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CSF findings in patients with anti-*N*-methyl-D-aspartate receptor-encephalitis

Rui Wang [a,1], Hong-Zhi Guan [b,1], Hai-Tao Ren [b,1], Wei Wang [a], Zhen Hong [a,*], Dong Zhou [a,**]

[a] Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China
[b] Department of Neurology, Peking Union Medical College Hospital, People's Republic of China

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ABSTRACT

Purpose: Anti-NMDAR-encephalitis is a recently described form of autoimmune encephalitis. Here, we characterize CSF changes in Chinese patients with anti-NMDAR encephalitis, and explore the relationship between CSF findings and disease outcome.
Methods: The presence of NMDAR antibodies in serum or CSF samples was evaluated in patients diagnosed with encephalitis between October 1, 2010 and August 1, 2014 at the West China Hospital. All patients fulfilling our diagnostic criteria were included and CSF findings were analyzed. Patient outcome was assessed after 4, 8, 12, 16, 20, and 24 months using the modified Rankin scale (mRS).
Results: Out of 3000 people with encephalitis screened, 43 patients were anti-NMDAR antibody positive in CSF or serum and included in this study. 62.8% of the patients identified with positive CSFs had positive serum anti-NMDAR samples, while 100% patients with positive serum had positive CSF samples. In the CSF white cell counts were elevated in 58.1% of cases; protein was increased in 18.6%; QAlb > Qlim(Alb) of the blood–CSF barrier was found in 29.3%; intrathecal immunoglobulin synthesis was detected in 17.1%, and 39.5% patients exhibited increased CSF pressures. A longer follow-up period was associated with better outcomes. There was no relationship between changes in CSF findings and outcome.
Conclusion: The sensitivity of NMDA receptor antibody testing is higher in CSF compared to serum. Other CSF abnormalities are present in some patients with Anti-NMDAR-encephalitis, however these changes do not appear to affect prognosis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a newly identified antibody-mediated disorder, having been formally recognized in 2007. Anti-NMDAR encephalitis has been increasingly identified as a cause of autoimmune and paraneoplastic or non-paraneoplastic encephalitis [1]. Electroencephalographic (EEG) tracings typically show non-specific, generalized slowing or epileptiform activity, and brain magnetic resonance imaging (MRI) in 50–77% of patients is either unremarkable or may show mild and transient nonspecific abnormalities in various regions of the brain [2]. Despite the severity of the disease, most patients show improvement after intensive care support, immunotherapy, and lengthy hospital stays with multidisciplinary care [3].

Analysis of cerebrospinal fluid (CSF) is widely used for routine neurological diagnostics in some neurological conditions to reveal constellations suggestive for ongoing acute or chronic CNS inflammation. To our knowledge, few studies have focused on CSF changes in anti-NMDAR encephalitis. Several studies have shown that patients with anti-NMDAR-encephalitis can have normal or changed CSF findings. A recent study identified abnormal CSF findings in 79% of patients [4], and a recent review [5] of CSF revealed lymphocytic pleocytosis in more than 90% of cases, intrathecal protein increase in 33% and oligoclonal bands in approximately 25%. In a published study on ab-LE (antibody-associated limbic encephalitis) in anti-NMDAR-encephalitis patients, elevated cell and protein counts were

* Corresponding author. Tel.: +86 28 8542 2549; fax: +86 28 8542 2549.
** Corresponding author.
E-mail addresses: 1046792011@qq.com (R. Wang), guanhz@263.net (H.-Z. Guan), rht20080808@163.com (H.-T. Ren), wangwei10102@aliyun.com (W. Wang), Hongzhengoog@aliyun.com (Z. Hong), zhoudong66@yahoo.de (D. Zhou).
[1] These authors contributed equally to the manuscript.

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reported in 48% and 32% of patients, respectively [6]. However, CSF findings in this type of encephalitis in Chinese patients have not been previously reported. Additionally, no study thus far has analyzed the impact of abnormal CSF findings on disease outcomes, which is critical for determining disease prognosis and thus warrants investigation.

Therefore, the aim of the current study was to prospectively analyze the characteristics of CSF changes in Chinese patients with anti-NMDAR encephalitis, and to identify a potential relationship between CSF findings and disease prognosis.

2. Patients and methods

2.1. Standard protocol approvals, registrations and patient consents

The study was approved by the Research Ethics Committee of the Medical School of Sichuan University. Each participant provided written informed consent prior to study enrollment.

2.2. Participants

We tested for the presence of NMDAR antibodies in serum or CSF samples of patients with encephalitis between October 1, 2011 and August 1, 2014 at the West China Hospital. Patients included in the study tested positive for NMDAR antibodies and met the following inclusion criteria: (1) encephalitic signs with psychiatric symptoms (agitation, paranoid thoughts, irritability, or hallucinations), seizures, or focal neurological signs, (2) detection of anti-NMDA receptor antibodies in CSF or serum. Exclusion criteria were as follows: (1) HIV infection, meningitis, brain abscess, prion diseases, cerebral malaria, brain tumor, or a diagnosis of a non-infectious central nervous system disease, such as acute demyelinating encephalomyelitis (ADEM). (2) Patients with laboratory evidence of infectious encephalitis, e.g. viral, bacteria, mycobacterium tuberculosis (TB), parasitic or fungal. (3) Patients diagnosed with epilepsy prior to the onset of encephalitis. Neurologists who have received the uniform training on the study interviewed all of the target patients in the inpatient clinic of our center. If diagnostic and inclusion criteria were met, a research assistant introduced the study to the patient and obtained informed consent.

2.3. Determination of antibodies to NMDAR

CSF examinations of patients were performed within one week of disease onset. 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, Lübeck, Germany) as previously described [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.

2.4. CSF examination

Intracranial pressure was evaluated by cerebrospinal fluid pressure gauge and a pressure $>$ 180 mm H_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 cell counts $>5/\mu l$ without erythrocytosis and CSF protein $>$ 500 mg/L [6]. Evaluation of blood–CSF-barrier function was performed using the nationally accepted parameter of age-dependent albumin-CSF/serum-quotient (QAlb). Dysfunction was defined as QAlb $>$ Qli-Qlim(Alb), where Qlim(Alb) was calculated as 4+ (α/15) where α represents the patient's age. Quantitative expressions of the intrathecal humoral immune response were based on calculation of the QIgG (IgG-CSF/serum quotient). The upper limits of the reference range, Qlim(IgG), were calculated against QAlb according to Reiber's revised hyperbolic function. Values for QIg exceeding Qlim (Ig) were considered to indicate intrathecal immunoglobulin synthesis. [8] The detection of organism-specific nucleic acids in CSF by polymerase chain reaction (PCR) was used for rapid diagnosis of CNS infections, such as nucleic acid testing for HSV, VZV and enteroviruses. Additionally, cultures for bacteria, tuberculosis, and fungus of CSF were all performed.

2.5. Evaluation of prognosis

Clinical outcome was evaluated using the modified Rankin Scale (mRS) [9] by calling the patients at 4, 8, 12, 16, 20, and 24 months after discharge from the hospital. Good outcomes were defined as mRS score 0–2.

2.6. Statistical analysis

All analyses were performed using the SAS 9.2 software package (SAS 2000). To compare mRS scores (follow-up at 4 months, 8 months, and 12 months) between groups, including the abnormal CSF findings group (i.e. elevated pressures, elevated total cell counts, and protein levels), normal CSF findings group, serum antibody-positive group and serum antibody-negative group, the mixed effect model was used for analysis of repeated measurement data. A p-value (two-sided) of <0.05 was considered as statistically significant.

3. Results

3.1. Demographic data and characteristics of the participants

A total of 3000 people with encephalitis were screened and 43 were included in this study. Demographic details of the 43 patients with anti-NMDAR-encephalitis are provided in Table 1. The study group was comprised of 24 (55.8%) female and 19 (44.2%) male

Table 1
Clinical characteristic of participants in the study.

Characteristic/symptoms	Patient
Age Medium, range	23 (9–39)
Sex	
Female (n, %)	24 (55.8%)
Male (n, %)	19 (44.2%)
Main symptoms	
Fever (*n*, %)	31 (72.1%)
Headache and/or dizziness (*n*, %)	12 (27.9%)
Psychiatric symptoms (*n*, %)	41 (95.3%)
Seizures (*n*, %)	37 (86.0%)
Abnormal movements (*n*, %)	15 (34.9%)
Disorders of consciousness (*n*, %)	29 (67.4%)
Hypoventilation (*n*, %)	13 (30.2%)
Treatment	
First-line treatments (steroids and/or immunoglobulin) (*n*, %)	35 (81.4%)
Second-line treatments (rituximab, cyclophosphamide) (*n*, %)	2 (4.65%)

patients. The median age was 23y (range 9–39). Clinical presentations, including prodromal symptoms, consisting of headache, fever, or upper respiratory-tract symptoms, and psychiatric symptoms, sub-acute memory disturbance, seizures, and abnormal movements (Table 1). All female patients had undergone extensive whole body/pelvic imaging, but surprisingly there was only one female patient with an underlying ovarian teratoma and no other tumors were found in any other female patient. Among the 19 males, one patient had been diagnosed with renal carcinoma and another with choriocarcinoma and teratoma. Participants in our study have a novel feature was the low paraneoplastic rate 3/43 (7%). In our cohort, 36 patients received intensive immunotherapies (e.g., steroids, intravenous immunoglobulins, rituximab, and cyclophosphamide). After intensive immunotherapies, the condition of thirty patients did not continue to deteriorate, four patients refused further treatment, and two patients died.

3.2. CSF findings within one week of anti-NMDAR–encephalitis onset

In 3000 people with encephalitis screened, there were 43 patients with anti-NMDAR antibody positive in CSF and 27 patients with anti-NMDAR antibody positive in serum. During the patients screened, 62.8% (27/43) of patients with positive CSFs had positive serum samples, while 100% (27/27) patients with positive serum had positive CSF samples. None of the patients exhibited anti-NMDAR positivity only in the serum. Totally, there were 43 patients with anti-NMDAR antibody positive in CSF or serum, which were included in this study according to the inclusion criteria.

Characteristics and abnormal CSF findings of the 43 patients are described in Table 2. Increased cranial pressure (>180 mm H_2O) was observed in 17/43 (39.5%) patients, elevated total cell counts in CSF were reported in 25/43 (58.1%) patients, and 8/43 (18.6%) patients exhibited elevated total protein counts. QAlb > Qlim(Alb) was found in 12/41 (29.3%) patients, which is an indicator for blood–CSF barrier dysfunction. Elevated QIgG was detected in 7/41 (17.1%) patients. Overall, CSF sugar and chlorine levels were normal in 40 patients. Repeated CSF investigations in eight patients showed that after therapy elevated total cell and protein came back to normal.

3.3. Correlation of CSF results with prognosis

Thirty-eight of the 43 inpatients were followed for at least 4 months, during which five were lost to follow-up and two died prior to discharge from the hospital. As shown in Fig. 1, for the first day in hospital, 41 out of 43 patients had baseline mRS scores greater than or equal to 3. At the 4-month of follow-up, 27 out of 38 patients (71%) had an improved outcome (mRS 0–2). After 8 months of follow-up, 14 out of 17 patients (82%) had an improved outcome (mRS 0–2) and 1 committed suicide after suffering from depression. After 12 months of follow-up, 11/11 patients (100%) had mRS scores of 0–2. The improved prognosis of the disease was time-dependent ($P < 0.05$), as a longer follow-up period was associated with better disease outcomes. After 24 months of follow-up, all 5 patients had recovered and resumed their normal life activities, including returning to work or school.

The comparison of mRS (at 4-month, 8-month, and 12-month follow up) between patients with normal and abnormal CSF findings or between serum antibody-positive and serum antibody-negative patients is presented in Table 3. There were no differences in mRS scores between serum antibody-positive and serum antibody-negative patients ($P > 0.05$). Furthermore, there were no statistically significant differences in mRS scores between the patients with normal and abnormal CSF pressure ($P > 0.05$), the patients with normal and abnormal total protein ($P > 0.05$), and the patients with normal and abnormal total cell count ($P > 0.05$).

4. Discussion

Of 43 patients with anti-NMDA-receptor encephalitis in our study, presence of NMDA-antibodies, cerebral pressures, elevated cell counts, and elevated protein counts were identified in CSF. Our results suggest that abnormal CSF findings did not affect patients' prognosis and that a longer follow-up period was associated with a better outcome.

In this study we determined that all 43 patients tested were positive for anti-NMDAR antibodies in CSF. However, only 27 patients tested positive for antibodies in serum. This result is consistent with the observations of Dalmau and colleagues, [2] who showed that, none of the 431 patients studied (412 with paired serum and CSF) showed antibody positivity exclusively in serum. Also, Titulaer et al. determined that detection of NMDAR antibodies was more sensitive in CSF (100%) than in serum (85%; $P < 0.0001$) in a comparison of 250 paired serum and CSF samples [4,10]. However, in a previous study by Jung-Ah Lim et al. in which both serum and CSF of 17 patients were tested for presence of (anti-NMDAR) antibodies, 13 patients exhibited antibody positivity only in serum [11]. Irani et al. [12], determined that the absolute levels of NMDA antibodies were higher in serum than in cerebrospinal fluid, and the analysis of Brenda et al. [7], found significantly higher serum antibody levels compared to CSF. The disparity may be arisen by different methods and details of procedure [13]. Some laboratories used commercial kits that provide fixed brain tissue and fixed antigen-expressing cells may detect nonpathogenic antibodies to intracellular and fixation-exposed epitopes, while, some employed live mammalian cells which exposed the patients' antibodies only to the extracellular domains of native antigens. We have to acknowledge a limitation

Table 2
CSF findings of patients with anti-NMDAR encephalitis.

CSF	Units	Reference range	Mean Std. deviation	Median range	Elevated *n*(%)
Intracranial pressure	mmH_2O	<180	N.A.[a]	N.A.[a]	17/43 (39.5)
Total cell, CSF	cells/μl	≤5	31.31 (88.35)	10(0–540)	25/43 (58.1)
Total protein, CSF	g/l	≤0.50	0.39 (0.22)	0.32(0.22–1.40)	8/43 (18.6)
Alb, CSF	g/l	≤0.30	0.219 (0.152)	0.141(0.0755–0.647)	10/41 (24.4)
QAlb	–	N.A.[a]	5.33 (3.55)	3.84(1.69–19.61)	12/41 (29.3)
IgG, CSF	g/l	≤0.04	0.0421 (0.0613)	0.0274(0.0127–0.411)	12/41 (29.3)
QIgG	–	N.A.[a]	3.25 (1.50)	2.81(1.70–9.25)	7/41 (17.1)

Median (with ranges) values as well as number and proportion of patients with elevated values are given; Alb, CSF, albumin concentration of CSF; QAlb, (AlbCSF/Alb serum)*1000; IgG, CSF, IgG concentration of CSF. QIgG, (IgGCSF/IgG serum)*1000; N.A, not available.
[a] Age-dependent.

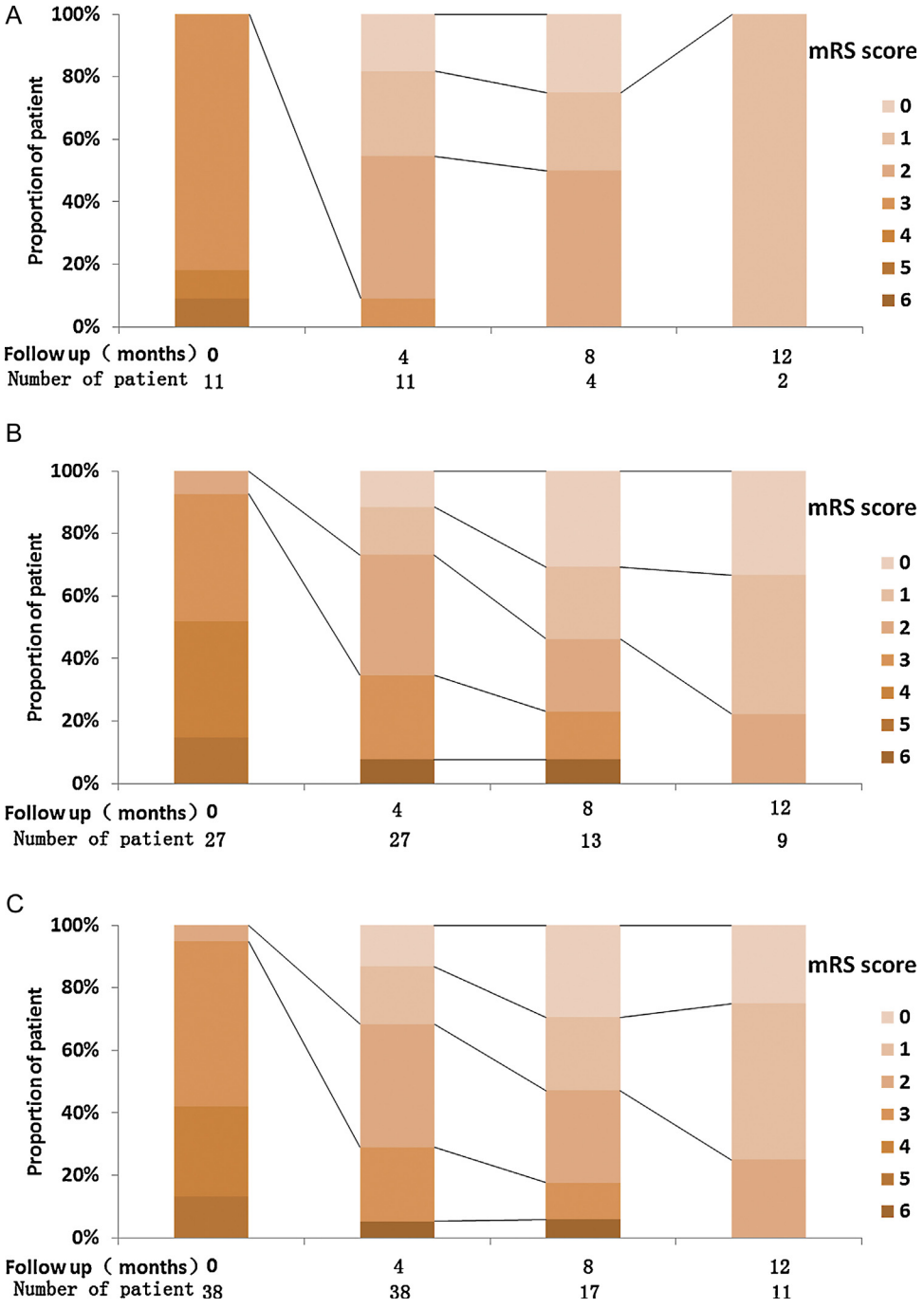

Fig. 1. Clinical outcome (mRS scores). (A) Clinical outcome in patients with abnormal findings; (B) clinical outcome in patients with normal CSF findings; (C) clinical outcome in all patients; follow up months: 0, means the first day patient in hospital, the baseline mRS scores.

that we did not do more titers in this study and to compare levels of NMDA antibodies in CSF and serum.

Of the 43 patients from whom we obtained CSF samples, 25 (58.1%) had elevated total cell counts, and 8 (18.6%) had elevated total protein counts, which is similar to what has been reported in other cases. Dalmau et al.'s [14] investigation of CSF revealed mild lymphocytic pleocytosis in 91% of cases, and intrathecal protein increase in 32% of cases. Also, Malter et al. [6], reported that in 14 anti-NMDAR-encephalitis patients, elevated cell counts were reported in 2/14 (14.3%) patients and elevated protein counts in 5/14 (35.7%) patients. And in their review of literature, in 109 anti-NMDAR-encephalitis patients elevated cell counts were found in 79/107 (74%) patients and elevated protein counts in 30/101 (30%) patients. while some case series reported slight CSF changes [1,15,16]. These studies are consistent in showing that in patients with anti-NMDAR-encephalitis, CSF findings are either normal or exhibit only slight changes. To date, there have been no reports demonstrating a relationship between intracranial pressure changes and anti-NMDAR encephalitis; therefore, our research is the first to show that 39.5% of patients with anti-NMDAR encephalitis have increased intracranial pressure.

To the best of our knowledge, few studies have reported a relationship between CSF findings and the prognosis of

Table 3
The relationship between CSF findings and mRS scores (follow up at 4 months, 8 months and 12 months).

Variable	mRS scores at 4 months		mRS scores at 8 months		mRS scores at 12 months	
	n (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value
Pressure						
Elevated	16/38 (42.1%)	0.2576	5/17 (29.4%)	0.784	4/11 (36.4%)	0.7083
Normal	22/38 (57.9%)		12/17 (70.6%)		7/11 (63.6%)	
Total protein						
Elevated	7/38 (18.4%)	0.5617	4/17 (23.5%)	0.0619	2/11 (18.2%)	0.4827
Normal	31/38 (81.6%)		13/17 (76.5%)		9/11 (81.8%)	
Total cell count						
Elevated	22/38 (57.9%)	0.066	10/17 (58.8%)	0.0653	7/11 (63.6%)	0.2388
Normal	16/38 (42.1%)		7/17 (41.2%)		4/11 (36.4%)	
Antibody in serum						
Positive	21/38 (55.3%)	0.2694	10/17 (58.8%)	0.9209	10/11 (90.9%)	0.9165
Negative	17/38 (44.7%)		7/17 (41.2%)		1/11 (9.1%)	

P-values < 0.05 were considered statistically significant.

anti-NMDAR encephalitis in any country. In the present study, one year after discharge from the hospital, the majority of patients had regained their independence and the ability to perform self-care, and had returned to the workplace or to school. In addition, we found that improved mRS scores were not significantly associated with changes in CSF findings. Based on this study, the prognoses may not be affected by abnormal CSF findings, but may be more related to the recovery time. Titulaer et al. [4] found that predictors of good outcome included lower severity of symptoms (assessed as no need for admission to an intensive care unit), the prompt initiation of immunotherapy, and tumor removal.

Previous studies have shown that albumin can serve as an indicator of compromised BBB function in a variety of pathophysiological conditions [17–19]. Pentylenetetrazole-induced seizures cause disruption of the BBB, allowing penetration of large blood-borne molecules, including albumin, into the CNS. Increased albumin concentrations in CSF are directly due to blood–CSF barrier dysfunction, as albumin originates exclusively from the blood [20]. In this study, we have found that a subset of patients exhibited blood–CSF barrier dysfunction, which illustrates the process of cerebral inflammation.

In our study, the paraneoplastic rate in patients with anti-NMDAR antibody positive in CSF or serum was 3/43 (7%), which seems to be lower than previous reports. Irani et al. [12], reported that there were 8/31 (26%) female patients with ovarian teratomas, and 1/13 (8%) males with Hodgkin's lymphoma. Also, Dalmau et al. [14], reported 58 (59%) of 98 patients had a neoplasm. The disparity may arise by the ethnicity differences.

Here we demonstrate that normal CSF findings do not rule out a diagnosis of anti-NMDAR-encephalitis, but are a frequent finding in the disease. Based on these results, we recommend that, once anti-NMDAR-encephalitis is clinically suspected, evaluation of NMDAR antibodies be performed, even in patients with normal or unremarkable CSF findings. This includes patients with the following characteristics: (1) encephalitic signs, including psychiatric symptoms (agitation, paranoid thoughts, irritability, or hallucinations), (2) seizures, and (3) exclusion of viral/bacterial etiology, especially in very young patients. Our findings encourage physicians to screen for immune-related causes in all patients with encephalitis, and run in parallel with other routine tests.

Conflict of interest

The authors declare that they have no conflicts of interest.

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