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ORIGINAL RESEARCH

Comparisons Between Infectious and Autoimmune Encephalitis: Clinical Signs, Biochemistry, Blood Counts, and Imaging Findings

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Objective: Infectious encephalitis (IE) and autoimmune encephalitis (AE) are symptomatically similar in clinic, however essentially different in pathogenesis. Therefore, the objective of this study was to identify specific features to distinguish the two types of encephalitis for early effective diagnosis and treatments through a comparative analysis.

Methods: Fifty-nine IE patients and 36 AE patients were enrolled. The patients with IE were divided into viral encephalitis (VE) and bacterial encephalitis (BE) according to the pathogens in cerebrospinal fluid (CSF). Patients with AE were categorized by with or without neural autoantibodies (NAAb). We further divided patients with NAAb into those with neural cell-surface antibodies (NSAbs) or intracellular antibodies (Abs). Clinical features, laboratory data, and imaging findings were compared between AE, IE, and subgroups.

Results: Memory deficits, involuntary movement, and seizures were relatively more commonly presenting symptoms in AE patients ($p < 0.05$). The positive rate of Pandy test was higher in IE patients ($p = 0.007$). Decreased leukocyte, erythrocyte, and platelet counts in blood were found in IE patients ($p < 0.05$). Lower serum calcium level was found in VE compared to BE ($p = 0.027$). Meanwhile, higher serum calcium level was found in patients with NSAbs compared with intracellular Abs ($p = 0.034$). However, higher levels of LDH in CSF were found in patients with intracellular Abs ($p = 0.009$). In magnetic resonance imaging, hippocampus lesions were more commonly present in patients with AE ($p = 0.042$). Compared with AE patients, more IE patients displayed the background electroencephalogram rhythm of slow-frequency delta ($p = 0.013$).

Conclusion: Involuntary movement and memory deficits were more specifically present in AE patients. CSF Pandy, blood routine test and hippocampus lesions detections were potential markers for distinguishing AE and IE. Further, CSF LDH, and serum calcium levels were potentially useful to distinguish subgroups of encephalitis.

Keywords: infectious encephalitis, autoimmune encephalitis, cell-surface antibodies, intracellular antibodies, imaging findings

Introduction

Encephalitis is caused by viral/bacterial infections, inflammation mediated by autoimmunity (acute disseminated encephalomyelitis (ADEM), Bickerstaff's brainstem encephalitis, and systemic autoimmune diseases), paraneoplastic syndrome, and other unclear causes.[1] Infectious encephalitis (IE) and autoimmune encephalitis (AE) are symptomatically similar in clinic, however essentially different in pathogenesis.[2] They are difficult to distinguish, thus bringing ambiguities in the treatments and managements of AE and IE with similar symptoms, such as fever,

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seizures, psychiatric disorders, behavioral disorders, memory deficit, disturbance of consciousness, speech dysfunction, involuntary movement, focal neurologic deficit, ataxia and autonomic dysfunction.[3,4] Virus can cross the blood–brain barrier and cause damage by direct virus mediated necrosis and indirect innate immune responses.[5] The pathogenic bacteria induce neural damage by secreting virulence factors and inhibiting the host's immune response.[6] Meanwhile, AE is caused by an antigen-specific cytotoxic T cells reaction or specific immune response mediated by antibodies (Abs).[7] Since the discovery of anti-NMDAR antibody in 2007,[8] different types of neural autoantibodies (NAAb) including neural cell-surface antibodies (NSAbs) and Intracellular Abs have been identified.[9]

IE and AE demonstrate similarity in clinical features, however they are different in their pathogenesis, therefore differences in specific features and lesions found in Magnetic Resonance Imaging (MRI), electroencephalogram (EEG) and laboratory data are distinguishable by further studies. Polymerase Chain Reaction (PCR) has been widely used for the diagnosis of IE, especially viral encephalitis (VE), although a negative test result does not exclude the diagnosis of encephalitis.[10] Cerebrospinal fluid (CSF) culture is extremely crucial in patients with bacterial encephalitis (BE) in order to determine the type of pathogens. Techniques such as immunoblotting, cell-based assays (CBA), immunochemistry and indirect immunofluorescence (IIF) assays can be used to identify highly specific autoantibodies responsible for AE.[11,12] Very different treatment plans are often applied to AE and IE patients, therefore, effective early identification and intervention is critical. In our study, we retrospectively analyzed the clinical characteristics, laboratory examinations, and imaging findings of IE and AE, in order to explore key features that potentially contribute to early diagnosis of such diseases, therefore benefiting the patients through appropriate treatment applications.

Materials and Methods

Definitions and Criteria

Clinical data for 59 patients with IE and 36 patients with AE were retrospectively collected at the Department of Neurology of Tianjin Medical University General Hospital from March 2009 to May 2020. Patients with AE met the following diagnostic criteria for definite AE with NAAb:[1] 1) subacute onset of working memory deficits, altered mental status, or psychiatric symptoms; 2) at least one of the following: a) new focal central nervous system (CNS) findings; b) seizures not explained by a previously known seizure disorder; c) CSF white blood cell (WBC) counts ≥ 5/mm^3; d) MRI features suggestive of encephalitis; 3) serum and/or CSF samples were positive for NAAb, at least one of the following: NSAbs: NMDA-receptor (R)-antibody (Ab) (N-methyl-D-aspartate), CASPR2-R-Ab (contactin-associated protein 2), AMPA-R-Ab (2-amino-3- (3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid), LGI1-R-Ab (leucine-rich glioma inactivated 1), GABAB-R-Ab (gamma-aminobutyric acid); Intracellular Abs: anti-GAD65 (glutamic acid decarboxylase), anti-CV2 (CRMP5), anti-PNMA2 (Ma2/Ta), anti-Hu (ANNA1), anti-Ri (ANNA2), anti-Yo (PCA-1), anti-Amphiphysin.

In addition, other patients with AE met the following diagnostic criteria for definite AE without NAAb:[1] 1) subacute onset of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system; 2) bilateral brain abnormalities on T2-weighted imaging (T2WI) or fluid attenuated inversion recovery (FLAIR) of MRI highly restricted to the medial temporal lobes. 3) At least one of the following: a) CSF WBC counts ≥ 5/mm^3; b) EEG with epileptic or slow-wave activity involving the temporal lobes. 4) Serum and CSF samples were negative for NAAb. ADEM, Bickerstaff's brainstem encephalitis, and various Ab-associated immunological systemic diseases, such as systemic lupus erythematosus were excluded from this study.

Patients who met the Consensus Statement of the IE Consortium reported in 2013 were enrolled in the IE groups. The Consensus include:[13] 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 neurologic findings; d) CSF WBC counts ≥ 5/mm^3, e) abnormal imaging findings consistent with encephalitis, f) abnormal EEG finding consistent with encephalitis; 3) CSF samples were tested by Real-Time quantitative Polymerase Chain Reaction (RT-qPCR) and bacteria culture and found at least one pathogen which was strongly associated with IE patients with positive CSF bacteria culture and definite drug susceptibility tests were included in BE group. Patients with positive viral nucleic acid were included in VE group. Patients with infections such as mycobacterium tuberculosis, parasites and fungi were excluded from this study.

Sample Collection and Laboratory Assays

The CSF of all patients was collected when virus infection-like symptoms (T >38°C, headache, etc) were present. DNA sequences were extracted from samples and amplified by Applied Biosystems ™ 7500 RT-qPCR instrument (Thermo Fisher Scientific, USA). The CSF of all patients was collected when bacterial infection-like symptoms (T >38°C, neck stiffness, etc) were present, and transferred to different culture bottles (Bactec Plus Aerobic/F, Bactec Lytic/10 Anaerobic/F, Bactec Peds Plus/F) (Becton, Dickinson and Company Sparks, MD 21152 USA) immediately, and underwent etiology inspection by Bacrec™ FX automated blood culture system (Becton, Dickinson and Company, USA) in microbiological laboratory. All serum and CSF samples from patients with AE were evaluated for NSAbs by IIF kits (Euroimmun, Lübeck, Germany) and CBA kits (Euroimmun, Lübeck, Germany) according to the manufacturer's instructions. All patients underwent serum and CSF laboratory tests, including all of the following: CSF examinations included: Pandy test, intracranial pressure, WBC counts, protein levels, chloride, glucose, lactate dehydrogenase (LDH), lactic acid (Lac), adenosine deaminase (ADA) and C-reactive protein (CRP). Blood examinations included: leukocyte, erythrocyte and platelet counts, and the levels of sodium, potassium, calcium, and chlorine.

MRI and EEG Data Acquisition

MRI data were acquired using a 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). All but two of the patients had brain MRI. The T1-weighted imaging (T1WI), T2WI, FLAIR and diffusion weighted imaging (DWI) of brain MRI were recorded. Seventy-seven (81%) patients underwent a 24-hour EEG recording (10–20 system according to international EEG convention). EEG data were classified according to their background waves (alpha, beta, delta, theta), epileptiform activity (sharp waves, spike waves, sharp (or spike) slow wave complexes, both), slow waves activity (delta and/or theta activity), and localization (frontal region, temporal region, other regions). MRI and EEG were interpreted by skilled radiologists and electroencephalographers.

Clinical Feature Scores

The degree of disability was graded as per the modified Rankin Scale (mRS). A mild case was defined as mRS score of 0–2 and a severe case as mRS score of 3–6. The level of consciousness was measured by the Glasgow Coma Score (GCS). Neurological functions for all patients were evaluated by 2 qualified neurologists according to the mRS and GCS at peak stage of diseases.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS 22.0) was used for statistical analysis. Figures were produced by GraphPad Prism Version 6. Mann–Whitney *U*-test was used for comparison of continuous variables and shown as mean ± SD, and the Pearson chi-squared test or Fisher's exact test was used for comparison of categorical variables shown as counts (percentages). A p value < 0.05 was considered statistically significant.

Results

The Abs of Patients with AE and the Pathogens of Patients with IE

The Abs of patients with AE (n = 36) and the pathogens of patients with IE (n = 59) were shown in Figure 1. Of 36 patients with AE, Abs were detected in 28 patients. Of the 59 patients with IE, 16 patients were infected with virus, 38 patients were infected with bacteria, and 5 patients had double infections.

The Serum and CSF Abs Titers of Patients with AE

Positive anti-NMDA-R Ab was detected in 11 CSF samples and 4 serum samples from 11 AE patients. Positive anti-LGI1 Ab was detected in 9 CSF samples and 8 serum samples from 10 AE patients. Positive anti-GABAB-R Ab was detected in 2 CSF samples and 2 serum samples of 2 patients. However, due to the update of detection technologies, abs titers were applied to only part of the patients, therefore the abs titer results were unknown for some of the patients (Figure 2). Patients with intracellular Abs were only obtained positive or negative results by CBA. All CSF samples and 3 serum samples from 6 patients had detection of positive intracellular Abs.

Clinical Characteristics and Laboratory Tests of Patients with IE and AE

As shown in Table 1, no significant differences were found in the onset age and gender between the two

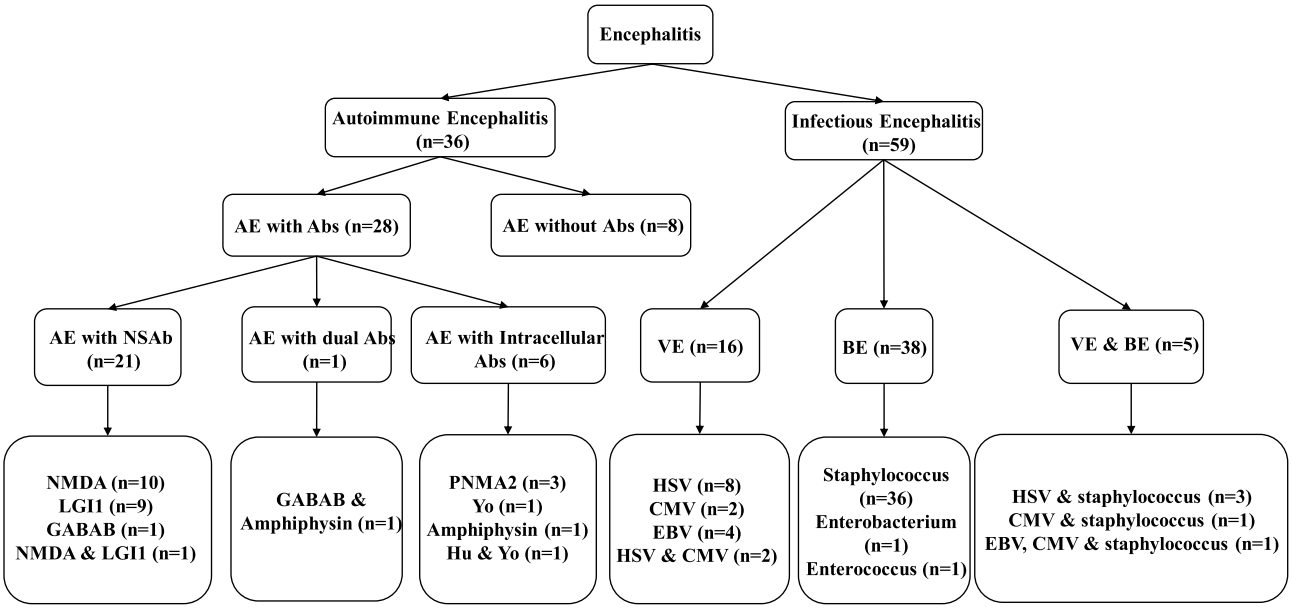

Figure 1 The antibodies of patients with AE and the pathogens of patients with IE.
Abbreviations: AE, autoimmune encephalitis; IE, infectious encephalitis; VE, viral encephalitis; BE, bacterial encephalitis; NSAbs, neuronal cell-surface antibodies; Abs, antibodies; NMDAR, N-methyl-d-aspartate receptor; LGI1, leucine rich glioma inactivated-1; GABAB, gamma-aminobutyric acid B; PNMA2, paraneoplastic antigen MA2; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; &, and; n, number.

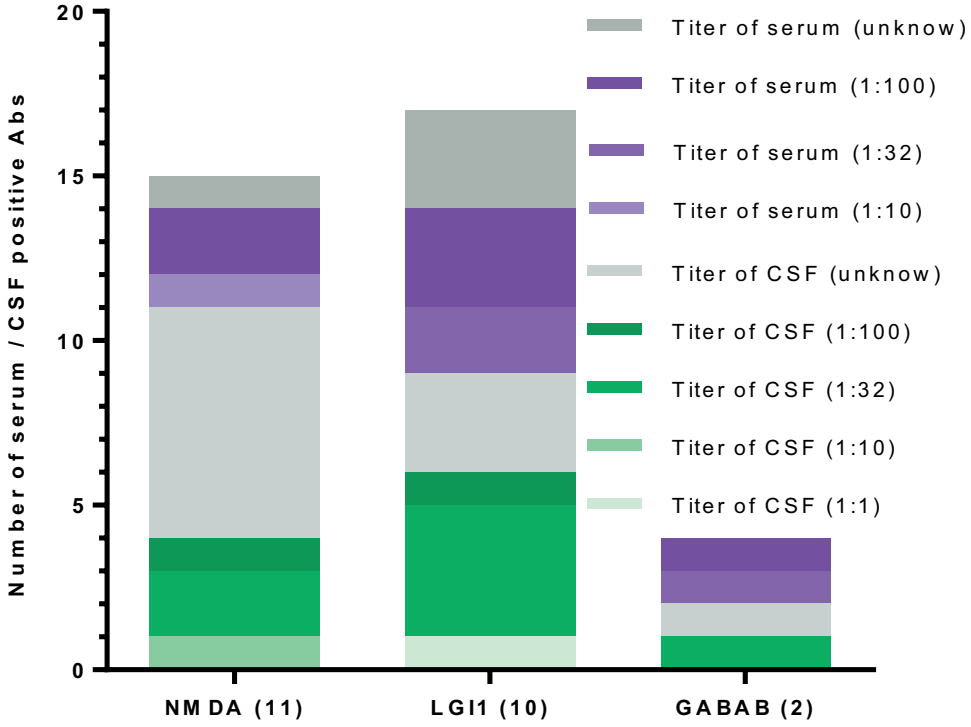

Figure 2 Abs titers of serum and CSF in AE patients with NSAbs.
Abbreviations: CSF, cerebral spinal fluid; Abs, antibodies; NMDAR, N-methyl-d-aspartate receptor; LGI1, leucine rich glioma inactivated-1; GABAB, gamma-aminobutyric acid B; AE, autoimmune encephalitis; NSAbs, neural cell-surface antibodies.

diseases (p = 0.160; p = 0.112). Headache and fever were more likely to occur in patients with IE (p = 0.002; p = 0.006). Involuntary movement, memory deficits, and seizure activity were more often observed

Table 1 Clinical Characteristics and Laboratory Results of Patients with AE and IE

	IE(n=59)	AE(n=36)	p
Onset age (years)	42.5 ± 18	47.1 ± 15.9	0.160
Female sex, No. (%)	26(44.1%)	10(27.8%)	0.112
Premonitory symptom, No. (%)	24(40.7%)	9(25.0%)	0.119
Onset symptom, No. (%)			
Headache	30(50.8%)	6(18.2%)	0.002*
Fever	40(67.8%)	14(38.9%)	0.006*
Psychiatric and behavior disorders	25(42.4%)	21(58.3%)	0.131
Seizure	25(42.4%)	23(63.9%)	0.042*
Decreased consciousness	32(54.2%)	20(55.6%)	0.900
Speech dysfunction	15(25.4%)	10(27.8%)	0.800
Involuntary movement	2(3.4%)	11(30.6%)	0.001*
Autonomic dysfunction	5(8.5%)	8(22.2%)	0.113
Ataxia	4(6.8%)	3(8.3%)	1.000
Memory deficit	5(8.5%)	13(36.1%)	0.001*
Sleep disorders	9(15.3%)	8(22.2%)	0.390
Focal neurologic deficit	12(20.3%)	9(25.0%)	0.595
Pulmonary infection complications	18(30.5%)	10(27.8%)	0.777
Tumor, No. (%)	3(5.15%)	4(11.1%)	0.493
Elapsed time between symptom onset and diagnosis (days)	7.2 ± 7.5	33.9 ± 48.7	<0.001**
Admission to hospital (days)	16.9 ± 8.4	20.7 ± 9.2	0.011*
ICU stay, No. (%)	17(28.8%)	5(13.9%)	0.094
Immunotherapy, No. (%)			
Glucocorticoid	15(25.4%)	24(66.7%)	<0.001**
IVIG	2(3.4%)	8(22.2%)	0.010*
Scores (at peak stage)			
mRS 0–2, No. (%)	24(40.7%)	14(38.9%)	0.863
mRS 3–6, No. (%)	35(59.3%)	22(61.1%)	0.863
GCS	11.2 ± 4.1	11.8 ± 3.5	0.770
The first CSF findings			
Intracranial hypertension (mmH2O)	183.1 ± 68.3	168.2 ± 67.5	0.193
CSF WBC (> 5 × 10^6/L), No. (%)	35(59.3%)	23(63.9%)	0.658
CSF protein level (g/L)	0.6 ± 0.4	0.5 ± 0.4	0.086
CSF chloride level (mmol/L)	124.2 ± 6.7	122.8 ± 13.4	0.890
CSF LDH level (U/L)	34.9 ± 36.2	27 ± 27.9	0.224
CSF Lac level (mmol/L)	2.3 ± 1.5	1.9 ± 1.4	0.210
CSF ADA level (U/L)	1.5 ± 1.7	1.1 ± 1.8	0.130
CSF CRP level (mg/L)	0.2 ± 1.0	0.1 ± 0.1	0.692
CSF/Blood glucose ratio (< 0.5), No. (%)	23(39.0%)	13(36.1%)	0.780
Positive rate of Pandy test, No. (%)	48(81.4%)	20(44.4%)	0.007*
The first blood findings			
Blood sodium level (mmol/L)	137.8 ± 5.6	137.3 ± 5	0.346
Blood potassium level (mmol/L)	3.7 ± 0.4	3.9 ± 0.4	0.168
Blood calcium level (mmol/L)	2.16 ± 0.22	2.20 ± 0.16	0.058
Blood chlorine level (mmol/L)	99.7 ± 4.7	97.2 ± 17	0.859
Blood leukocyte count (× 10^9/L)	7.5 ± 2.8	10.3 ± 3.6	<0.001**
Blood erythrocyte count (× 10^{12}/L)	4.1 ± 0.7	4.6 ± 0.6	0.001*
Blood platelet count (× 10^9/L)	227 ± 82.8	277.1 ± 118.4	0.034*

(*Continued*)

Table 1 (Continued).

	IE(n=59)	AE(n=36)	p
The MRI findings			
Hippocampus, No. (%)	13(22.0%)	15(41.7%)	0.042*
Amygdala, No. (%)	12(20.3%)	12(33.3%)	0.157
Memory deficit and hippocampus, No. (%)	1(1.7%)	6(16.7%)	0.011*
Memory deficit and amygdala, No. (%)	1(1.7%)	6(16.7%)	0.011*
The EEG findings			
Alpha rhythm predominate, No. (%)	22(48.9%)	17(53.1%)	0.714
Beta rhythm predominate, No. (%)	5(11.1%)	2(6.3%)	0.693
Delta rhythm predominate, No. (%)	19(42.2%)	5(15.6%)	0.013*
Thet rhythm predominate, No. (%)	20(44.4%)	10(31.3%)	0.242
Delta and/or theta activity, No. (%)	22(48.9%)	17(53.1%)	0.714
Sharp wave, No. (%)	12(26.7%)	12(37.5%)	0.312
Spike wave, No. (%)	1(2.2%)	4(12.5%)	0.154
Sharp-slow complex wave, No. (%)	6(13.3%)	4(12.5%)	1.000
Spike-slow wave, No. (%)	5(11.1%)	1(3.1%)	0.391
Frontal region predominate, No. (%)	14(31.1%)	15(46.9%)	0.159
Temporal region predominate, No. (%)	8(17.8%)	10(31.3%)	0.169
Other regions, No. (%)	4(8.9%)	7(21.9%)	0.185

Notes: Data are presented as No. (%) or mean ± standard deviation; significant differences are indicated by *p < 0.05; **p < 0.001.
Abbreviations: AE, autoimmune encephalitis; IE, infectious encephalitis; No., number; CSF, cerebral spinal fluid; mRS, modified Rankin Scale; GCS, Glasgow Coma Score; IVIG, intravenous immunoglobulin; WBC, white blood cell; ICU, intensive care unit; CRP, C-reactive protein; LDH, lactate dehydrogenase; Lac, lactic acid; ADA, adenosine deaminase; MRI, magnetic resonance imaging; EEG, electroencephalogram.

in AE patients (p = 0.001; p = 0.001; p = 0.042). The day of admission to hospital (p = 0.011) and the time from symptom onset to diagnosis (p < 0.001) were longer in AE patients. However, other symptoms were similar between the two groups. No significant differences were found in mRS and GCS of AE and IE patients. Higher positive rate of Pandy test was found in IE patients than AE patients (p = 0.007). Lower leukocyte, erythrocyte, and platelet counts were found in IE patients than AE patients (p < 0.001; p = 0.001; p = 0.034). For the clinical treatments, 54 (91.5%) patients with IE received anti-infective therapies, while 15 (25.4%) IE patients received corticosteroids. The majority (66.7%) of AE patients received corticosteroids, 8 (22.2%) AE patients received intravenous immunoglobulin, and only 1 (2.8%) AE patient was treated with rituximab. The EEG information was collected and analyzed. The background waves of IE patients more frequently exhibited delta rhythm than AE patients (p = 0.013). Delta and/or theta activities were the most common abnormal wave in both IE (48.9%) and AE patients (53.1%) (Table 1).

Subgroup Analysis of Clinical Characteristics and Laboratory Results: Comparisons of Patients with VE and BE; Differences of AE Patients with NSAbs, Intracellular Abs and NAAb Negative

We further divided patients with IE (n = 59) into VE group (n = 16) and BE group (n = 38). Five patients with double infection were excluded. Headache was more prevalent in the patients with BE compared to those with VE (p = 0.027), and the levels of serum calcium were lower in patients with VE (p = 0.027). There were 21 AE patients with NSAbs, 6 AE patients with Intracellular Abs and 8 AE patients without NAAb. Only 1 AE patient with double Abs (GABAB and Amphiphysin) was excluded. The levels of CSF LDH were higher in patients with intracellular Abs than NSAbs (p = 0.009). Levels of CSF protein, LDH, Lac and ADA were higher in AE patients without NAAb than those with NSAbs (p = 0.010, p = 0.048, p = 0.030, p = 0.039). As for blood tests, serum calcium levels were higher in AE patients with NSAbs than patients with intracellular Abs (p = 0.034). Patients with intracellular

Abs presented significantly decreased levels of erythrocyte count in blood (p = 0.007). Additionally, patients with NSAbs had significantly longer duration of hospital stays (p = 0.021) (Table 2).

Lesion Distribution of Brain MRI in Patients with AE and IE

All patients underwent brain MRI examinations except for 2 patients: a young male and a female with unstable clinical conditions. Computed tomography (CT) scan of the brain was performed in those 2 IE patients and the imaging results were normal. Patients with AE were more likely associated with hippocampal lesions than IE patients (p = 0.042), they were also found more likely to suffer memory deficits (p = 0.010) (Table 1). Differences of lesion distribution between the two groups were shown in Figure 3. A total number of 30 (52.6%) IE patients and 25 (69.4%) AE patients demonstrated intracranial abnormal signal. Temporal lobe lesions were the most commonly found feature in brain MRI of 21 (70%) IE patients and 20 (80%) AE patients, however, no statistical significance was found between the two groups. Among these patients, 13 IE patients and 15 AE patients demonstrated hippocampal lesions. The second most common brain region with observed lesions was amygdaloid in both groups. Followed by that, frontal lobe in IE patients,

Table 2 Subgroup Analysis of Clinical Characteristics and Laboratory Results: Comparisons of Patients with VE and BE; Differences of AE Patients with NSAbs and Intracellular Abs

	IE		AE		
	VE	BE	NSAbs	Intracellular Abs	NAAb negative
Onset symptom, No. (%)					
Headache	4(25.0%)	22(57.9%)*	3(14.3%)	1(16.7%)	2(25.0%)
Fever	13(81.3%)	23(60.5%)	6(28.6%)	3(50.0%)	5(62.5%)
Seizure	9(56.3%)	13(34.2%)	15(71.4%)	3(50.0%)	4(50.0%)
Involuntary movement	1(6.3%)	1(2.6%)	9(42.9%)	1(16.7%)	1(12.5%)
Memory deficit	2(12.5%)	3(7.9%)	11(52.4%)	1(16.7%)	1(12.5%)
Elapsed time between symptom onset and diagnosis (days)	7.8 ± 7.3	7.2 ± 8	41.8 ± 60.1	38.7 ± 31	10.9 ± 7.8[b]
Admission to hospital (days)	18.6 ± 9.3	15.9 ± 8.4	21.3 ± 8.5	15.2 ± 3.7[#]	23.5 ± 12.8
ICU stay, No. (%)	6(37.5%)	10(26.3%)	3(14.3%)	1(16.7%)	1(12.5%)
The first CSF findings					
CSF WBC (> 5 × 10^6/L), No. (%)	8(50.0%)	23(60.5%)	13(61.9%)	3(50.0%)	7(87.5%)
CSF protein level (g/L)	0.7 ± 0.6	0.6 ± 0.4	0.4 ± 0.1	0.8 ± 0.6	0.7 ± 0.5 [a]
CSF chloride level (mmol/L)	124.1 ± 5	124.6 ± 7.5	125.4 ± 6.2	122.7 ± 7.1	114.9 ± 25.6
CSF LDH level (U/L)	47.1 ± 41.5	29.8 ± 35.3	19.3 ± 11.4	49.2 ± 58.6[#]	32.9 ± 19.7 [a]
CSF Lac level (mmol/L)	2.4 ± 1.8	2.2 ± 1.4	1.6 ± 0.4	3.1 ± 3.3	1.9 ± 0.3 [a]
CSF ADA level (U/L)	1.5 ± 1.6	1.4 ± 1.6	0.8 ± 1.5	2.4 ± 3.1	1.2 ± 1.1 [a]
CSF CRP level (mg/L)	0.6 ± 1.8	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0
Positive rate of Pandy test, No. (%)	12(75%)	32(84.25%)	10(47.6%)	5(83.3%)	5(62.5%)
The first serum findings					
Blood sodium level (mmol/L)	137.8 ± 5.2	138.1 ± 5.5	136.4 ± 4.9	138.7 ± 4.5	138.7 ± 5.7
Blood potassium level (mmol/L)	3.6 ± 0.4	3.8 ± 0.5	3.9 ± 0.4	3.7 ± 0.5	3.9 ± 0.4
Blood calcium level (mmol/L)	2.1 ± 0.2	2.2 ± 0.2*	2.2 ± 0.2	2.1 ± 0.1[#]	2.2 ± 0.2
Blood chlorine level (mmol/L)	100.2 ± 4.5	99.7 ± 4.6	98.6 ± 5.2	102 ± 4.6	89.7 ± 35.5
Blood leukocyte count (× 10^9/L)	6.7 ± 2.1	7.7 ± 3	10.5 ± 4	8.9 ± 3.2	10.4 ± 3
Blood erythrocyte count (× 10^{12}/L)	3.8 ± 1.1	4.2 ± 0.6	4.7 ± 0.6	4 ± 0.5[#]	4.7 ± 0.7
Blood platelet count (× 10^9/L)	199.4 ± 72.6	236.3 ± 89.1	272 ± 106	248.7 ± 90.2	311.4 ± 173.5

Notes: Data are presented as No. (%) or mean ± standard deviation; significant differences are indicated by *VE versus BE, p < 0.05; [#]NSAbs versus Intracellular Abs, p < 0.05; [a]NSAbs versus NAAb negative p < 0.05; [b]Intracellular Abs versus NAAb negative p < 0.05.

Abbreviations: AE, autoimmune encephalitis; IE, infectious encephalitis; VE, viral encephalitis; BE, bacterial encephalitis; No., number; CSF, cerebral spinal fluid; mRS, modified Rankin Scale; GCS, Glasgow Coma Score; IVIG, intravenous immunoglobulin; WBC, white blood cell; ICU, intensive care unit; CRP, C-reactive protein; LDH, lactate dehydrogenase; Lac, lactic acid; ADA, adenosine deaminase; Abs, antibodies; NSAbs, neural cell-surface antibodies; NAAb, neural autoantibodies.

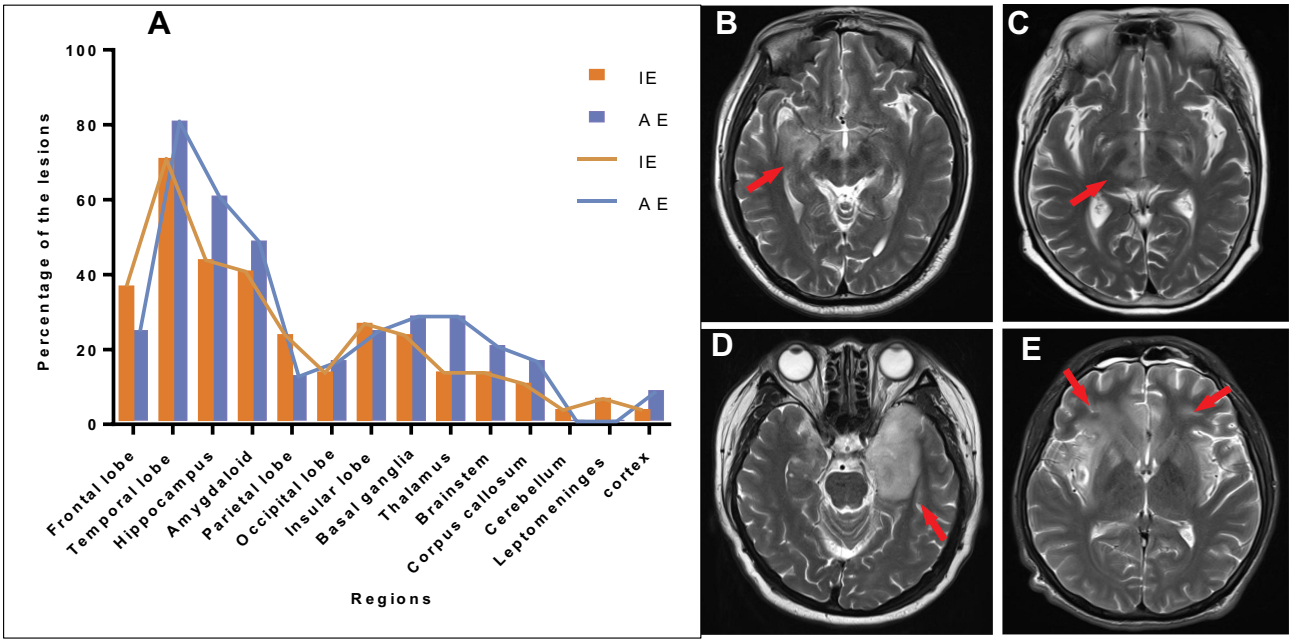

Figure 3 Lesions' distribution in brain MRI in patients with AE and IE, and abnormal MRI images in 4 patients. The lesions' distribution of 30 IE patients and 25 AE patients with abnormal MRI image (**A**). Brain MRIs show T2 hyperintensities relatively restricted to the unilateral medial temporal lobe in a patient with AE ((**B**), arrows). Panel (**C**) shows thalamus T2 hyperintensities in a patient with AE (arrow). Panel (**D**) shows unilateral temporal lobe T2 hyperintensities in a patient with IE (arrow). Panel (**E**) shows bilateral deep frontal lobe T2 hyperintensities in a patient with IE (arrow).
Abbreviations: AE, autoimmune encephalitis; IE, infectious encephalitis.

and both thalamus and basal ganglia in AE patients were also commonly damaged. Meanwhile, brain regions such as cerebellum, leptomeninges and cortex were the least common regions with observed lesions (Figure 3).

Discussion

IE and AE are symptomatically similar, however very different in terms of pathogenesis and clinical treatments. The symptoms, laboratory results, and MRI presentations were often confusing especially in patients with critical conditions. Therefore, accurate distinguishing of such diseases is crucial for patients with limited medical records at the early stages of the diseases.

Specific clinical presentations were the first step during diagnosis. Fever and headache were more commonly found in IE patients, while in subgroups of IE, BE patients were more prone to suffering headache than VE patients. Previous studies also reported that IE patients more frequently presented with fever and headache,[2,14] which was consistent with our results. A large amount of literature demonstrated that meningitis was mediated by the activated human immune defence system caused by infective pathogen invasion. Meanwhile, bacteria also damaged meninges by producing bacterial toxins. The inflammation of meninges subsequently stimulated nerve roots and caused the headache.[6,15] NMDAR include N-methyl-D-aspartate receptor 1 (NR1), NR2, and NR3 subunits, in which the mechanisms of headache were mainly associated with NR2 subunit.[16] NR2 was over-expressed in synapses, where the terminations of nociceptive afferents were.[17] In this study, a total of 6 AE patients demonstrated headache, while 5 of them were found to present anti-NMDAR antibodies. However, the detailed characteristics of the headache were not recorded in most of our patients. Hence, the differences in the feature of headache between IE and AE were not clear. For future studies, detailed data regarding headache would be needed. Furthermore, involuntary movement, memory deficits and seizures were found to be more prevalent in AE patients than IE patients. Manifestations of involuntary movement included repetitive rhythmic ocular, jaw, facial, lingual, limb and trunk movements, opisthotonus, and dystonic limb posturing.[18] Fronto-striatal disinhibition, cortico-limbic, hypothalamus and brainstem disconnections, the dysfunctions of basal ganglia were associated with involuntary movement.[19,20] A previous study found that the antibody-mediated NMDAR decreases inactivated GABA-ergic neurons, therefore leading to movement disorders.[20] In our study, 6 out of 10 NMDAR-Abs positive patients demonstrated involuntary movement, while the major cause of

movement disorders in patients with anti-Ma2 encephalitis was cytotoxic T-cell-mediated neurologic damage of basal ganglia.[21] Vigliani et al also found that a minority of patients with intracellular Abs presented with involuntary movement.[22] In this study, a total number of 11 (30.6%) AE patients presented with involuntary movement, significantly higher than IE patients. Similarly, Hou et al found that 25 (45.5%) AE patients presented with involuntary movement.[23] Gable et al also reported that involuntary movement was more commonly found in AE patients (20 individuals, 63%) than IE patients (3 individuals, 6%).[14]

Atrophy of hippocampus was closely correlated with memory deficits. Hansen et al found that in different periods of the course of AE, 4/7 AE patients demonstrated varying degrees of atrophies of hippocampal volume, which was associated with the decline of verbal memory and figural memory.[24] We also found that AE patients were more likely to present hippocampus lesions than IE patients. Patients with LGI1-Ab demonstrated memory disorders, due to the fact that the LGI1 gene transcripts were enriched in CA3 region of the hippocampus.[25,26] In this study, 9 patients with anti-LGI1 encephalitis were enrolled, while 4 of them demonstrated memory deficits. The CA1 region of the hippocampus contained the highest density of NMDAR in the brain, and the internalization of NMDAR in CA1 region caused severe memory deficits.[27] In this study, 6 out of 10 anti-NMDAR encephalitis patients demonstrated memory deficits. The hippocampus function was damaged due to the binding of Ma2 to cytoplasmic protein in the area of limbic system.[28] Similarly, limbic system damage caused also be caused by anti-Hu and anti-CV2 autoimmunity, as those antigen expressions were exclusively limited within neurons.[29] As mentioned previously, AE patients were more likely to suffer from memory impairments, while in our study, a small proportion of IE patients also demonstrated memory problems. Of the 4 IE patients with memory decline, 2 cases were infected with Herpes simplex virus (HSV). Previous research reported that HSV infection was associated with memory decline. Receptors of HSV for viral entry were expressed in the hippocampus thus making the hippocampus vulnerable to HSV infection.[30] NAAb-mediated inhibitory synaptic transmission decrease and intrinsic excitability increase were the triggers of epilepsy in AE patients.[31] The loss of the LGI1 receptor expression inhibited AMPA receptor-mediated synaptic transmission, reduced AMPA receptor, and therefore caused seizures.[32] There were 7/9 patients with LGI1-Abs who presented with seizures. Yeo et al also found that anti-LGI1 /CASPR2 seropositive patients were more likely to be associated with seizures.[33] Our data demonstrated that AE patients (63.9%) were more likely to develop seizures than those with IE (42.4%). A similar study also found that epileptic seizures were more prevalent in AE patients (88%) than in IE patients (21%).[2] Therefore, in clinic, it was of critical importance to detect specific autoantibodies related to AE for accurate diagnosis of patients who demonstrated symptoms such as involuntary movement, memory deficit, and seizures.

Previous research found the robust link between viral/bacterial infections and the declined counts of leukocyte, erythrocyte, and platelet.[6,34–36] Epstein-Barr virus was found to infect B-cells and provoke oligoclonal expansion of suppressor T-cells, which destroyed the hematopoiesis of bone marrow, and subsequently caused the decrease of erythrocyte count. The pathophysiology of decline in platelet count was found to be caused by the binding of Epstein-Barr virus to platelet, leading to the presence of platelet-destroying agglutinin.[37] In this study, most BE patients were infected with bacterial staphylococcus, which produced cytolysins, including leukocidins and hemolysins, therefore causing decreases in the numbers of erythrocytes and leukocytes.[6] Interestingly, the erythrocyte counts were decreased in AE patients with intracellular Abs compared to those with NSAbs. Intracellular Abs, also known as onconeuronal Abs, are associated with specific paraneoplastic syndrome. A previous study found that patients with intracellular Abs often presented with poor response to immunotherapy and unfavorable prognosis.[11] However, the underlying mechanisms of erythrocyte damage in intracellular Abs-positive individuals remain unclear.

CSF data were an important reference in the determination of the causes of encephalitis. The Pandy test was a qualitative method to quickly detect abnormal protein concentrations in CSF by precipitation, and globulins played an important role in the process of precipitation. The increased globulin in CSF was caused by the activation of immune and defence system by foreign invaders, such as bacteria and virus, and subsequent positive Pandy test.[38] We found that the positive rates of Pandy tests were higher in IE patients than AE patients. CNS diseases, such as cerebral infarction, hemorrhage, infections and prolonged seizures, are also associated with increases in the levels of CSF LDH.[39] The CSF LDH was significantly higher in AE patients with intracellular Abs than those

with NSAbs. This was potentially due to the cytotoxic T-cells-mediated neural damage and death of AE patients with Intracellular Abs.[40] Elishkevitz et al reported that the damage of neurons caused the rise of CSF LDH in patients with multiple sclerosis.[41] Likewise, the levels of CSF protein, LDH, Lac and ADA were found to be higher in AE patients without NAAb than those with NSAbs. However, the potential causes were still not well understood, and worthful for further studies.

In this study, the serum calcium levels were found to be lower in VE patients than BE patients. HSV or CMV infections induced the activation of Akt-mediated signaling pathway, which was a modulator of calcium influx. In turn, the activation of Akt promoted HSV or CMV entry. Calcium influx elevation caused decreased serum calcium.[42,43] The calcium entry into intracellular via NMDAR was activated by the Akt-mediated signaling pathway, and the disturbance of NMDAR blocked the calcium influx in patients with anti-NMDAR encephalitis.[44] The disruption of LGI1 receptor decreased the expression of AMPA receptor, a major mediator of calcium influx.[45] Collectively, the levels of serum calcium were increased due to reduced calcium influx in AE patients with NSAbs.

Detection of brain lesions by MRI scans revealed that temporal lobe lesions were the most common abnormal imaging feature in both types of encephalitis. Consistent with previous studies, it was suggested that lesions in the medial temporal lobes and the hippocampus were often involved in AE and HSV encephalitis patients. In this study, 8 out of 13 patients with HSV infection demonstrated hippocampal lesions. As revealed by EEG results, more IE patients presented with increases in delta background waves than AE patients.[46–48] The slow-frequency wavebands delta usually appeared during the night. Viral infection of CNS caused increases of delta rhythm presented with circadian rhythm dysfunction.[49]

Taken together, our study suggested that the combination of symptomatic differences was potentially useful for preliminary distinguishing of AE and IE in clinic. Followed by that, further distinguishing was performed between AE patients with NSAbs and those with Intracellular Abs, and between VE and BE, according to the key differences. This two-stepped diagnosis strategy was potentially useful for accurate and effective early diagnosis, therefore targeted therapies could be applied in time. However, this study had a retrospective single-center design and was therefore limited. Thus, multicenter and maximus sample clinical analysis iare necessary in further studies.

Conclusion

In conclusion, in this study, we found that AE patients were more likely to be associated with involuntary movement, memory deficits, and seizures. As revealed by CSF detections, IE patients demonstrated higher positive rates in Pandy tests, while AE patients with intracellular Abs demonstrated higher levels of LDH than those with NSAbs. In addition, serum erythrocyte and platelet counts were found to be decreased in IE patients. The serum calcium levels were found to be lower in patients with VE than BE, and higher in patients with NSAbs than intracellular Abs. The hippocampal lesions revealed by MRI and EEG delta background rhythm were more commonly found in AE patients. All these features gave a clue for distinguishing AE and IE patients, and their respective subgroups. Further imaging analyses were potentially useful in differential diagnosis of these two types of encephalitis.

Ethical Approval

The study was approved by the Ethics Committee of Tianjin Medical University General Hospital (Ethical NO.IRB2020-WZ-113) and all the participants provided informed consent. The participants were informed about the purpose of the study, and that it was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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