Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Abnormal CSF-Specific OCBs in Neuronal Surface Antibody-Associated Autoimmune Encephalitis Differentiating from Viral Encephalitis

Shan Qiao[1,2,*], Chong Zhang[1,3,*], Haiyun Li[4,*], Tianyu Zhou[1,3], Aihua Wang[1], Shanchao Zhang[1,5,6]

[1]Department of Neurology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Institute of Neuroimmunology, Jinan, People`s Republic of China; [2]Department of Medical Genetics, School of Basic Medical Sciences, Cheeloo College of, Medicine, Shandong University, Jinan, People's Republic of China; [3]Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, People`s Republic of China; [4]Department of Geriatric Medicine, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China; [5]School of Medicine, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China; [6]Department of Neurology, Beijing Friendship Hospital, Capital Medical University, Beijing, People`s Republic of China

*These authors contributed equally to this work

Correspondence: Shanchao Zhang, Department of Neurology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Institute of Neuroimmunology, Jinan, People`s Republic of China, Email zhangshanchao2012@163.com

Purpose: The present study aimed to examine the clinical distinctions among patients with neuronal surface antibody-associated autoimmune encephalitis (NSAE) diagnosed with anti-N-methyl-D-aspartate receptor encephalitis (NMDAR-E), anti-leucine-rich glioma-inactivated 1 encephalitis (LGI1-E), and anti-gamma aminobutyric acid-B receptor encephalitis (GABABR-E), compared with those with viral encephalitis (VE). Additionally, the study aimed to assess the impact of cerebrospinal fluid (CSF) oligoclonal bands (OCBs) on the severity and prognosis of NSAE.

Patients and Methods: This retrospective analysis included patients with NSAE, encompassing NMDAR-E, LGI1-E, and GABABR-E, alongside individuals with VE. Participants with NSAE were categorized into two groups based on the presence or absence of CSF-specific OCBs. Data regarding demographics, clinical manifestations, magnetic resonance imaging (MRI) findings, CSF analyses and prognosis were collected and analyzed.

Results: The findings indicated that younger female with NSAE exhibited a higher incidence of seizure onset, disruption of the blood-CSF barrier (BCSFB), and elevated Q_{Alb}/Q_{Lim} ratios compared to VE patients, with NSAE patients demonstrating more severe clinical outcomes at discharge. Among the 185 NSAE patients, 43 (23.24%) were positive for OCBs, while 142 (76.76%) negative. The OCB-positive cohort displayed a greater prevalence of younger females and NMDAR-E (both $P<0.05$). No significant differences were observed in CSF white blood cell counts, protein concentrations, or immunoglobulin G levels between the two groups (all $P>0.05$). The modified Rankin Scale (mRS) scores at discharge and the final follow-up were higher in the OCB-positive group than the OCB-negative group (both $P<0.05$). Both univariate and multivariate analyses identified OCBs and NSAE subtypes as independent risk factors influencing the clinical prognosis of NSAE.

Conclusion: In comparison to VE patients, NSAE patients with positive OCBs were more frequently female and exhibited CSF pleocytosis, particularly among those with NMDAR-E. Importantly, the presence of positive OCBs emerged as an independent predictor of unfavorable outcomes in patients with NMDAR-E, LGI1-E, and GABABR-E.

Keywords: autoimmune encephalitis, oligoclonal bands, prognosis, cerebrospinal fluid, viral encephalitis

Introduction

In China, three prevalent types of neuronal surface antibody-associated autoimmune encephalitis (NSAE) include NMDA receptor encephalitis (NMDAR-E), leucine-rich glioma inactivated protein-1 encephalitis (LGI1-E), and gamma-aminobutyric acid-B receptor encephalitis (GABABR-E). Patients suffering from these NSAE subtypes display various

Received: 18 November 2024
Accepted: 30 January 2025
Published: 17 February 2025

clinical symptoms, such as seizures, psychiatric and behavioral issues, speech difficulties, autonomic nervous system dysfunction, cognitive impairments and involuntary movements.[1,2] However, the precise mechanisms behind these NSAE subtypes are not fully understood. Research indicates that immune responses involving B cells may significantly contribute to the pathogenesis of these conditions.[3,4] The detection of immunoglobulin G (IgG) oligoclonal bands (OCBs) is an immune marker indicating the intrathecal production of immunoglobulins by activated B-cell clones mainly within the central nervous system (CNS).[5] OCBs have been found in various immune-mediated and infectious neurological disorders, including multiple sclerosis (MS), neurosyphilis, Behçet's disease, and neurosarcoidosis.[6–8] In MS, OCBs are regarded as important biological marker.[9] Previous studies have shown that CSF OCBs can be present in AE, with AE patients who have positive OCBs showing significantly higher median CASE and mRS scores before receiving immunotherapy compared to those with negative OCBs.[10–12] However, there is limited researches on the relationship between OCBs and disease characteristics or clinical outcomes in a larger group of patients with NMDAR-E, LGI1-E, and GABABR-E. Consequently, we performed a retrospective analysis of the clinical and paraclinical characteristics of patients with NMDAR-E, LGI1-E, or GABABR-E based on their CSF OCBs status, as well as the association between OCBs and the severity and prognosis of NSAE.

Materials and Methods

Patients and Data Collection

Patients were retrospectively recruited from February 2016 to March 2023, with 185 NSAE subjects diagnosed with AE meeting specific inclusion criteria, as outlined in our previous study,[11] and 38 subjects with viral encephalitis (VE). For NSAE patients, the criteria included a confirmed diagnosis of AE with positive CSF and/or serum anti-NMDAR, anti-LGI1, or anti-GABABR antibody, as defined using a fixed cell-based assay (Euroimmun, Germany).[13] Data for NSAE patients were excluded for the following reasons: (1) laboratory evidence of infectious encephalitis (eg, viral, bacterial, mycobacterial tuberculosis); (2) incomplete data or a history of other central nervous system diseases (eg, multiple sclerosis, epilepsy, stroke, intracranial tumors, toxic-metabolic encephalopathy, schizophrenia or related conditions prior to the onset of encephalitis); and (3) presence of coexisting antibodies, such as myelin oligodendrocyte glycoprotein (MOG) antibody, aquaporin 4 (AQP4) antibody, and other AE neuronal antibody.

All VE patients met the clinical diagnostic criteria according to the Chinese Society of Neurology guidelines and had compatible laboratory and imaging results,[14,15] including (1) altered mental status lasting > 24h; (2) at least 2 of the following: (a) fever ≥ 38° C within the 72 h before or after presentation, (b) generalized or partial seizures, (c) new onset of focal neurological findings, (d) CSF WBC counts ≥ 5/mm3, (e) abnormal imaging findings consistent with encephalitis, (f) abnormal EEG finding consistent with encephalitis; (3) Patient CSF samples tested positive for viruses, including HSV-1 and −2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), pseudorabies virus (PRV) and parvovirus B19, through real-time PCR or metagenomic next-generation sequencing (mNGS) and were negative for antibodies against neuronal autoantigens. Patients with infections such as mycobacterium tuberculosis, parasites and fungi and other pathogens were excluded from this study.

The 185 NSAE patients were recruited from The First Affiliated Hospital of Shandong First Medical University and Qilu Hospital, Shandong University, comprising 102 with NMDAR-E, 68 with LGI1-E and 15 with GABABR-E. The 38 VE patients, including 13 with HSV encephalitis, 14 with VZV encephalitis, 7 with EBV encephalitis, 2 with PRV encephalitis and 2 with parvovirus B19 encephalitis, were also sourced from The First Affiliated Hospital of Shandong First Medical University. Clinical data, including demographic details, age at onset, prodromal symptoms, clinical manifestations, CSF findings, CSF-specific OCBs, presence of coexisting tumors, MRI results, ICU requirements and treatment regimens, were gathered through a retrospective review of medical records. Paired serum and CSF samples were tested for CSF-specific OCBs during the initial lumbar puncture (LP) of the recruited patients. Follow-up data were collected through clinical examinations during return visits and telephone interviews. The modified Rankin scale (mRS) was utilized to assess each patient's neurological status, and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score was calculated for each patient with NMDAR-E.[16]

Definitions

Pleocytosis was defined as having more than 5 leukocytes per microliter. The parameter of Q_{Alb} was used to estimate the permeability of brain barriers.[17] As Q_{Alb} is age dependent, the age-normalized Q_{Alb} (Q_{Alb}/Q_{lim}) was determined by dividing Q_{Alb} by the age-specific upper limit (Q_{lim}; $4+age/15\times10^{-3}$).[18] A break in the blood-CSF barrier (BCSFB) was indicated by a Q_{Alb}/Q_{lim} ratio greater than 1. mRS score ≤2 was indicative of good functional status, while a score >2 indicated poor functional status.

Blood and CSF Analysis

The samples of serum and CSF were acquired simultaneously at acute stage of NSAE and VE. The CSF samples were tested for white blood cells, total protein, albumin, and IgG et al. Paired serum and CSF were tested for OCBs using isoelectric focusing followed by IgG immunofixation during the recruited patients` initial LP.

Acquirement and Interpretation of Neuroimaging

Brain magnetic resonance imaging (MRI) examinations were performed during the acute stage of NSAE and VE using 1.5 T or 3.0 T scanner. Images were independently evaluated by two neurologists (SQ and AHW). Brain MRI abnormalities were defined as new-onset brain lesions with abnormal signals on T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), diffusion weighted or contrast enhanced T1-weighted images.

Statistical Analysis

The findings were presented as percentages, medians and interquartile ranges (IQR). The Kolmogorov–Smirnov test was utilized to assess the distribution of the variables. Univariate analyses were conducted using the Chi-square test or Fisher's exact test for categorical data, and the Mann–Whitney *U*-test for continuous data when the distribution was non-normal. The Student's *t*-test or Mann–Whitney *U*-test was employed for two groups, while the Kruskal–Wallis test followed by the Dunn multiple comparisons test was used for more than two groups. Multivariate logistic regression analyses were carried out after adjusting for various potential confounding factors to identify the risk factors associated with long-term prognosis. Odds ratios (OR) and 95% confidence intervals (CI) were provided for the risk estimates. A p-value < 0.05 was deemed statistically significant. The statistical analyses were conducted using SPSS (version 25.0) and R software (version 4.0.2).

Results

Demographic and Clinical Characteristics of the Participants

In our study, we consecutively recruited 185 patients with NSAE and 38 patients with VE. Table S1 presented the demographic and clinical characteristics of these two groups. A greater percentage of female patients was observed in the NSAE group compared to the VE group (48.1% vs 28.9%, P=0.031). The median age of onset for NSAE was 38.0 years (IQR: 16.0, 62.0), which was lower than the median age for VE at 53.0 years (IQR: 27.0, 63.5). Seizures were more frequently the initial symptom in NSAE patients than in VE patients (81.08% vs 44.7%, P<0.001). In terms of CSF tests, NSAE patients had significantly higher levels of CSF protein compared to VE patients (P=0.001). The Q_{Alb}/Q_{Lim} ratio was also notably higher in NSAE patients (1.56 [IQR: 0.86, 2.79] vs 0.70 [IQR: 0.48, 1.01], P<0.001), as was the rate of BCSFB disruption (70.8% vs 26.3%, P<0.001). However, there were no significant differences in CSF white blood cell (WBC) counts or CSF IgG levels between the two groups (all P>0.05). Regarding MRI findings, the incidence of lesions in the frontal lobe, parietal lobe, basal ganglia and white matter were significantly higher in VE patients than that in NSAE patients (all P<0.05). Additionally, the mRS scores at discharge were significantly higher for NSAE patients compared to VE patients (P<0.001).

OCBs and Clinical Manifestations

As indicated in Table 1, the OCB positive group had a higher percentage of females compared to the OCB negative group (67.40% vs 42.30%, P=0.040). Additionally, the patients in the OCB positive group were significantly younger than those

Table 1 Comparison of Demographic and Clinical Characteristics Between OCB(+) and OCB(-) Groups of NSAE

	OCB Positive Group (n=43)	OCB Negative Group (n=142)	P value
Female, n(%)	29 (67.40)	60 (42.30)	0.040
Onset age, median (IQR)	24.0 (12.0, 55.0)	44.0 (17.75, 62.26)	0.018
Presence of antibody, n(%)			
CSF	33 (76.74)	117 (82.40)	0.881
Serum	29 (67.40)	114 (80.30)	0.078
Antibody types, n(%)			
NMDAR	34 (79.07)	68 (47.90)	<0.001
LGI1	5 (11.63)	63 (44.40)	
GABABR	5 (11.63)	10 (7.04)	
Disease duration, days, median (IQR)	21 (11.0–45.5)	28.0 (14.0–28.5)	0.174
Prodromal symptoms, n(%)	14 (32.56)	34 (23.90)	0.259
Concomitant tumors	3 (6.98)	14 (9.85)	0.566
Initial symptoms, n(%)			
Seizures	35 (81.40)	115 (80.99)	0.952
Psychiatric symptoms	31 (72.09)	93 (65.49)	0.765
Memory dysfunction	21 (48.83)	82 (57.75)	0.609
Other	21 (48.83)	54 (38.03)	0.320
mRS at admission, median (IQR)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	0.003
ICU requirement, n (%)	6 (14.0)	16 (11.3)	0.634

Abbreviations: NSAE, neuronal surface antibody-associated autoimmune encephalitis; OCB, oligoclonal band; CSF, cerebrospinal fluid; GABABR, gamma-aminobutyric acid B receptor; IQR, interquartile range; LGI1, leucine-rich glioma-inactivated 1; mRS, modified Rankin Scale; NMDAR, N-methyl-D-aspartate receptor; ICU, intensive care unit.

in the OCB negative group (P=0.018). There were notable differences in NSAE subtypes between the two groups (P<0.001), with a higher percentage of positive OCB in NMDAR-E patients (79.07% vs 47.90%) and a lower percentage in LGI1-E patients (11.63% vs 44.40%). Regarding disease severity, the mRS scores at admission were higher in the OCB positive group compared to the OCB negative group (P=0.003). However, there were no significant differences in prodromal symptoms, disease duration at admission, presence of concomitant tumors, or ICU requirements during hospitalization between the two groups (all P>0.05). The initial symptoms, such as seizures, psychiatric issues, memory problems and others, were similar across both subgroups (P>0.05) as shown in Table 1. Among NMDAR-E patients, concomitant tumors were more frequently found in the OCB negative group compared to the OCB positive group (11.8% vs 0.0%, P=0.037), with no significant differences in other characteristics, as presented in Table S2.

OCBs and Serum/CSF Profiles, Brain Lesions on MRI

According to Table 2, there were no significant differences in CSF WBC, CSF protein levels, CSF IgG and Q_{Alb}/Q_{Lim} between the two groups (all P>0.05). However, a higher percentage of NSAE patients with pleocytosis was found in the OCB positive group compared to the OCB negative group (P=0.025). NSAE patients in the OCB positive group showed no significant differences in brain lesions on MRI compared with those in the OCB negative group (P>0.05). Regarding lesion distribution, the occurrence rates of lesions in the frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, brainstem, cerebellum, and white matter were comparable between the OCB positive and OCB negative groups (all P>0.05) (Table 2). For patients with NMDAR-E, the CSF parameters were also similar between the OCB positive and OCB negative groups, as were the brain MRI regions (all P>0.05) (Table S3).

OCBs and Clinical Outcomes

As indicated in Table 3, the majority of patients received first-line immunotherapies, such as steroids and intravenous immunoglobulin, during their hospital stay, with similar treatment rates in both OCB positive and OCB negative groups

Table 2 Comparison of Paraclinical Profiles Between OCB(+) and OCB(-) Groups of NSAE

	OCB Positive Group (n=43)	OCB Negative Group (n=142)	P value
CSF analyses, median (IQR)			
WBC,×10^6/L	4.0 (1.0, 22.0)	2 (1.0, 12.5)	0.866
Pleocytosis, n(%)	22 (51.2)	46 (32.4)	0.025
Protein, g/L	0.50 (0.21, 1.09)	0.44 (0.24, 0.77)	0.826
CSF IgG, mg/L	42.80 (23.30, 79.34)	34.95 (22.20, 62.78)	0.286
Q_{Alb}/Q_{Lim}	1.75 (0.87, 4.16)	1.48 (0.85, 2.68)	0.823
Blood-CSF barrier break, n(%)	31 (72.10)	99 (67.72)	0.765
Brain lesions, n(%)	16 (37.2)	47 (33.1)	0.618
Temporal lobe	8 (18.6)	35 (24.6)	0.411
Frontal lobe	3 (7.0)	10 (7.0)	0.998
Parietal lobe	2 (4.7)	8 (5.6)	0.999
Occipital lobe	1 (2.3)	6 (4.2)	0.908
Basal ganglion	2 (4.7)	8 (5.6)	0.999
Brainstem	2 (4.7)	2 (1.4)	0.201
Cerebellar	1 (2.3)	2 (1.4)	0.677
White matter	5 (11.6)	7 (4.9)	0.227
Both lesions	12 (27.9)	30 (20.1)	0.352

Abbreviations: NSAE, neuronal surface antibody-associated autoimmune encephalitis; CSF, cerebrospinal fluid; IgG, immunoglobulin G; IQR, interquartile range; Qalb, cerebrospinal fluid / serum albumin quotient; WBC, white blood cell.

Table 3 Comparison of Clinical Outcome Between OCB(+) and OCB(-) Groups of NSAE

	OCB Positive Group (n=43)	OCB Negative Group (n=142)	P value
First-line immunotherapies, n(%)			
Steroids	33 (76.7)	107 (75.4)	0.781
IVIG	32 (74.4)	110 (77.46)	0.901
Second-line immunotherapies, n(%)	9 (20.9)	25 (17.6)	0.622
The mRS at discharge, median (IQR)	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	0.019
Follow-up time, years, median (IQR)	1.50 (0.83, 2.42)	1.33 (0.75, 2.08)	0.124
The mRS at last follow-up, median (IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 1.0)	0.014

Abbreviations: NSAE, neuronal surface antibody-associated autoimmune encephalitis; IQR, interquartile range; IVIG, intravenous immunoglobulin; mRS, modified Rankin Score.

(both P>0.05). The median years of follow-up time did not differ between OCB positive and OCB negative groups (1.50 [IQR: 0.83, 2.42] vs 1.33 [IQR: 0.75, 2.08], P=0.124) (P>0.05). The mRS scores at discharge were significantly higher in the OCB positive group compared to the OCB negative group (2.0 [IQR: 2.0, 3.0] vs 2.0 [IQR: 1.0, 2.0], P=0.019). At the last follow-up, the median mRS scores remained higher in the OCB positive group than in the OCB negative group (1.0 [IQR: 0.0, 2.0] vs 1.0 [IQR: 0.0, 1.0], P=0.014) (Table 3, Figure 1A and B). However, among the patients with NMDAR-E, the mRS scores at the last follow-up were significantly higher in the OCB positive group compared to the OCB negative group (1.0 [IQR: 0.0, 2.0] vs 1.0 [IQR: 0.0, 1.0], P=0.037) despite no difference in the median follow-up time (1.50 [IQR: 0.69, 2.25] vs 1.17 [IQR: 0.75, 1.98], P>0.05) (Table S4). To further investigate the relationship between OCBs and long-term outcomes, the patients were categorized into a good prognosis group (mRS ≤2, n=149) and a poor prognosis group (mRS >2, n=36). In the univariate analysis, as shown in Table S5, all factors, not including gender, NSAE subtype, concomitant tumor, BCSFB disruption and OCBs, were not statistically different between the good and poor prognosis groups (all P>0.05).

https://doi.org/10.2147/JIR.S504003

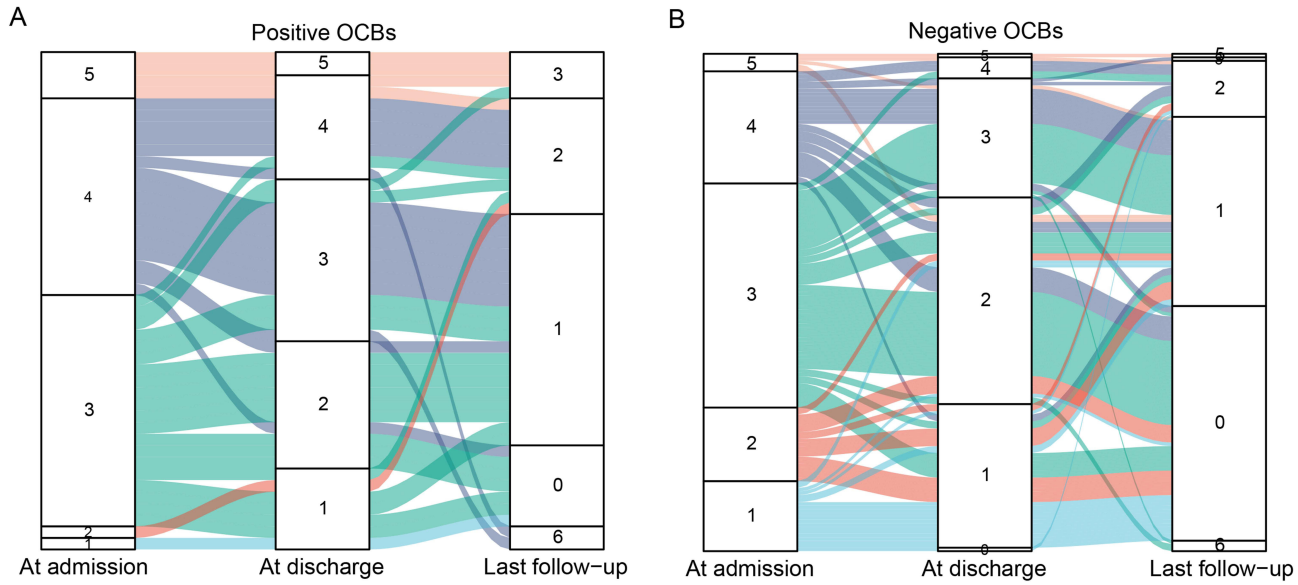

Figure 1 Sankey diagrams for visualizing the changes of modified Rankin Scale (mRS) scores from admission to discharge and to last follow-up in AE patients with positive OCB (**A**) and negative OCB (**B**). The flow lines between the three sidebars represent changes in individual scores.

To evaluate the significance of OCB as an independent risk factor, we conducted multivariate analyses considering various confounding factors in NMDAR-E, LGI1-E, and GABABR-E. As presented in Table S6, multivariate logistic regression models indicated that, unlike NMDAR-E and LGI1-E which predicted favorable outcomes compared to GABABR-E (OR=0.037, 95% CI=0.09–0.163, P<0.001; OR=0.024, 95% CI=0.05–0.117, P<0.001), Positive OCB was identified as an independent risk factor for poor prognosis (OR=3.185, 95% CI=1.254–8.095, P=0.015).

Discussion

NSAE vs VE

VE and NSAE exhibit similarities in clinical manifestations. However, they differ significantly in their underlying pathogenesis and treatment protocols. Consequently, prompt and accurate identification, along with timely intervention, is essential. Diagnostic methods such as polymerase chain reaction (PCR) and next-generation sequencing (NGS) have been extensively employed for the identification of VE.[19] Various techniques, including immunoblotting, cell-based assays (CBA), immunohistochemistry, and indirect immunofluorescence (IIF) assays, are utilized to detect highly specific autoantibodies associated with AE.[20] It is important to note that negative results for pathogens or specific autoantibodies do not rule out the possibility of VE or AE.[19] Clinically, there are notable differences in specific features and lesions observed in brain imaging, electroencephalograms (EEG), and laboratory findings between VE and NSAE. Our recent retrospective study analyzed the clinical characteristics, CSF auxiliary examinations, and imaging findings that differentiate VE from NSAE within our patient cohort. Additionally, we explored the relationship between CSF-specific OCBs and the distinct features and prognosis of NSAE.

OCB+ vs OCB- Patients with NSAE

OCBs serve as an important clinical marker for multiple sclerosis (MS), being present in up to 95% of MS cases, and their diagnostic and prognostic roles in CSF analysis are well recognized.[21–23] OCB is included in the diagnostic criteria for NMDAR-E, which aids in identifying potential cases of this condition.[13] Furthermore, specific OCB in CSF is part of the criteria for diagnosing probable AE in patients who test negative for autoantibodies.[24] Therefore, OCBs testing is crucial for accurate diagnosis and treatment planning, especially when antibodies are absent. A previous study analyzed the inflammatory CSF parameters in three AE subgroups respectively, including NMDAR, LGI1 and GABABR encephalitis, but not in the whole patient cohort, and then acquired potential predictors for the occurrence of NMDAR

or LGI1 encephalitis.[11] Our current study reanalyze the clinical data in our previous study,[11] and indicated that OCBs positivity is an independent prognostic factor for poor outcomes in NSAE cases involving NMDAR-E, LGI1-E, and GABABR-E. Although these three conditions are distinct, OCBs may play a significant role in their pathogenesis and progression.

Our investigation initially identified a higher prevalence of younger female patients and an increased incidence of seizure onset in individuals with NSAE compared to those with VE, corroborating findings from prior research.[10] Given that brain MRI results are typically normal during the acute phases of autoimmune encephalitis onset,[25] abnormal MRI findings were more frequently observed in the VE cohort in our study. Although neuroimaging may not consistently assist in identifying a specific etiology in cases of VE, certain distinctive neuroimaging patterns have been associated with particular viral pathogens.[26] For example, lesions in the brainstem, cerebellum, or temporal lobes, with or without ischemic or hemorrhagic changes, are characteristic of VZV encephalitis.[27] Similarly, findings related to HSV encephalitis are often noted in the medial temporal lobe, cingulate gyrus, and the orbital surface of the frontal lobes.[28] In contrast to previous studies,[29] our VE cohort did not exhibit elevated CSF leukocyte counts or significant BCSFB disruption when compared to the NSAE cohort. This discrepancy may be explained by the predominance of patients with NMDAR encephalitis within the overall NSAE population, which has been documented to present with a pronounced and severe inflammatory response in the CSF.[11]

Next, we analyzed the discrepant clinic features in the presence or absence of CSF-specific OCBs in NSAE. In our study, the overall OCBs positivity rate among NSAE patients was 23.24%, with the highest rate in NMDAR-E at 33.33% and the lowest in the LGI1-E group at 7.35%. These findings are consistent with previous reports of OCBs positivity in NMDAR-E, while the occurrence of OCBs in LGI1-E remains notably low at just 5%.[10,30] There were no significant differences in major clinical symptoms between the OCBs positive and negative groups. We observed that females, particularly younger ones, were more prevalent among NSAE patients with positive OCBs, suggesting that female may be a risk factor for abnormal immune globulin synthesis. In studies of anti-MOG-IgG associated disorders (MOGAD),[31] a higher proportion of female patients tested positive for OCBs compared to males. Additionally, in a cohort study of MS, female patients with OCBs showed a higher annual relapse rate.[32] Key diagnostic parameters for AE include CSF pleocytosis, specific OCBs in CSF, and elevated CSF IgG levels, with CSF pleocytosis being particularly important for confirming AE diagnosis.[11,30] Previous research has shown that AE subtypes with frequent CSF pleocytosis often also have high OCBs positivity.[30,33] However, our data indicated no significant differences in CSF cell count, CSF IgG levels, or Q_{Alb} elevation between OCB positive and negative groups in NMDAR-E, LGI1-E, and GABABR-E. To account for the influence of different NSAE subtypes on these CSF parameters, we further analyzed NMDAR-E patients and found no significant differences in CSF WBC count, pleocytosis, IgG levels, or Q_{Alb} elevation between OCBs positive and negative cases.

In our study, a significant proportion of patients demonstrated favorable long-term functional outcomes, aligning with the results reported in previous studies.[34–36] The mRS scores at both discharge and the final follow-up were markedly higher in the group with positive OCBs compared to those with negative OCBs. However, the frequency of first-line and second-line immunotherapies administered did not differ between the two groups in our study. It is widely acknowledged that patients with AE derive substantial benefits from the early initiation of immunotherapy following disease onset.[37,38] The timing of first-line and second-line immunotherapy is influenced by factors such as the duration of hospitalization, disease severity, progression, and therapeutic responses, rather than the status of CSF-specific OCBs. Furthermore, multivariate logistic regression analysis indicated that positive OCBs serve as an independent risk factor for poor prognosis in cases of NMDAR-E, LGI1-E, and GABABR-E. These results suggest that patients exhibiting severe intrathecal immune responses may demonstrate reduced responsiveness to first-line immunotherapies and experience poorer short- and long-term outcomes. The NMDAR-E cohort exhibited similar trends. An increased presence of immune cells and autoantibodies within CNS may elicit a heightened immune response in the brain, resulting in unfavorable prognoses. Consequently, the status of OCBs may serve as a potential prognostic indicator for patients with NMDAR-E, LGI1-E, or GABABR-E.

Our findings further indicated that neurological dysfunction at discharge, as assessed by the mRS, was more pronounced in the OCBs positive group compared to the OCBs negative group. For NMDAR-E, the majority of clinical

and paraclinical characteristics were consistent with the overall profile of AE. Notably, the incidence of concurrent tumors was lower in the OCBs positive group within our study. The severity of the disease at admission did not significantly differ between the OCBs positive and negative groups in our cohort of NMDAR-E, LGI1-E, and GABABR-E. Correspondingly, our results indicated that the severity of the disease at admission, as measured by mRS, was not significantly different between the OCBs positive and negative groups. However, another study reported that AE patients with positive CSF-specific OCBs were more likely to exhibit greater disease severity than those with negative OCBs.[12] NMDAR-E patients with compromised blood-brain barriers tended to present with increased disease severity prior to the initiation of immunotherapy.[39] In the context of other inflammatory CNS disorders, OCB positivity was found to be unrelated to disease severity in MS patients.[22] Therefore, the relationship between initial disease severity and OCB status warrants further exploration.

Our study is subject to several limitations. First, the retrospective nature of the cohort study may have introduced information bias. Second, the exclusion of patients who did not undergo OCB testing could lead to selection bias. The timing of immunotherapy initiation varied among AE patients due to the interval between disease onset and hospital treatment, which may have influenced clinical outcomes during follow-up. Third, the limited number of cases for NMDAR-E, LGI1-E, and GABABR-E restricted our ability to conduct subgroup analyses beyond NMDAR-E, however, the findings in the primary cohort were not validated in the external patient cohort. Consequently, further research involving prospective multicenter studies with larger patient populations and extended follow-up periods is necessary to validate our findings.

Conclusion

In conclusion, our study primarily examined the clinical manifestations, CSF auxiliary tests, and outcomes of patients diagnosed with NSAE in comparison to those with VE. The results indicated that certain clinical features, such as younger age, female sex, predisposition to seizures, significant disruption of the BCSFB, and normal neuroimaging findings, were more prevalent in patients diagnosed with AE. Following this, the NSAE cohort was further analyzed to investigate the relationship between OCBs in CSF and various clinical characteristics, CSF findings, neuroimaging results, and, importantly, long-term clinical outcomes. This analysis demonstrated that the NSAE group, which included cases of NMDAR, LGI1, and GABABR encephalitis, exhibited these associations collectively rather than within specific encephalitis subtypes. Additionally, the presence of CSF-specific OCBs in NSAE was found to correlate with disease severity and poor prognosis, indicating their potential as biomarkers. We recommend the initial assessment of CSF-specific OCBs as a strategy to monitor disease progression and predict clinical outcomes, as well as to identify patients at risk of severe illness early in the treatment process, which may facilitate the initiation and enhancement of clinical management strategies during the acute phase of the disease.

Abbreviations

NSAE, neuronal surface antibody-associated autoimmune encephalitis; NMDAR-E, anti-N-methyl-D-aspartate receptor encephalitis; LGI1-E, anti-leucine-rich glioma-inactivated 1 encephalitis; GABABR-E, anti-gamma aminobutyric acid-B receptor encephalitis; VE, viral encephalitis; VZV, varicella zoster virus; EBV, Epstein-Barr virus; PRV, pseudorabies virus; mNGS, metagenomic next-generation sequencing; CSF, cerebrospinal fluid; LP, lumbar puncture; OCBs, oligoclonal bands; AE, autoimmune encephalitis; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MS, multiple sclerosis; ICU, intensive care unit; CASE, Clinical Assessment Scale in Autoimmune Encephalitis; MOG, myelin oligodendrocyte glycoprotein; AQP4, aquaporin 4; FLAIR, fluid attenuated inversion recovery; IQR, interquartile range; OR, odds ratio; CI, confidence interval; MOGAD, anti-MOG-IgG associated-disorders; BCSFB, blood-CSF barrier.

Data Sharing Statement

Anonymized data not published within this article will be made available upon reasonable request from any qualified investigator.

Ethics Approval and Consent to Participate

Our study complied with the Declaration of Helsinki and Basel Declaration, and was approved by Institutional Review Board of The First Affiliated Hospital of Shandong First Medical University and Qilu Hospital, Shandong University, and the participants were fully informed about the purpose of the study and patient consent was acquired prior to the initiation of the experiment.

Acknowledgments

We thank the patients for participating in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants from the Natural Science Foundation of Shandong Province, China (No. ZR2016HP04, No.ZR2024MH269), and China Postdoctoral Science Foundation (2021M691227).

Disclosure

The authors report no conflicts of interest in this work.

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