/FLAIR hyper-intense lesions in temporal lobes or hippocampus. Frequently, patients presented with

cognitive deficits, including memory disturbances, and imaging shows that the hippocampus, a structure critically involved in the formation of memory, is affected. This post-inflammatory atrophy of the hippocampus contributes to persistent memory impairment and the neurological disability seen in patients in due course of the disease.

In a study of resting-state functional MRI analysis, Finke et al. [19] found that anti-NMDAR encephalitis was associated with characteristic alterations of functional connectivity and widespread changes of white matter integrity despite normal findings in routine MRI. In addition, recently, another study [20] of resting-state functional MRI analysis reported that structural MRI was normal in 31 (72%) of 43 anti-NMDAR encephalitis patients, but they also found a characteristic pattern of whole-brain functional connectivity alterations in anti-NMDAR encephalitis that was well suited to explain the major clinical symptoms of the disorder. Considering the usually unremarkable structural routine MRI in NMDAR encephalitis, these results may help to explain the clinico-radiological paradox in anti-NMDAR encephalitis and advance the pathophysiological understanding of the disease.

To the best of our knowledge, few studies have reported a relationship between routine MRI findings and the prognosis of anti-NMDAR encephalitis in any country. In our study, it seems that improved mRS scores were significantly associated with MRI findings. Based on this, patients with normal MRI findings have a faster recovery time than patients with abnormal MRI findings. The reason for this may simply be that the disease states of patients with abnormal MRI findings were worse. However, we still lack a quantifiable index of the severity of the disease.

The main findings of this study are that the abnormalities identified on routine MRI studies are often mild, transient, and non-specific, preferentially seen in fluid-attenuated inversion recovery (FLAIR) sequences, usually involving cortical and subcortical regions of the brain and hippocampus, but sometimes affecting the basal ganglia. Neuroimaging failed to aid in the diagnosis of immune encephalitis. Encephalitis patients with normal or mild abnormal brain MRI should be tested for NMDAR antibodies to avoid any delays in treatment initiation.

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Author contributions RW, HXL, DZ, and ZH conceptualized and designed the study. RW and HXL, XL, YL, C C, CL, and XC acquired the data. RW and ZH carried out the statistical analysis. RW, HXL, DZ, and ZH interpreted the data. RW, DZ, and ZH drafted the manuscript and all participated in the revision of the manuscript. DZ and ZH organized funding. ZH is the guarantor.

Compliance with ethical standards

Conflicts of interest None of the authors has any conflicts of interest to declare.

Ethical standards The study was approved by the Research Ethics Committee of the Medical School of Sichuan University. All participants have provided written consent to participate in the study.

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