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A comparison of infectious and autoimmune meningoencephalitis: Clinical presentation, biochemical markers and MRI findings

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Abstract

Objective: This study investigates distinguishing patterns in lesion distribution, relevant clinical presentation and biochemical markers in MRI to differentiate infective encephalitis (IE) and autoimmune encephalitis (AE). *Methods:* Retrospective study of adult patients with a confirmed diagnosis of IE and AE admitted to the Neurology unit from January 2012 to December 2020 with MRI Brain. Selected cases with confirmed IE (according to the 2013 Infective Encephalitis Consortium diagnostic criteria) or antibody-positive AE (detection of Neuronal auto-antibody from blood or CSF), coupled by clinical presentation. MRI brain lesion distribution, lobar involvement, enhancement, haemorrhage, vasculopathy and atrophy were analysed. *Results:* Forty-seven patients (21 IE and 26 AE, respectively) were selected. IE group are older (48.0 ± 16.81) compared to AE (28.4 ± 14.10). Fever and vomiting were significant in IE ($p<0.001$), whereas psychosis, seizure, movement disorder, and tumour (ovarian teratoma) were significant in the AE cohort. Cerebrospinal fluid (CSF) analysis showed elevated leucocytes with polymorphism and high protein levels in IE (2.081 g/L ± 2.93 vs AE (0.352g/L ± 0.18). MR imaging detected abnormal findings in 61.9% of cases with infectious encephalitis (IE), while 76.9% of cases with autoimmune encephalitis (AE) exhibited normal MRI results. Asymmetrical lesions and inferior frontal lobe distribution (57.1%) were significantly prevalent in IE ($p<0.05$). Enhancement patterns and haemorrhage were rarely observed in AE patients.
Conclusion: IE presented at an older age, with the majority having MRI findings such as asymmetrical lesions, leptomeningeal enhancement, and involvement of medial temporal, hippocampus and inferior frontal cortex. IE clinically presents with fever, vomiting, and elevated CSF leucocytes and protein levels. AE presents at a younger age with seizure, psychosis, movement disorder, tumour (ovarian teratoma). Fewer AE have MRI findings, and if present, tend to be symmetrical in distribution. Lobar involvement in the inferior frontal was the MRI feature that significantly favoured the diagnosis of IE compared to AE. IE and AE have distinct clinical, biochemical, and MRI abnormalities that can be discriminated between the 2 entities.

Keywords: Infectious encephalitis, autoimmune encephalitis, viral encephalitis, bacterial encephalitis, MRI Brain.

INTRODUCTION

Encephalitis is a diffuse infective or inflammatory process of the brain that is clinically translated into brain dysfunction.[1] Various etiologies cause encephalitis, such as bacterial or viral infection, autoimmune-mediated inflammation, paraneoplastic, and encephalitis of unknown origin.[1]

IE may be a potentially life-threatening condition caused by various pathogens of bacterial and viral origin. AE is a cohort of recently identified encephalitis syndrome associated with immune-mediated auto-antibodies to neuronal antigens. Both autoimmune and infective encephalitis share the clinical features of altered cognition.[2] Association with seizure

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is well documented in both entities, and CSF lymphocytosis can be present in AE and viral encephalitis. Hence, brain imaging is an essential tool for diagnosing acute encephalitis. A computed tomography (CT) brain is commonly done for easier availability and to exclude causes that contraindicate a lumbar puncture, such as obstructive hydrocephalus. Following a lumbar puncture, the subsequently performed imaging of choice would be an MRI brain.[3] Pattern recognition in brain MRI can aid diagnosis and sometimes indicate the causative pathogen. Also, an MRI can estimate the degree of brain insult and complications, thus prognosticating the patient's outcome.

Although the clinical presentation of infectious encephalitis (IE) and autoimmune encephalitis (AE) can be similar, their pathogenesis and treatment approaches differ, with the latter tending to worsen infection. Thus, prompt and accurate diagnosis is crucial for good outcomes. Therefore, this study retrospectively analyses the clinical presentation, biochemistry, and MRI findings for each cohort of infectious encephalitis (IE) and autoimmune encephalitis (AE) patients, intending to identify important differentiating features that can result in early diagnosis and appropriate treatment initiation.

METHOD

A retrospective study of adult patients with a confirmed diagnosis of infective or autoimmune encephalitis admitted to the Neurology unit from January 2012 to December 2020 who had an MRI study performed. Patient demographic data (age, gender, race) and relevant clinical history were obtained from the electronic medical record (EMR) system. This study was conducted following the accepted guidelines given by the local Medical Ethics Committee (MECID No: 2020104-9131). Clinical data were retrospectively collected, and patients were divided into IE and AE categories.

Diagnosis of IE is based on the criteria mentioned in the Consensus Statement of the IE Consortium 2013.[4] The criteria include the following:

1) Cognition alteration which has lasted for more than 24 hours
2) A minimum of 2 of the criteria as mentioned below:
   a) Temperature recording of ≥ 38°C, within 3 days before or after clinical presentation
   b) Generalized or partial seizures
   c) New onset of focal neurologic findings
   d) SF pleocytosis (WBC counts >5/mm^3)
   e) Abnormal imaging findings consistent with encephalitis
3) Positive blood or CSF culture
4) Rapid recovery following the initiation of anti-microbial treatment

The following criteria were used for patients with definite AE with neuronal auto-antibody.[5]

1) Subacute presentation of memory impairment altered cognition or psychiatric symptoms.
2) At least one criterion is mentioned below:
   a. New focal neurological findings
   b. New onset seizure or a new seizure semiology in a known case of seizure disorder
   c. CSF white blood cell count (WBC) pleocytosis (≥ 5/mm3)
3) Positive neuronal auto-antibody in blood and CSF samples

CSF samples were tested by Real-Time quantitative Polymerase Chain Reaction (RT-qPCR) for meningitis viral panel, Latex agglutination assay for CSF bacterial antigen, and viral and bacterial culture. Patients with positive CSF/ blood bacteria culture and/ or CSF polymorph predominant pleocytosis were included in the bacterial encephalitis (BE) group. On the other hand, patients with CSF lymphocytosis and/ or positive viral PCR/ culture were included in the viral encephalitis (VE) group. Even though the detection of an infective organism confirms the diagnosis of IE, a negative culture in CSF and/ or blood, which is reported in >50% of cases, would not exclude the diagnosis. Hence, it will be labelled as presumed bacterial or viral encephalitis.[6,7]

Patients with antibody-positive AE (by detection of known neuronal auto-antibody from the blood or CSF, coupled by clinical presentation) were included in autoimmune encephalitis.

Exclusion Criteria:

1. Motion or other artefacts noted in the MRI report or on image inspection.
2. Patients with infections such as mycobacterium tuberculosis, cryptococcus, toxoplasmosis, parasites and fungi were excluded from this study.
3. Poor clinical information, no blood/CSF findings and poor MRI data

MRI brain features were analysed for lesion distribution, lobar involvement, enhancement pattern, haemorrhage, vessel vasculopathy, and

cerebral atrophy. In addition, the demographic data, clinical presentation, biochemistry, and MRI findings were analysed for each cohort of IE (infectious encephalitis) and autoimmune encephalitis (AE) patients.

MRI acquisition

MRI Brain was done via a 3.0 Tesla Signa® HDx MR System (GE Healthcare) or the Siemens Magnetom Prisma TIMDOT Engine 3T (Siemens Healthcare) with a dedicated 8-channel head coil at MRI 3T and 64-channel head coil. The patient was scanned in a supine position. The total examination time was approximately 30 minutes.

Statistical analysis

All statistical analysis was performed using version 26 of the IBM Statistical Package for Social Sciences software application (IBM SPSS). Categorical and numerical/continuous variable was used in this study. Categorical data included gender, ethnicity, MRI imaging findings, clinical presentation, and outcome. Numerical/continuous variables included age, CSF parameters, and blood WBC. Categorical variables will be presented as frequency and percentage (%), while numerical variables will be presented as the median and interquartile range (IQR) as they were not normally distributed. The Shapiro-Wilk test was employed for normality distribution pattern determination. For the numerical variable, statistical analysis to determine the difference between IE/AE was performed using a non-parametric test (Mann-Whitney test), as all the numerical variables were not normally distributed. Pearson's Chi-square test or Fisher's exact test was used to analyse the association between factors/variables of infectious and autoimmune encephalitis. A probability value of less than 0.05 (p-value < 0.05) will be considered statistically significant.

RESULTS

Patient demographics and clinical manifestations

A total of 103 encephalitis patients were included from January 2012 to December 2020. Out of them, 56 patients have no radiological images. Hence, 47 patients constituted the study sample, with 21 having infectious encephalitis (IE) and 26 having autoimmune encephalitis (AE). The frequencies and associations of patient demographics and encephalitis are presented in Table 1. In cases of infective encephalitis (IE), there was a slight predominance of male patients, accounting for 52.4% of cases, whereas autoimmune encephalitis (AE) exhibited a higher proportion of female patients, comprising 57.7% of cases. IE patients were mainly in the age group of 40 to 59, while AE patients were notably more prevalent among younger adults aged 20 to 39. In this study, the incidence of infective encephalitis is the highest among individuals of Chinese ethnicity, constituting 38.1% of cases, whereas both the Malay and Chinese communities showed equal rates of occurrence in autoimmune encephalitis. Fever (100%) and vomiting (42.9%) were the main symptoms in IE patients. In AE, fever and vomiting were significantly less prevalent, while psychosis (100%), seizure (92.3%), movement disorder (69.2%) and ovarian teratoma (23.1%) were frequently encountered. Movement disorders in AE patients include orofacial dyskinesia (72.2%), orofacial dyskinesia and dystonia (16.7%), dystonia (6.3%) and cerebellar ataxia (6.3%).

Biochemical analysis of blood and CSF

Blood and cerebrospinal fluid (CSF) analyses between IE and AE were summarised in Table 2. The diagnostic test reported a high proportion of white blood cells for both IE (76.2%) and AE (67.2%) patients. The mean for white blood count was 13.37×10^9/L and 12.19×10^9/L for IE and AE, respectively. However, blood parameters showed no significant difference between encephalitis. In IE blood culture, some microorganisms were positively detected in 5 patients, including Herpes IgM, *Strep pneumonia*, NS1 and Dengue IgM. Only 1 AE patient was detected positive for *bacillus capitis*.

CSF profiles were characterised by increased leucocytes count in IE as compared to AE (mean 675.48 μL vs 77.46 μL, respectively). Elevated CSF polymorphism was observed in 35.19% of IE cases compared to 9.58% in AE cases. IE patients also demonstrated significantly higher mean protein concentration (of 2.081 g/L) in contrast to AE patients (of 0.352 g/L). However, glucose levels remained within the normal range for both types of encephalitis. Additionally, there were 3 causative agents; namely herpes simplex virus (HSV-1), *Streptococcus pneumonia*, and dengue type 2 (DEN2), identified in the CSF samples of IE patients. On the other hand, no microorganism was detected in the CSF samples of AE patients.

Within the AE cohort, 25 patients were positive for anti N-methyl-D-aspartate receptor (NMDAR)

Table 1: Patient demographics and clinical manifestation between infectious and auto-immune encephalitis

Variable	Infectious Encephalitis N=21	Autoimmune Encephalitis N=26	P-value
Demographic Data			
Gender			
• Male	11 (52.4%)	11 (42.3%)	0.491
• Female	10 (47.6%)	15 (57.7%)	
Age (years) (n, %)	48.0 ± 16.806	28.4 ± 14.097	<0.001*
• <20	2 (9.5%)	6 (23.1%)	
• 20-39	3 (14.3%)	16 (61.5%)	
• 40-59	12 (57.1%)	3 (11.5%)	
• ≥60	4 (19.0 %)	1 (3.8%)	
Ethnicity (n, %)			
• Chinese	8 (38.1%)	12 (46.2%)	0.022*
• Malay	4 (19.0%)	12 (46.2%)	
• Indian	5 (23.8%)	2 (7.7%)	
• Others	4 (19.0%)	0 (0.0%)	
Clinical Presentations (n, %)			
• Fever	21 (100%)	7 (26.9%)	<0.001*
• Headache	11 (52.4%)	7 (26.9%)	0.069
• Vomiting	9 (42.9%)	1 (3.8%)	0.002*
• Confusion	19 (90.5%)	26 (100%)	0.194
• Seizure	6 (28.6%)	24 (92.3%)	<0.001*
• Psychosis	2 (9.5%)	26 (100%)	<0.001*
• Movement Disorder	0 (0.0%)	18 (69.2%)	<0.001*
• Reduced consciousness	14 (66.7%)	20 (76.9%)	0.324
• Ventilated	7 (33.3%)	10 (38.5%)	0.478
• Tumour (Ovarian teratoma)	0 (0.0%)	6 (23.1%)	0.021*

*Statistically significant when p<0.05

antibody and 1 patient was positive for both anti-leucine-rich glioma-inactivated-1 (LGI-1) and contactin associated protein receptor-2 (CASPR-2) antibodies.

Abnormality in MRI changes

The brain MRI is normal in approximately 38.1% and 76.9% in IE and AE, respectively. Routine MRI at disease onset showed abnormal findings in all patients with IE and AE (Table 3). Brain MRI images showed multiple asymmetrical lesions in IE patients (92.3%), whereas symmetrical lesions were more prominent in AE patients (83.3%) Figure 1. Patients with IE frequently have lesion distribution patterns in the cortical, subcortical, and gyral regions. The majority of lobar involvement was observed in IE as compared with AE, with the most common location of lobar involvement in IE being the medial temporal lobe (61.5%), hippocampus (61.5%), amygdala (53.8%) and inferior frontal (53.8%). Meanwhile, brain regions such as corpus callosum and cerebellum were the least common regions with observed lesions in both types of encephalitis. Notably, leptomeningeal enhancement was highly present in IE patients (38.5%), and none were observed in AE patients. Hemorrhage and vessel vasculopathy were rarely observed in AE patients. Remarkably, the presence of lobar involvement in the inferior frontal region is the crucial MRI feature that significantly distinguishes IE from AE.

DISCUSSION

Encephalitis has occasionally become a global burden. The difficulty in the diagnosis of infectious and autoimmune encephalitis remarkably contributes to the problem, as IE and AE can be symptomatically similar in presentation. Misdiagnosis of encephalitis leads to different therapeutical management, clinical outcomes, and possibility of permanent neurological deficits. Thus, it is crucial to accurately distinguish between IE and AE at the early stages of the disease. This study evaluates clinical symptoms,

Table 2: Biochemical analysis of blood and cerebrospinal fluid (CSF) between infectious and autoimmune encephalitis

Variable	Infectious Encephalitis N=21	Autoimmune Encephalitis N=26	P-value
Blood Biochemical Analysis			
White Blood Cell (mean, 10^9/L)	13.367 ± 6.746	12.188 ± 6.214	0.607
White Blood Cell (n, %)			
• Low	0 (0.0%)	0 (0.0%)	0.596
• Normal	5 (23.8%)	8 (30.8%)	
• High	16 (76.2%)	18 (69.2%)	
Blood Culture (n, %)			
• NG	16 (76.2%)	25 (96.2%)	0.184
• Strep pneumoniae	2 (9.5%)	0 (0.0%)	
• Dengue	1 (4.8 %)	0 (0.0%)	
• Herpes	1 (4.8%)	0 (0.0%)	
• NS1 and Dengue IgM	1 (4.8%)	0 (0.0%)	
• Bacillus capitis	0 (0.0%)	1 (3.8%)	
CSF Biochemical Analysis			
Polymorph (mean, %)	35.19 ± 40.122	9.58 ± 22.981	0.061
Lymphocyte (mean, µL)	41.00 ± 41.893	32.53 ± 43.937	0.236
Leucocytes (mean, /uL)	675.48	77.46	0.003*
• Low	5 (23.8%)	16 (61.5%)	0.007*
• Normal	0 (0.0%)	2 (7.7%)	
• High	16 (76.2%)	8 (30.8%)	
Glucose (mean, mmol/L)	3.490 ± 2.574	4.104 ± 1.100	0.015*
• Low	5 (23.8%)	0 (0.0%)	0.018*
• Normal	13 (61.9%)	24 (92.3%)	
• High	3 (14.3%)	2 (7.7%)	
Protein (mean, g/L)	2.081 ± 2.931	0.352 ± 0.176	<0.001*
• Low	0 (0.0%)	0 (0.0%)	0.001*
• Normal	2 (9.5%)	15 (57.7%)	
• High	19 (90.5%)	11 (42.3%)	
CSF culture (n, %)			
• NG	15 (71.4%)	26 (100%)	0.036*
• HSV-1	2 (9.5%)	0 (0.0%)	
• Strep pneumonia	3 (14.3%)	0 (0.0%)	
• DEN2	1 (4.8%)	0 (0.0%)	

*Statistically significant when p<0.05
*Abbreviations: CSF cerebrospinal fluid, NA not available, NG negative

diagnostic tests and radiological parameters to provide possible differential diagnostic values in encephalitis.

In term of age of presentation, AE has the tendency to affect younger adult as compared to the older age group in the IE counterpart. This is in accordance with several studies that reported the same observation.[8-10] Clinical manifestations were associated with the specific types of encephalitis. Fever and vomiting were the prominent presentation in IE, where else neuropsychiatric presentation consisting of acute psychosis and seizure, followed by involuntary movements and cognitive decline were prominent in the AE group. This is consistent with other studies which reported a higher incidence of febrile illness associated with headache and vomiting in the IE group that might represent an

Table 3: MRI abnormality between infectious and auto-immune encephalitis

Variable	Infectious Encephalitis N=21	Autoimmune Encephalitis N=26	P-value
MRI Parameter			
Normal MRI			
• Yes	8 (38.1%)	20 (76.9%)	0.007
• No	13 (61.9%)	6 (23.1%)	
Symmetrical Lesion (n, %) n=13, n=6			
• Symmetrical	1 (7.7%)	5 (83.3%)	0.001*
• Asymmetrical	12 (92.3%)	1 (16.7%)	
Lesion Distribution Pattern (n, %)	N=13	N=6	
Cortical Lesion	12 (92.3%)	6 (100.0%)	0.310
Subcortical	6 (46.2%)	3 (50.0%)	0.876
Gyral Expansion	10 (76.9%)	4 (66.7%)	0.637
Ependymal	0 (0.0%)	0 (0.0%)	NS
Subependymal	2 (15.4%)	0 (0.0%)	0.310
White Matter	1 (7.7%)	0 (0.0%)	0.485
Lobar Involvement (n, %)			
Inferior Frontal	7 (53.8%)	0 (0.0%)	0.024*
Medial Temporal Lobe	8 (61.5%)	1 (16.7%)	0.069
Lateral Temporal Lobe	5 (38.5%)	2 (33.3%)	0.636
Hippocampus	8 (61.5%)	1 (16.7%)	0.069
Amygdala	7 (53.8%)	1 (16.7%)	0.127
Parietal Lobe	6 (46.2%)	1 (16.7%)	0.216
Occipital	3 (23.1%)	2 (33.3%)	0.637
Insular Lobe	4 (30.8%)	1 (16.7%)	0.516
Basal Ganglia	3 (23.1%)	0 (0.0%)	0.200
Thalamus	3 (23.1%)	0 (0.0%)	0.200
Corpus Callosum	1 (7.7%)	0 (0.0%)	0.485
Brainstem	3 (23.1%)	0 (0.0%)	0.200
Cerebellum	0 (0.0%)	0 (0.0%)	NS
Enhancement Pattern (n, %)			
Gyriform	3 (23.1%)	0 (0.0%)	0.405
Ependymal	2 (15.4%)	0 (0.0%)	0.533
Subependymal	1 (7.7%)	0 (0.0%)	0.678
Pachymenigeal	3 (23.1%)	0 (0.0%)	0.405
Leptomeningeal	5 (38.5%)	0 (0.0%)	0.203
Ring Enhancement	4 (30.8%)	0 (0.0%)	0.294
Hemorrhage (n, %)			
Patechial	0 (0.0%)	0 (0.0%)	NS
Parenchymal	2 (14.3%)	0 (0.0%)	0.485
Subarachnoid	0 (0.0%)	0 (0.0%)	NS
Vessels Vasculopathy (n, %)	N=18	N=18	
Small	2 (11.1%)	0 (0.0%)	0.243
Large	1 (9.1%)	0 (0.0%)	0.500
Aneurysm	0 (0.0%)	0 (0.0%)	NS
Dissection	0 (0.0%)	0 (0.0%)	NS
Cerebral Atrophy	0 (0.0%)	0 (0.0%)	NS

*Statistically significant within the group ($p<0.05$)

*NS No statistical analysis can be performed due to insufficient number of subjects in the group

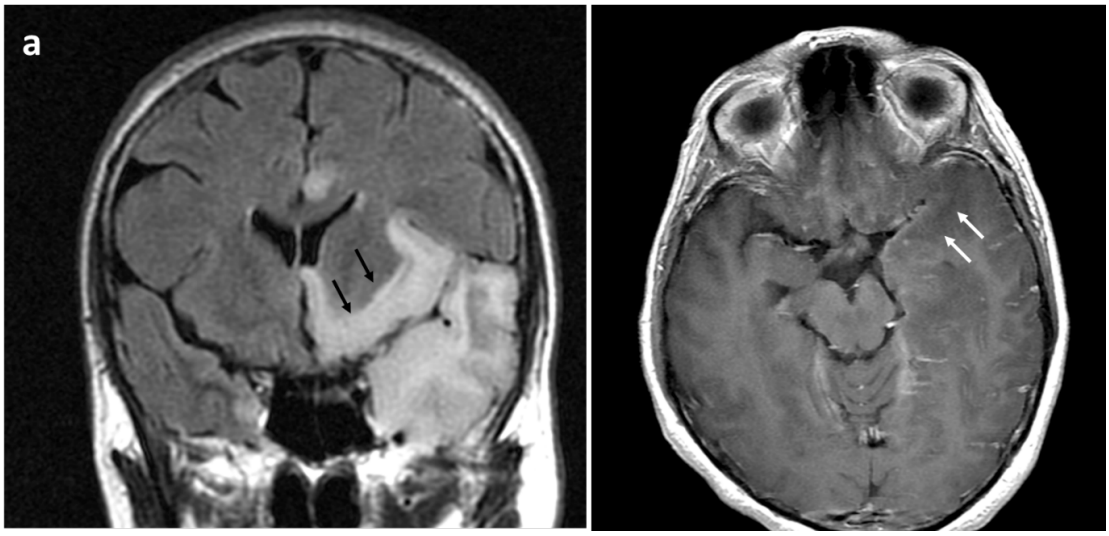

Figure 1 a. A 58-year-old male with infectious encephalitis, CSF grew Strep pneumonia. The MRI image on the right of Fig 1a shows Coronal FLAIR images which demonstrates an asymmetrical hyperintense lesion in the left inferior frontal (black arrow), right cingulate and right temporal lobe. The MRI image on the left of Figure 1a shows axial T1W post gadolinium images which demonstrates leptomeningeal enhancement (white arrow).

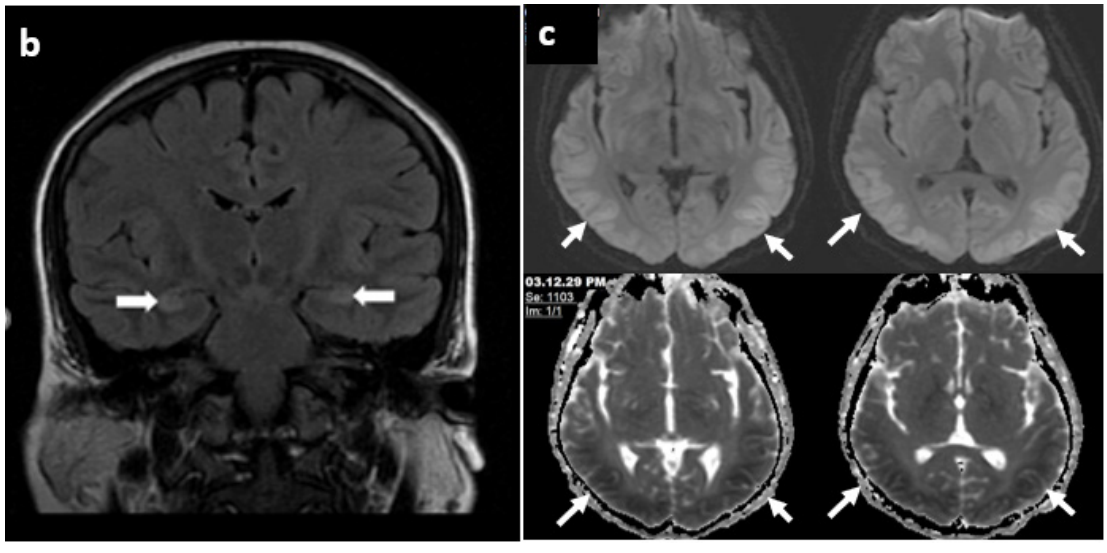

Figure 1 (b-c). A 25 years-old female with NMDARE encephalitis, the MRI image on figure 1b shows coronal FLAIR image which demonstrates symmetrical FLAIR hyperintense signal at bilateral hippocampus (white arrow). Figure 1c: 43-year-old male with NMDARE encephalitis, DWI (above) and ADC map(below) demonstrates areas of cortical restricted diffusion at both occipital and posterior temporal regions (white arrow).

elevated intra-cranial pressure, as opposed to a broader spectrum of neurological presentation in AE.[11-13] 71% of anti-NMDAR encephalitis patients had seizures with different seizure semiology namely, focal seizure, focal seizure with secondary generalisation, generalised tonic-clonic seizure (GTCS) and status epilepticus.[14] Acute psychosis was found to be early in the disease onset.[15,16] Several studies show a strong association between AE and ovarian tumours.[17-19]

CSF leucocyte and protein were the best discriminators of IE from AE. This was partly due to the significantly high leucocyte concentration in IE compared to AE. Previous studies with data on CSF in encephalitis also found increased total leucocyte levels.[20,21] This is likely due to the high

Table 4: Summary of distinguishing features of infective and autoimmune encephalitis

	Infective Encephalitis (IE)	Autoimmune Encephalitis (AE)
Age	Adult 48.0 ± 16.806	Younger Adult 28.5 ± 14.097
Clinical Presentation	Fever and vomiting	Seizure, psychosis, movement disorder and ovarian teratoma
Biochemical CSF Analysis	Elevated leucocytes and protein concentration. Presence of causative agents in CSF cultures.	Low leucocytes and protein concentration. No microorganism was detected in CSF cultures.
MRI abnormalities	• Abnormal MRI in 61.9% • 92.3% asymmetrical lesions • Involves medial temporal, hippocampus, amygdala and inferior frontal • Showed leptomeningeal enhancement • A few lesion patterns were observed in small and large vessel vasculopathy	• Normal MRI findings in 76.9% • 83.3% symmetrical lesions • Lesions less frequently involve the inferior frontal compared to IE • Leptomeningeal enhancement was not detected. • No lesion patterns were observed in small and large vessel vasculopathy

secretion of leucocytes in the subarachnoid space in response to the presence of viral or bacterial particles.[22] Additionally, the level of protein and glucose provides important information on the indicators of blood-brain barrier breakdown and the presence of glucose-consuming cells or organisms.[20]

The majority of IE showed abnormal findings on MRI versus in AE. This is in accordance with the findings from several reports.[16,23-25] Twenty patients from autoimmune encephalitis had normal MRI brain findings. Similar normal imaging findings in AE are also observed in other studies.[26,27] In contrast to unremarkable conventional MRI studies, the authors report extensive white matter damage in DTI analyses with decreased fractional anisotropy.[23,24] In the IE group, the majority (92.3%) showed asymmetrical lesion distribution, whereas in the AE, if lesions are present, the majority (83.3%) tend to be symmetrical in distribution. These findings are in accordance with a previous study that found that in the AE group, lesions tend to be multiple and symmetrical, affecting the limbic system.[28] In both of these cohorts, involvement of the hippocampus and medial temporal lobe was the most common abnormal MRI imaging features in both types of encephalitis, thus it was not a good discriminator to distinguish both entities, which is consistent with previous studies which suggested medial temporal lobes and the hippocampus were often involved in infective and autoimmune encephalitis.[1,27,28] This study also found that inferior frontal involvement is significantly more common in IE than in AE. This may be explained as some of the IE cases had CSF growth of HSV-1, which typically involves medial temporal and basifrontal areas bilaterally.[29]

Additionally, extensive MRI changes that include lesion distribution patterns and lobar involvement were prevalent in IE patients. Enhancement patterns observed in the MRI brain of IE patients show a wide variation in the degree and distribution involving the gyriform, ependymal, subependymal, pachymeningeal, and ring enhancement. Similar MRI findings were obtained by Armangue *et al*.[30], enhancement patterns were present in IE patients but none in AE. Evidently, there was a notably higher occurrence of leptomeningeal enhancement in infectious encephalitis (IE) in comparison to autoimmune encephalitis (AE), indicating that the infectious disease might contribute to an increased permeability of the blood-brain barrier.[31] However, haemorrhage and vessel vasculopathy are independently associated with the subtype of encephalitis.

In conclusion, our study provides strong evidence for MRI abnormality that can assist in differentiating between IE and AE in addition to clinical and biochemical parameters. IE usually affects an older group of patients with the majority having abnormal MRI findings such as asymmetrical lesions, leptomeningeal enhancement, and involvement of the inferior frontal cortex. Clinically, IE presents with fever,

vomiting, and elevated CSF leucocytes and protein levels. On the other hand, AE presents with fewer MRI lesions which tend to be symmetrical. They have a younger age of onset, with a broader spectrum of neuropsychiatric manifestation consisting of seizure, psychosis and movement disorder, with association with underlying tumour (ovarian teratoma).

A few limitations were identified in this retrospective study and could be improvised in future prospective studies:

1. The retrospective nature of this study resulted in fewer MRI images that could be analysed. However, there were 103 patients admitted and treated for encephalitis from January 2012 to December 2020. Only 50 patients were finally included, as many had no MRI Brain done during the initial presentation for encephalitis.
2. The timing and the frequency of the MRI study performed from the initial clinical presentation have yet to be discovered. This could affect the detection of abnormalities in the MRI.
3. The study cohort for autoimmune encephalitis is mainly NMDARE (25 out of 26 patients). Therefore, the higher number of NMDARE may also heavily weigh the findings. As for IE, there were only 8 patients with bacterial and 13 patients with viral encephalitis.
4. Some critical patient data, such as biochemical parameters, needed to be better recorded.
5. This was also a single-centre, small-scaled study. Increasing collaboration for a larger sample size with longer study duration is recommended in the future.

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