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MAJOR ARTICLE

In Children, *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis Incidence Exceeds That of Japanese Encephalitis in Vietnam

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Background. The recognition of autoimmune causes of encephalitis has led to epidemiological shifts in the worldwide characteristics of encephalitis. *N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis leads to well-established complex neuropsychiatric manifestations. In low- and middle-income countries, including Vietnam, its relative incidence, especially in children, is unknown and most neurologists currently consider infectious encephalitis prior to autoimmune etiologies.

Methods. The study was prospectively conducted at Children's Hospital 1 in Ho Chi Minh City between March 2020 and December 2022. Any child admitted to the Department of Infectious Diseases and Neurology fulfilling the case definition of encephalitis was eligible to participate. Cerebrospinal fluid samples were collected alongside meta-clinical data for analysis.

Results. We recruited 164 children with a clinical diagnosis of encephalitis. Etiologies were determined as NMDAR antibody encephalitis in 23 of 164 cases (14.0%), Japanese encephalitis virus in 14 of 164 (8.5%), and herpes simplex virus in 4 of 164 (2.4%). Clinical categorizations suggested idiopathic viral encephalitis in another 71 (43.3%), and autoimmune encephalitis of unknown origin in the remaining 52. Factors including demographics, specific clinical features, cerebrospinal fluid and electroencephalogram findings, and length of hospital stay were significantly different between NMDAR antibody encephalitis and Japanese encephalitis.

Conclusions. At a tertiary children's hospital in Vietnam, the prevalence of NMDAR antibody encephalitis exceeds that of Japanese encephalitis, the most common infectious encephalitis cause in Southeast Asia. NMDAR antibody encephalitis is associated with long hospital stay and poor outcomes. These findings should change pediatric diagnostics, to earlier consider autoimmune treatments in this clinical setting.

Keywords. children; encephalitis; herpes simplex virus; Japanese encephalitis virus; *N*-methyl-D-aspartate receptor antibody encephalitis.

Traditionally, infectious pathogens are regarded as the most common causes of encephalitis worldwide [1, 2]. Of these, Japanese encephalitis virus (JEV), a mosquito-borne arbovirus responsible for Japanese encephalitis (JE), is the leading cause of infectious encephalitis in Asia, especially Southeast Asia, and is associated with high morbidity and mortality [3]. Despite the availability of effective vaccines, a recent study in Cambodia, Vietnam, Laos, and Myanmar showed that in 664 children with encephalitis, JEV was the leading cause, accounting for 33% [4]. A mathematical modeling study based on age-stratified case data estimated that globally in 2015, JEV was responsible for 100 308 encephalitis cases (95% confidence interval [CI], 61 720–157 522) and 25 125 associated deaths (95% CI, 14 550–46 031) [5].

Over the last decade, autoimmune encephalitis has been increasingly recognized as an important cause of encephalitis in children, with antibodies against *N*-methyl-D-aspartate receptor (NMDAR) antibody (Ab) the leading cause in this age group. Studies from high-income counties, including the United States, Denmark, and Germany, have shown that the frequency of autoimmune encephalitis has now exceeded infectious etiologies [6–10].

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This shift in encephalitis epidemiology has challenged routine diagnosis and clinical management of these patients [6–12]. Yet, as existing literature is currently dominated by studies from developed countries, it remains unclear whether this shift is observed in low- and middle-income countries (LMICs) [13–15]. Here, we aim to contrast the frequencies of autoimmune and infectious encephalitis in patients admitted to a major children's hospital in southern Vietnam.

METHODS

Study Design and Setting

The prospective study was conducted at Children's Hospital 1 (CH1) in Ho Chi Minh City (HCMC) in Vietnam between March 2020 and December 2022. CH1 is a 1600-bed hospital and is the largest tertiary referral hospital for children coming from southern provinces of Vietnam, with a catchment population of >40 million, including an estimated 11 million children.

Inclusion and Exclusion Criteria

Inclusion criteria were any child (aged ≤16 years) who was admitted to the Department of Infectious Diseases and Neurology of CH1 during the study period and fulfilled the clinical diagnostic criteria of encephalitis. Patients were excluded if no informed consent was obtained.

Encephalitis Case Definition

The case definition was as follows: the diagnosis of encephalitis with altered mental status (ie, decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours, with no alternative cause identified, and ≥2 of the following criteria: documented fever ≥38°C (100.4°F) within 72 hours (before or after) presentation, generalized or partial seizures not fully attributable to preexisting seizure disorder, new-onset focal neurologic findings, cerebrospinal fluid (CSF) white blood cell count ≥5 cells/μL, abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is new or appears to have acute onset, and electroencephalogram (EEG) consistent with encephalitis and not attributable to any other cause [16–19].

Clinical Diagnostic Criteria of Probable Autoimmune Encephalitis

As part of routine care, any patients presenting with clinically suspected encephalitis were further assessed for probable autoimmune encephalitis to inform laboratory diagnostic testing. The diagnostic criteria for probable autoimmune encephalitis were made when all 3 of the following criteria were met: (1) subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms; (2) at least 1 of the following: new focal central nervous system findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis (white blood cell count of >5 cells/μL), or magnetic resonance imaging (MRI) features suggestive of encephalitis; and (3) reasonable exclusion of alternative causes [16–19]. Enrolled patients who did not meet those predefined criteria of probable autoimmune encephalitis were considered as having infectious encephalitis.

Data Collection

At enrollment, the study participants had acute CSF samples collected alongside meta-clinical data, including dates of birth, admission, and discharge; demographic data; clinical features; laboratory and imaging results; diagnoses; and treatment. Patient consciousness level was evaluated using the pediatric Glasgow Coma Scale (GCS) [20]. The modified Rankin scale for children was used to assess the degree of disability or dependence in daily activities [21]. The neurological sequelae including paralysis, developmental delay, altered mental status, speech disorder, and motor disturbance were developed by all encephalitis subtype.

Routine Laboratory Diagnostic Approach

As part of routine care at CH1, the CSF of patients presenting with brain infections is subject to culture and/or examined by microscopy for detection of bacterial, viral, and fungal infections with the use of standard methods when appropriate. Additionally, the CSF of patients with clinically suspected encephalitis was tested for the presence of herpes simplex virus (HSV) DNA and JEV immunoglobulin M (IgM) using real-time polymerase chain reaction (PCR) and an IgM capture enzyme-linked immunosorbent assay, respectively [22].

The CSF of patients with clinical presentations compatible with autoimmune encephalitis [17–19] was tested for antibodies against NMDAR and, where available, antibodies against other antigens (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPA-R1/R2], γ-aminobutyric acid-A [$GABA_{A/B1/B2}R$], leucine-rich glioma-inactivated 1 [LGI1], contactin-associated protein-like 2 [CASPR2], and dipeptidyl-peptidase-like protein 6 [DPPX]). For autoimmune encephalitis diagnosis, we used commercial fixed cell–based assays (EUROIMMUN, Lübeck, Germany) [23]. The CSF of patients with autoimmune encephalitis was also tested for viral causes (Figure 1).

Data Analysis

Descriptive statistics were employed to compare between the epidemiology, clinical presentation, laboratory findings, treatment, and outcomes of patients with NMDAR-Ab encephalitis and those with JE. For these analyses, where appropriate, we applied Pearson χ^2, Fisher exact, and Wilcoxon rank-sum

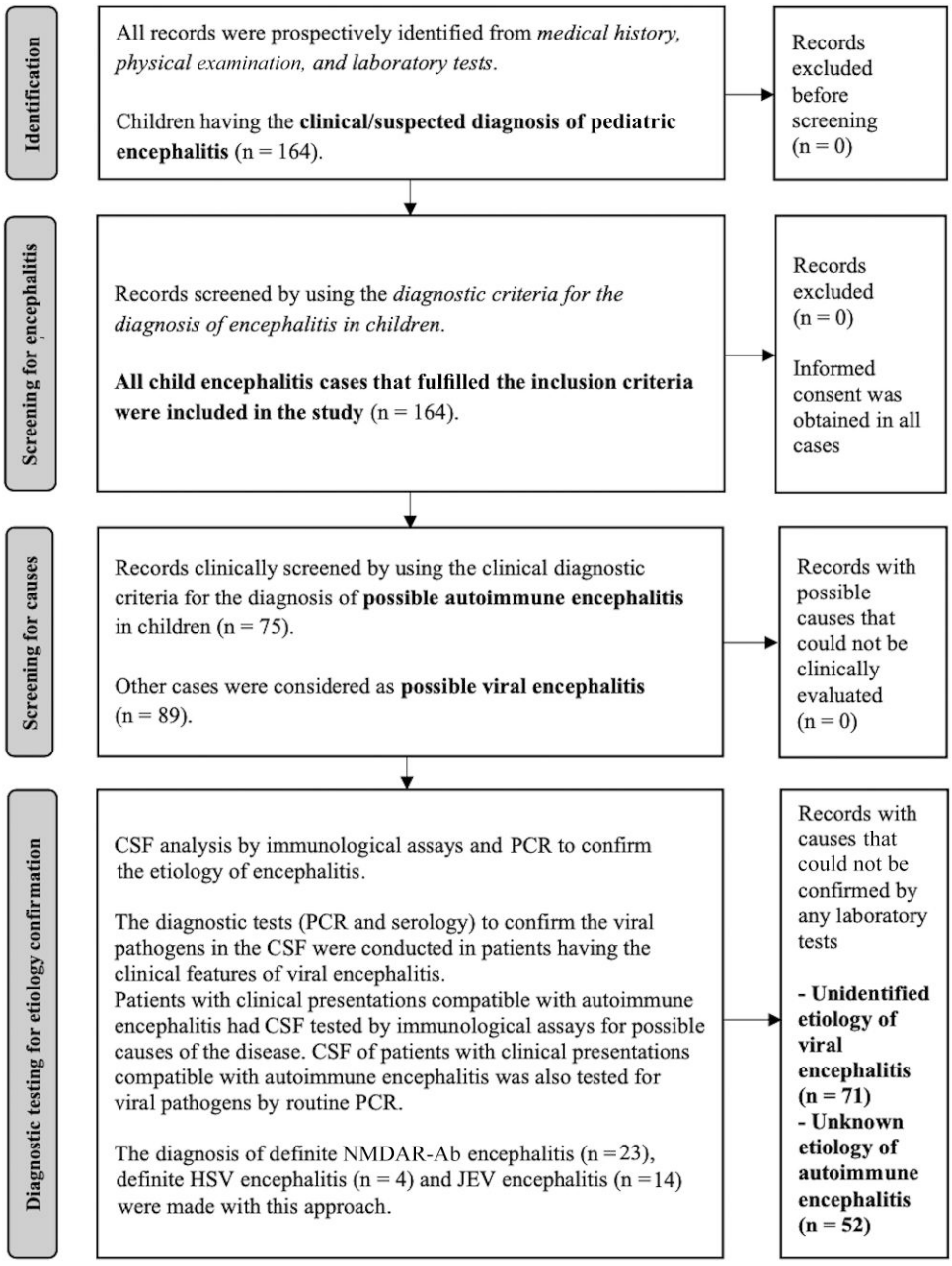

Figure 1. Flowchart for the identification, screening, and diagnosis of encephalitis. Abbreviations: CSF, cerebrospinal fluid; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; NMDAR-Ab, *N*-methyl-D-aspartate receptor antibody; PCR, polymerase chain reaction.

tests. All statistical analyses were performed using Stata version 18 (StataCorp LP, College Station, Texas) and R 4.1.0 (R Core Team, 2021) software.

Ethics

The study was approved by the ethics committee of CH1 (1503/QD-BVND1) and the Oxford Tropical Research Ethics Committee (OxTREC 7-20). Written informed consent was obtained from a parent or guardian of the study participants, and if the study participant was ≥12 years old, an assent form was also obtained.

RESULTS

Study Patients and Results of Laboratory Diagnosis

A total of 164 children with a clinical diagnosis of encephalitis, 85 (51.8%) male and 79 (48.2%) female, were enrolled in the

study between March 2020 and December 2022. Of these, 75 cases (45.7%) had signs and symptoms meeting the predefined criteria of probable autoimmune encephalitis. The remaining 89 (54.3%) were classified as having infectious encephalitis.

Of the 75 patients with probable autoimmune encephalitis, all CSF samples were examined for NMDAR-Ab, while 22 were also tested for antibodies against AMPA-R1/R2, $GABA_A/_{B1}/_{B2}R$, LGI1, CASPR2, or DPPX. CSF antibodies against NMDAR were detected in 23 of 75 (30.7%) patients, and none had antibodies against the remaining antigens.

Of the 89 patients with a clinical diagnosis of infectious encephalitis, JEV and HSV were detected in 14 (15.7%) and 4 (4.5%), respectively. Collectively, of the 164 enrolled patients, NMDAR-Ab encephalitis was detected in 23 (14.0%), while JEV or HSV was detected in 18 (11.0%; JEV in 14/164 [8.4%] and HSV in 4/164 [2.6%]) (Figure 1).

Demographics, Clinical Features, and Laboratory Findings

Clinical features of NMDAR-Ab encephalitis and JE were compared, and 4 HSV patients were excluded (Supplementary Tables 1 and 2). While there were considerable similarities in clinical presentations between patients with confirmed NMDAR-Ab encephalitis and probable autoimmune encephalitis (Supplementary Table 1), JE features were different (Table 1). Supplementary Table 3 shows detailed data on NMDAR-Ab encephalitis (n = 23), undefined autoimmune encephalitis (n = 52), defined infectious encephalitis (n = 18), and undefined infectious encephalitis (n = 71).

Of the 23 patients with NMDAR-Ab encephalitis, females were predominant (19/23 [82.6%]), and males were all <12 years of age. Patients with NMDAR-Ab encephalitis were older than those with JE and 16 of 23 (69.6%) came from outside HCMC (Table 1); in contrast, 12 of 14 (85.7%) JE patients were male and all were from outside HCMC ($P = .031$).

Fever recorded at enrollment was documented in all 14 JE patients, but in just over half (56.5% [13/23]) of patients with NMDAR-Ab encephalitis, with a longer fever duration recorded in the former (median, 7 [interquartile range {IQR}, 5–10] days vs 3 [IQR, 3–7] days; $P = .014$). Likewise, patients with JE were associated with a lower level of consciousness than those with NMDAR-Ab encephalitis (median GCS score, 8 [IQR, 8–11] vs 11 [IQR, 9–12]). In terms of neurological features, signs and symptoms such as psychiatric disorder, cognitive dysfunction, language changes, abnormal movement, and dyskinesias were almost exclusively found in patients with NMDAR-Ab encephalitis (Figure 2).

Compared with JE patients, NMDAR-Ab encephalitis patients had lower CSF white cell counts (median, 11 [IQR, 3–28] cells/μL vs 99 [IQR, 59–300] cells/μL; $P = .0006$; Figure 3), lower CSF protein levels (median, 0.3 [IQR, 0.2–0.4] g/L vs 0.8 [IQR, 0.6–0.9] g/L; $P < .0001$), and lower CSF lactate levels (median, 1.6 [IQR, 1.5–1.9] mmol/L vs 2.1 [IQR, 1.8–2.6] mmol/L; $P = .0109$). Both patient groups had similar CSF/plasma glucose ratios (Figure 3). The CSF of patients with clinical presentations compatible with autoimmune encephalitis was also tested for viral pathogens by routine PCR: only 1 showed positivity, with CSF PCR HSV detected and the subsequent development of CSF NMDAR-Ab 2 months later. No association was observed between JEV and NMDAR-Ab encephalitis. However, symptomatic infectious prodrome (ie, fever, headache, and flu-like symptoms) was found in 13 of 23 (56.5%) patients with NMDAR-Ab encephalitis. JEV vaccine history within 4–6 weeks was not available; therefore, we unfortunately could not assess the speculation about JEV vaccine triggering NMDAR-Ab encephalitis.

MRI and EEG Findings

On MRI, in patients with NMDAR-Ab encephalitis, abnormalities were frequently detected in the limbic system (15/23 [65.2%]) and cerebral cortex (13/23 [56.5%]), whereas thalami were affected in all JE patients. From the 23 patients with NMDAR-Ab encephalitis, EEG showed slow waves and delta brush in 12 (52.2%) and 3 (13.0%), respectively (Table 1). No remarkable signals of EEG were documented in patients with JE.

Treatment

In our local practice, immunotherapy was initiated when autoimmune encephalitis was clinically suspected without waiting for confirmatory test results, and followed recent International Consensus Recommendations [24]. First-line immunotherapies included methylprednisone (21 cases [91.3%]) and immunoglobulin (9 cases [39.1%]), with cyclophosphamide (n = 7 [30.4%]) (available at our center since May 2020) and rituximab (n = 4 [17.4%]) (available at our center since June 2022) as second-line immunotherapies (Table 1).

Outcomes

There was a significant association between days of illness before admission and sequelae ($P = .039$) but not mortality ($P = .068$). Patients with NMDAR-Ab encephalitis had a longer duration of hospital stay than patients with JE (median, 38 [IQR, 15–53] days vs 15 [IQR, 11–20] days; $P = .021$). At discharge, fatal outcome was documented in 1 patient with NMDAR-Ab encephalitis, but not in JE patients. In addition, there was no statistically significant difference of the modified Rankin scale and neurological sequelae between patients with NMDAR-Ab and patients with JE (Table 1).

DISCUSSION

Here we report the first description of NMDAR-Ab encephalitis in children admitted to a tertiary referral hospital for children in southern Vietnam. We identify NMDAR-Ab at a higher frequency than JE, the most common cause of viral

Table 1. Clinical Features of Patients With Encephalitis

Characteristic	NMDAR-Ab Encephalitis (n = 23)	JEV Encephalitis (n = 14)	HSV Encephalitis (n = 4)	Defined Encephalitis (n = 41)	Undefined Encephalitis (n = 123)	*P* Value[a]	*P* Value[b]
Demographic features							
Female sex	19 (82.6)	2 (14.3)	3 (75.0)	24 (58.5)	55 (44.7)	<.001	.125
Age, y, median (IQR)	10.0 (9.0–13.0)	4.5 (1.0–9.0)	9.0 (3.5–13.5)	9.0 (3.0–12.0)	9.0 (5.0–12.0)	.007	.672
From Ho Chi Minh City	7 (30.4)	0 (0.0)	0 (0.0)	7 (17.1)	36 (29.3)	.031	.104
From other provinces	16 (69.6)	14 (100.0)	4 (100.0)	34 (82.9)	87 (70.7)		
Clinical features							
Illness days before admission, median (IQR)	4.0 (3.0–10.0)	5.0 (3.0–6.0)	4.5 (2.0–15.0)	4.0 (3.0–10.0)	4.0 (3.0–7.0)	.975	.493
Fever	13 (56.5)	14 (100.0)	4 (100.0)	31 (75.6)	84 (68.3)	.006	.375
Highest temperature during hospitalization, °C, median (IQR)	38.8 (38.5–39.0)	39.0 (39.0–40.0)	39.4 (38.6–40.0)	39.0 (38.8–40.0)	39.0 (38.5–39.5)	.007	.282
Duration of fever, d, median (IQR)	3.0 (3.0–7.0)	7.0 (5.0–10.0)	8.0 (6.0–10.0)	6.0 (4.0–10.0)	4.0 (3.0–6.0)	.014	.041
GCS score, median (IQR)	11 (9–12)	8 (8–11)	7 (4–10)	11 (8–12)	12 (10–13)	.036	<.001
Seizure	17 (73.9)	6 (42.9)	4 (100.0)	27 (65.9)	76 (61.8)	.059	.641
Neurologic deficits	6 (26.1)	7 (50.0)	2 (50.0)	15 (36.6)	23 (18.7)	.139	.019
Abnormal muscular tone	8 (34.8)	4 (28.6)	2 (50.0)	14 (34.2)	31 (25.2)	.695	.266
MRI findings							
Cerebral cortex	13 (56.5)	2 (14.3)	4 (100.0)	19 (46.3)	43 (35.0)	.011	.193
Limbic system	15 (65.2)	2 (14.3)	0 (0.0)	17 (41.5)	24 (19.5)	.003	.005
Thalamus	9 (39.1)	14 (100.0)	0 (0.0)	23 (56.1)	4 (3.3)	<.001	<.001
Mid-brain	9 (39.1)	3 (21.4)	0 (0.0)	12 (29.3)	4 (3.3)	.265	<.001
Cerebellum	7 (30.4)	3 (21.4)	0 (0.0)	10 (24.4)	11 (8.9)	.550	.010
Brain stem	4 (17.4)	1 (7.1)	0 (0.0)	5 (12.2)	8 (6.5)	.377	.243
EEG abnormality							
Delta brush	3 (13.0)	0 (0.0)	0 (0.0)	3 (7.3)	1 (0.8)	.275	.019
Slow waves	12 (52.2)	0 (0.0)	3 (75.0)	15 (36.6)	27 (22.0)	.001	.063
Spike waves	2 (8.7)	0 (0.0)	0 (0.0)	2 (4.9)	8 (6.5)	.517	.706
Beta waves	1 (4.3)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1.000	.250
Seizure	1 (4.3)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.8)	1.000	.411
Fast activity	2 (8.7)	0 (0.0)	0 (0.0)	2 (4.9)	3 (2.4)	.517	.431
Slow baseline activity	1 (4.3)	0 (0.0)	1 (25.0)	2 (4.9)	11 (8.9)	1.000	.404
Low voltage	1 (4.3)	0 (0.0)	1 (25.0)	2 (4.9)	1 (0.8)	1.000	.093
Treatment							
Corticosteroid	21 (91.3)	1 (7.1)	1 (25.0)	23 (56.1)	60 (48.8)	<.001	.417
Immunoglobulin	9 (39.1)	0 (0.0)	0 (0.0)	9 (22.0)	18 (14.6)	.007	.274
Cyclophosphamide	7 (30.4)	0 (0.0)	0 (0.0)	7 (17.1)	2 (1.6)	.031	<.001
Rituximab	4 (17.4)	0 (0.0)	0 (0.0)	4 (9.8)	2 (1.6)	.276	.016
Acyclovir	18 (78.3)	10 (71.4)	4 (100.0)	32 (78.0)	93 (75.6)	.639	.751
Mannitol	14 (60.9)	12 (85.7)	2 (50.0)	28 (68.3)	59 (48.0)	.109	.024
Sodium chloride 3%	3 (13.0)	3 (21.4)	2 (50.0)	8 (19.5)	15 (12.2)	.502	.243
Outcomes							
Length of hospital stay, d, median (IQR)	38.0 (15.0–53.0)	15.0 (11.0–20.0)	22.0 (16.0–47.5)	22.0 (12.0–46.0)	15.0 (10.0–21.0)	.021	.002
Mortality	1 (4.3)	0 (0.0)	0 (0.0)	1 (2.4)	2 (1.6)	1.000	.737
Sequelae	13 (56.5)	9 (64.3)	3 (75.0)	25 (61.0)	39 (31.7)	.641	.001
Modified Rankin scale	2 (0–3)	1 (0–2)	2 (1–3)	1 (0–2)	0 (0–1)	.553	.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Ab, antibody; EEG, electroencephalogram; GCS, Glasgow Coma Scale; HSV, herpes simplex virus; IQR, interquartile range; JEV, Japanese encephalitis virus; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor.

[a]Comparisons are made between NMDAR Ab encephalitis and JEV encephalitis using Pearson χ^2 test, Fisher exact test, and Wilcoxon rank-sum test. A *P* value <.05 is statistically significant.

[b]Comparisons are made between defined encephalitis and undefined encephalitis using Pearson χ^2 test, Fisher exact test, and Wilcoxon rank-sum test. A *P* value <.05 is statistically significant.

encephalitis in Asia, including Vietnam [25–27]. Additionally, we show that compared with JE, NMDAR-Ab encephalitis was associated with a different set of clinical features and longer hospital stays.

Autoimmune encephalitis may have a sex predominance, of which NMDAR-Ab encephalitis is more frequently seen in female patients [7, 28]. It has been hypothesized that sex-related tumor incidence may be the reason for this difference [28],

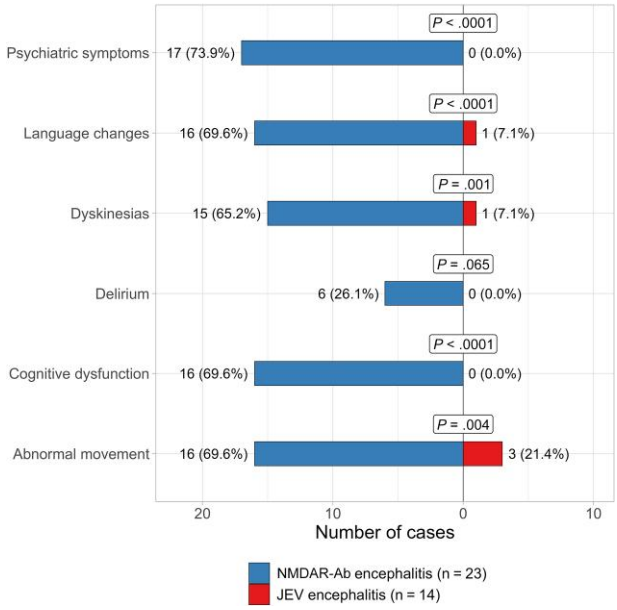

Figure 2. Frequency of psychological disorders and other features predominantly recorded in patients with *N*-methyl-D-aspartate receptor antibody encephalitis as compared to that of patients with Japanese encephalitis. Psychiatric symptoms were described in terms of agitation, hallucinations, sleep disorders, and mood changes. Abnormal movement included dyskinesias, dystonia, stereotypical movement disorder, chorea, catatonia, bradykinesia, and tremor. Dyskinesias were described as lingual, orofacial, or limb dyskinesias. Abbreviations: JEV, Japanese encephalitis virus; NMDAR-Ab, *N*-methyl-D-aspartate receptor antibody.

but no tumor was found in our patient population. Our results were consistent with the California Encephalitis Project, a major study, in which 65% of NMDAR-Ab encephalitis occurred in patients <18 years of age, and this was a predilection, which was not observed with viral encephalitis [7].

Our findings are consistent with those from higher-income countries such as the United States, which also show that the frequency of autoimmune causes, especially NMDAR-Ab, now exceeds that of infectious etiologies [6, 7]. Since 2015, JEV vaccine was introduced into Vietnam's national expanded vaccination program. A dedicated study would be needed to assess the extent to which JEV vaccine has shaped the epidemiology of encephalitis as a whole in Vietnam. This is, however, beyond the scope of the present study.

When comparing patients with NMDAR-Ab encephalitis and those with probable autoimmune encephalitis but seronegative for antibodies against NMDAR, we found considerable similarities in clinical presentations and neuroinflammation features between the 2 groups. However, we did not find evidence of antibodies against AMPA-R1/R2, $GABA_A/_{B1}/_{B2}R$, LGI1, CASPR2, or DPPX antigens in a subset of 22 patients with probable autoimmune encephalitis. The causes remained undefined in 52 of 75 (69.3%) patients with probable autoimmune encephalitis. While the data further emphasize that NMDAR-Ab is the most common cause of autoimmune encephalitis in children [29–32], future research should

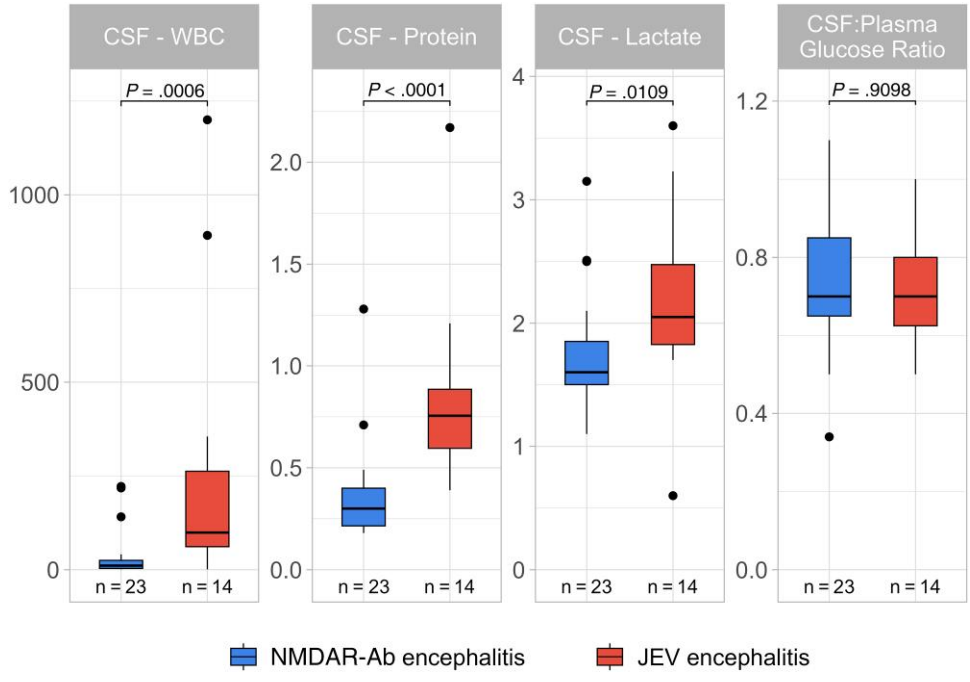

Figure 3. Cerebrospinal fluid laboratory data of *N*-methyl-D-aspartate receptor antibody encephalitis in comparison with that of patients with Japanese encephalitis. Abbreviations: CSF, cerebrospinal fluid; JEV, Japanese encephalitis virus; NMDAR-Ab, *N*-methyl-D-aspartate receptor antibody; WBC, white blood cell.

comprehensively look at all of the 23 possible autoantibodies currently recognized as potential causes of autoimmune encephalitis [33].

Currently, treatment pathways of NMDAR-Ab encephalitis include first-line immunotherapy (intravenous steroids, intravenous immunoglobulins, and plasma exchange) and, if no improvement, second-line therapy (rituximab and cyclophosphamide) [24, 31]. Early treatment has been shown to be associated with better clinical outcome in patients with autoimmune encephalitis. The identification of features commonly found in patients with NMDAR-Ab encephalitis such as sex, neuroinflammation, and, in particular, clinical manifestations (psychological and movement disorder and language change) are consistent with findings from previous studies [9, 11, 24, 34–36]. These features therefore should be useful for clinicians in approaching children with encephalitis, especially in resource-limited settings where diagnostic assays are not readily available.

We appreciate that there are many more pathogens (other than JEV and HSV as well as bacteria) of infectious encephalitis. The bacterial infections are excluded in all cases of encephalitis, especially autoimmune cases, with routine test of CSF samples (cells, biochemical characteristics, latex test for bacteria, Gram stain, and culture). However, unfortunately, we could only find exactly 14 JEV and 4 HSV cases causing infectious encephalitis with our routine diagnostic testing. Acute disseminated encephalomyelitis (ADEM) is a common presentation of myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD), a group of central nervous system demyelinating diseases. However, the detection of MOG antibodies in plasma and CSF by immunofluorescence assays to confirm the diagnosis is currently not available at our center. We do send plasma samples for MOG test to a certified testing center, but not in the context of this study. In our study, the MRI and EEG studies did not find any images associated with ADEM and MOGAD.

The strength of our study is that it was conducted at a tertiary referral hospital for children in Vietnam, a low- and middle-income country, where limited data exist regarding the epidemiology of autoimmune encephalitis [37]. Therefore, these results have added to the growing body of knowledge about the burden associated with NMDAR-Ab encephalitis worldwide. However, owing to the nature of a single hospital-based study, the obtained results from a study with limited number of cases might not be generalizable to the wider community in Vietnam and may misestimate overall etiologies of encephalitis. In the SouthEast Asia Encephalitis Project [4], centered around encephalitis in the Greater Mekong region over approximately 3 years, 4 hospitals in Cambodia, Vietnam, Laos, and Myanmar recruited 664 children with encephalitis. Given different likely catchments, this rate of approximately 50 cases/year/hospital was equivalent to our findings of 164 children in 2.8 years from 1 hospital (~58 cases/year/hospital). Additionally, the coronavirus disease 2019 lockdown during the study period could be a potential bias toward the admission of more patients from outside HCMC, resulting an overestimation of disease burden. Finally, our study was limited by the intrinsic difficulties in defining undiagnosed encephalitis: In the absence of microbiological and immunological confirmations, encephalitis cases in our study have been defined based on compatible manifestations of autoimmune encephalitis or viral encephalitis suggested by guidelines [18, 19, 38–40].

CONCLUSIONS

In summary, our study has revealed that NDMAR-Ab encephalitis is an important differential diagnosis in Vietnamese children presenting with clinically suspected encephalitis. The disease is associated with long hospitalization and poor outcome. Our findings could change pediatric diagnostics and treatment interventions, to move toward more appropriate approaches in Vietnam.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. N. H. T. H. conceptualized the study, performed data analysis, and drafted, reviewed, and edited the full manuscript. N. D. T. performed data analysis and drafted, reviewed, and edited the full manuscript. T. B. T. performed data analysis. T. H. K., N. M. T., T. T. T., N. A. N., N. T. K. T., L. N. T. N., N. N. Q. M., N. T. H., and D. T. Q. were responsible for enrolling participants into studies from which cerebrospinal fluid samples were collected. L. Q. T. and L. V. T. performed microbiological diagnostics of encephalitis. H. C. T., C. L. T., L. V. T., and S. R. I. reviewed and edited the full manuscript. All authors reviewed and approved the manuscript for submission.

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