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ORIGINAL ARTICLE

Anti-N-methyl-D-aspartate Receptor Encephalitis Magnetic Resonance Imaging and Clinical Features: A Case Series

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ABSTRACT

Introduction: *Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a neuro-immunological disease presenting with a variety of neuropsychiatric features and magnetic resonance imaging (MRI) findings. This case series investigates the patterns of MRI features of these patients and their possible correlation with clinical parameters.*

Methods: *Clinical records and brain MRI features of 17 patients diagnosed with anti-NMDAR encephalitis were reviewed retrospectively. Correlation of imaging features with clinical parameters, including demographics, presentation, and clinical outcome, was investigated.*

Results: *Seven patients (41.2%) had abnormal brain MRI findings at presentation. The temporal lobe (excluding the hippocampus) was the commonest site of involvement, followed by the hippocampus and the insula. Normal MRI findings at presentation and hippocampal involvement showed no correlation with the clinical parameters. Interval development of cerebral atrophy (global or localised medial temporal atrophy) on repeat imaging was associated with worse functional outcome measured on the modified Rankin scale ($p = 0.008$) and with a lower rate of symptom-free recovery ($p = 0.045$).*

Conclusion: *More than half of our study subjects had normal brain MRI findings at presentation. The temporal lobe (excluding the hippocampus) was the commonest site of abnormal signal. Interval development of cerebral atrophy was associated with worse functional outcome and lower rate of symptom-free recovery.*

Key Words: *Anti-N-methyl-D-aspartate receptor encephalitis, Autoimmune diseases of the nervous system, Magnetic resonance imaging, Paraneoplastic syndromes, Neuroimmunomodulation*

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Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: This study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref 2020.428). The requirement of informed consent for the study was waived. All clinical investigations were conducted in accordance with the principles expressed in the Declaration of Helsinki. All patient records were anonymised prior to analysis.

中文摘要

抗N-甲基-D-天冬氨酸受體腦炎的磁共振成像和臨床特徵：病例系列

招卓倫、黃健開、賴銘曦、黎仰文

引言：抗-N-甲基-D-天冬氨酸受體（抗NMDAR）腦炎是一種神經免疫疾病，具有多種神經精神和磁共振成像（MRI）表現。本病例系列研究該病患者的MRI表現及其與臨床參數的可能相關性。

方法：回顧分析17例抗NMDAR腦炎患者的臨床記錄和腦部MRI表現，並研究影像表現與臨床參數的相關性，包括人口統計學、起病表現和臨床結果。

結果：7例（41.2%）就診時腦部MRI結果異常。顳葉（不包括海馬體）是最常見的受累部位，其次是海馬體和島葉。就診時MRI結果正常和海馬體受累顯示與臨床參數無關。一段時間內重複成像顯示發生腦萎縮（整體或局部內側顳葉萎縮）與改良版Rankin量表測量出的較差功能結果（$p = 0.008$）及較低無症狀康復率（$p = 0.045$）相關。

結論：超過一半研究對象在就診時的腦部MRI結果正常。 顳葉（不包括海馬體）是異常信號的最常見部位。一段時間內發生腦萎縮與功能較差的結果及較低無症狀康復率相關。

INTRODUCTION

N-methyl-D-aspartate (NMDA) receptors are heteromeric receptors for glutamate and glycine, which bind to receptor subunits (one NR1 and multiple NR2 subunits) for activation of NMDA receptors and their downstream cascade.[1] They play crucial roles in synaptic transmission as well as in processes such as dendritic sprouting, synaptic modification, and control of gene expression.[2]

Disturbance of NMDA receptor activity is associated with neuropsychiatric abnormalities, including cognitive impairment and physiologic abnormalities observed in schizophrenia; as well as with excitotoxicity implicated in disorders including epilepsy, Parkinson's disease, and Huntington's disease.[2,3]

Anti-NMDA receptor (anti-NMDAR) encephalitis is a disease associated with autoantibodies generated against the NMDA receptors. It was first described by Dalmau et al in 2007 in women with ovarian teratomas presenting with psychiatric and neurological symptoms, who were all noted to have antibodies reacting with NMDA receptors.[4]

Subsequent studies and case reports have shown that the condition can affect all ages and both sexes, with or without associated neoplasm.[5-7]

A broad spectrum of symptomatology has been described, ranging from a non-specific flu-like prodrome (which could include fever, upper respiratory symptoms and gastrointestinal disturbance), cognitive disturbance (amnesia, impaired short-term memory), psychiatric symptoms (confusion, delusions and hallucinations), neurological symptoms (dyskinesia, convulsions), to life-threatening conditions such as coma, autonomic nervous system instability, or status epilepticus.[8-12]

Larger-scale studies that focused on the imaging aspects of anti-NMDAR encephalitis have had some limitations. For example, brain imaging findings in patients have been noted to be highly variable in previous case reports and studies.[13,14] Normal findings on brain magnetic resonance imaging (MRI) at presentation are not uncommon in patients with the disease and, when there are abnormalities, any parts of the brain can be affected.[13-16]

Recent studies have investigated the imaging features in advanced imaging protocols (including functional connectivity, diffusion tensor imaging, and voxel-based morphometry), looking for correlations between the imaging features and clinical parameters of the disease, to establish the role of imaging in this relatively new disease entity.[16-18]

The aim of this study was to review the imaging features and clinical parameters of patients with anti-NMDAR encephalitis.

METHODS

Patients

Patients were identified from electronic patient records, including clinical data analysis and reporting system and the radiology information system, from three regional hospitals in Hong Kong. Search criteria were the primary ICD-9/10 diagnostic code corresponding to anti-NMDAR encephalitis and keywords of imaging requests with 'NMDA'. Inclusion criteria were patients admitted between 2005 and 2020; testing positive for anti-NMDA receptor antibodies (in either serum or cerebrospinal fluid); with brain MRI obtained at presentation; and with images available for review.

Data Collection

The electronic records of each included case were reviewed. The collection of patient information, including epidemiological and demographic variables (age, sex, clinical presentation), cerebrospinal fluid and serum analysis, imaging (MRI and, where appropriate, computed tomography and ultrasound), treatment, and clinical progress/outcome, was performed by manual review of electronic patient records. The functional outcome of each patient was graded on a modified Rankin scale according to the most recent follow-up clinical data.

Brain Magnetic Resonance Imaging

The multicentre nature of the study and the various clinical setups did not allow standardisation of sequences.

Images were acquired on different scanners, including Philips Achieva 1.5 T, Philips Ingenia 1.5 T, Philips Achieva TX 3 T (Philips, Inc. Best, the Netherlands) and GE Signa Architect 3 T (GE Healthcare, Inc., Milwaukee [WI], United States).

The most frequently performed sequences were T1-weighted spin-echo with and without contrast enhancement, T2-weighted spin-echo, diffusion-weighted imaging (DWI), T2-weighted gradient-echo or susceptibility-weighted imaging, and fluid-attenuated inversion recovery (FLAIR).

Interpretation of Magnetic Resonance Imaging

All MRIs of the included patients, including those performed at presentation and, if any, those performed at subsequent reassessment, was reviewed after anonymisation by two experienced radiologists independently (both with >12 years of experience in neuroradiology).

Statistical Analysis

Imaging features, presenting symptoms, associated clinical conditions, and clinical progress are described with descriptive statistics (Tables 1 and 2).

Inferential statistical analysis was performed by comparing the different qualitative variables, including brain MRI features and clinical parameters including demographics, presentation, and clinical progress. Independent variables including imaging features and clinical symptoms are categorised using methods employed in existing literature. Inferential statistical analysis was accomplished with Fisher's exact test for categorical variables, and the Mann-Whitney *U* test for ordinal and continuous variables.

The statistical analysis was performed using commercial software (SPSS Windows version 24.0; IBM Corp, Armonk [NY], United States). Results with p value ≤0.05 were considered as statistically significant.

RESULTS

Demographics and Clinical Parameters

A total of 19 patients, who tested positive for anti-NMDA

Table 1. Summary of presenting symptoms and clinical outcomes (n = 17).*

	Frequency
Presentation	
Confusion	15 (88.2%)
Fever	14 (82.4%)
Hallucinations	12 (70.6%)
Dyskinesia	10 (58.8%)
Seizure	8 (47.1%)
Headache	5 (29.4%)
Autonomic dysfunction	4 (23.5%)
Cognitive impairment	4 (23.5%)
Numbness	1 (5.9%)
Clinical outcome	
Symptom-free recovery	7 (41.2%)
Clinical relapse	3 (17.6%)
Epilepsy†	2 (11.8%)
Recovery with symptoms‡	4 (23.5%)
Expired	1 (5.9%)

* Data are shown as No. (%).
† Requiring long-term antiepileptic medication.
‡ Residual symptoms include impaired memory, mood disorder, and limb tremor.

receptor antibodies either in serum or cerebrospinal fluid, were identified. Two of these patients were excluded, one due to simultaneous herpes simplex virus encephalitis, and the other because no brain imaging had been performed. Finally, 17 patients were included, with median age at diagnosis 29 years (range, 5-42 years; 2 male, 15 female). Two were paediatric patients, aged 5 and 12 years (Table 1).

Four female patients (23.5%) were found to have neoplasms, all of which were ovarian teratomas (3 mature teratomas and 1 immature teratoma). All four underwent subsequent surgical resection of the tumours.

Sixteen patients (94.1%) received immunotherapy, with steroid and intravenous immunoglobulin being the commonest agents employed. One patient (5.9%) refused immunotherapy and was given only antipsychotic and antidepression medications.

Three patients (17.6%) had at least one episode of clinical relapse after recovery from the presenting symptoms, which included two patients with seizure and fever and one with acute delirium and hallucinations. Two patients (11.8%) were noted to have ongoing epilepsy requiring long-term antiepileptic medication.

Imaging Features

Signal anomalies are defined as hyperintense signal in T2-weighted sequences, with or without restricted diffusion and post-gadolinium enhancement.

Ten (58.8%) of the seventeen patients were noted to have normal brain MRI findings at presentation, with a spectrum of abnormalities in the other seven (41.2%) patients (Table 2, Figures 1 and 2).

Of the seven patients with abnormal MRI brain at time of presentation, the most frequently affected locations were

Table 2. Summary of abnormal features in magnetic resonance imaging brain at presentation.

Patient†	Hippocampus	Frontal	Temporal‡	Parietal	Occipital	Insula	Cerebellum	Deep white matter
4			Right					
6								Right
7					Right		Bilateral	
8	Bilateral	Bilateral	Bilateral			Bilateral		
11			Right	Right		Right		
12	Left		Left			Left		
15	Left							
Frequency (n = 7)*	3 (42.9%)	1 (14.3%)	4 (57.1%)	1 (14.3%)	1 (14.3%)	3 (42.9%)	1 (14.3%)	1 (14.3%)

* Data are shown as No. (%).
† Patient numbered by chronological order of diagnosis.
‡ Temporal lobe excluding the hippocampus.

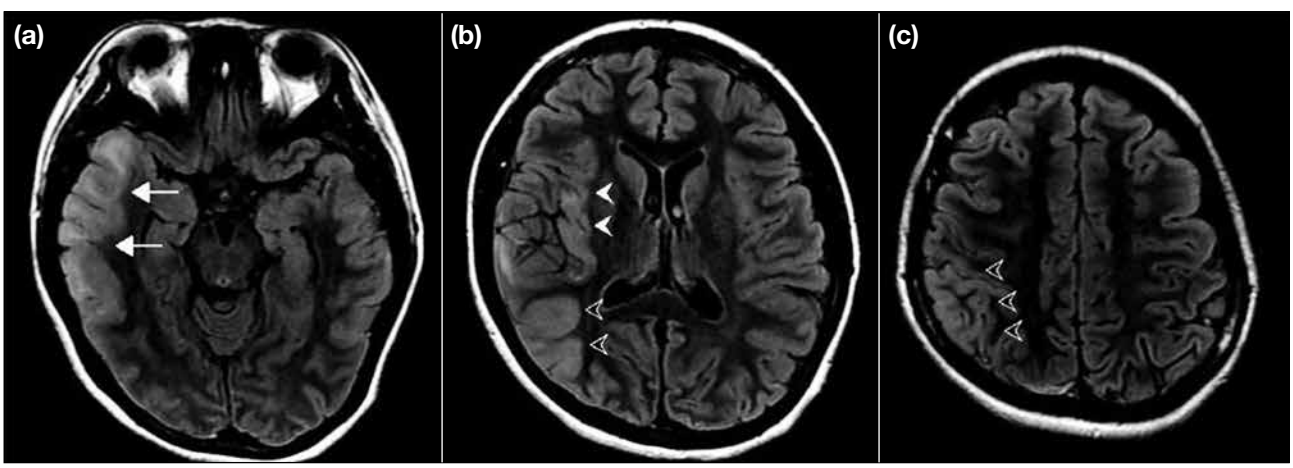

Figure 1. Magnetic resonance imaging (MRI) scans of the brain of a 28-year-old patient presenting with seizure and fever (corresponding to patient 11 in Table 2). Axial fluid-attenuated inversion recovery MRI scans at the levels of (a) temporal lobe, (b) insula cortex and (c) high parietal cortex showing high signal in the right temporal lobe subcortical region (white arrows), cortical thickening with cortical hyperintensity at right insular cortex (white arrowheads), and at right parietal cortex (open arrowheads).

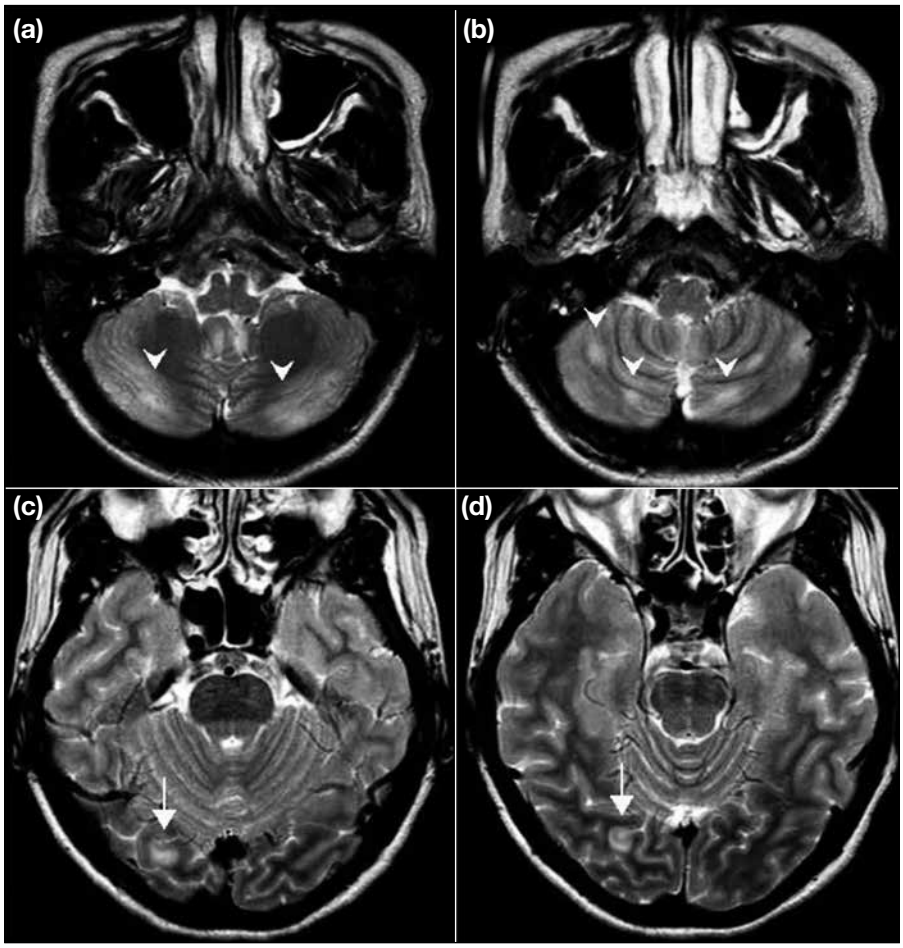

Figure 2. Magnetic resonance imaging (MRI) scans of the brain at presentation of a 29-year-old patient presented with fever, dyskinesia, and hallucination, with association of an ovarian teratoma (corresponding to patient 7 in Table 2). Axial T2-weighted MRI scans at levels of (a, b) cerebella and (c, d) inferior occipital lobes showing ill-defined foci of hyperintense signal in both cerebellar hemispheres (white arrowheads) and the right inferior occipital lobe (white arrows).

the temporal lobe excluding the hippocampus (n = 4, 57.1%), followed by the hippocampus (n = 3, 42.9%) and insula (n = 3, 42.9%). Four (57.1%) patients showed lesions in more than one location. There was only one (14.3%) patient in whom the hippocampus was the only location that showed abnormal signal.

Eleven out of the 17 patients (65%) had repeat MRI examinations at least 2 months after clinical recovery from initial presentation. Five of these 11 patients had normal MRI at time of presentation, whereas six had abnormal MRI. The median time interval to the first repeat MRI since hospital discharge was 18 months (range, 2.5-180 months). Five of the 11 patients had normal scans, either from resolution of previous abnormal findings or remaining normal since presentation. Of the other six patients with abnormal repeat MRIs, three showed new locations of abnormality, whereas five showed interval development of cerebral atrophy (3 patients with global atrophy and 2 with localised medial temporal lobe atrophy). Figure 3 shows a patient with a normal MRI at presentation, who developed multiple abnormal findings on repeat MRI during a clinical relapse.

Among the 11 patients with repeat MRI examinations, analysis of the imaging features at presentation showed no significant correlation with subsequent development of cerebral atrophy at reassessment.

Association between Imaging Features and Clinical Observations

The relationship between imaging features and clinical parameters was investigated. The sex and age of our patients showed no significant correlation with normal MRI brain at time of presentation, hippocampal involvement, or development of cerebral atrophy.

Normal MRI at presentation and involvement of the hippocampus had no significant correlation with any the clinical parameters considered in our patients, including presentation, association of tumour/teratoma, serum antibody results, or clinical outcome.

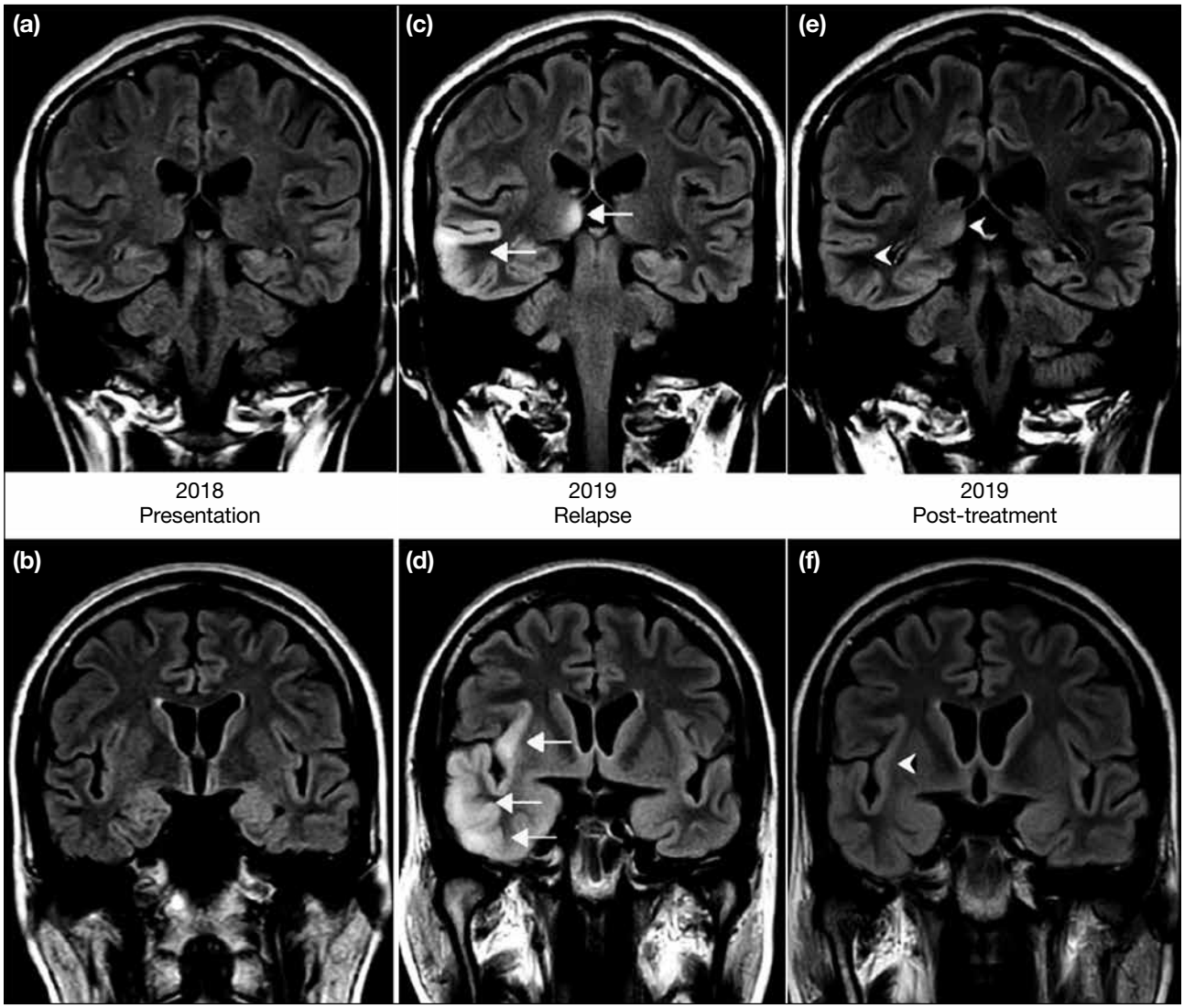

Figure 3. Serial magnetic resonance imaging (MRI) scans of a patient with clinical relapse 1 year after initial presentation and recovery. Coronal fluid-attenuated inversion recovery of scan at (a, b) presentation in 2018, (c, d) during clinical relapse in 2019 and (e, f) after immunotherapy for relapse, showing a normal MRI of the brain at presentation, but new hyperintense lesions in the right thalamus, right insular cortex, and right temporal cortex during clinical relapse (white arrows). Residual high signal at right thalamus, right insular cortex and right temporal cortex after treatment for relapse (white arrowheads).

Among the 11 patients with repeat MRI, interval development of cerebral atrophy (either global atrophy or localised medial temporal atrophy) was noted to be associated with worse functional outcome as evidenced by a higher modified Rankin scale score ($p = 0.008$). Patients who did not show any cerebral atrophy on repeat imaging had a higher rate of symptom-free recovery ($p = 0.045$). Figure 4 features the progressive global cerebral atrophy observed on serial repeat MRIs of a patient with a progressively deteriorating clinical course and poor functional outcome.

DISCUSSION

Anti-NMDAR encephalitis has been noted to have variable and nonspecific MRI brain features including locations of involvement and signal characteristics.[13,14] Common involvement of the temporal lobe and hippocampus renders viral encephalitis (particularly herpes simplex virus), and other autoimmune paraneoplastic encephalitis high on the list of radiological differential diagnosis. Extrahippocampal involvement of vascular territories with restricted diffusion should also raise suspicion of an acute ischaemic event, whereas thalamic and basal

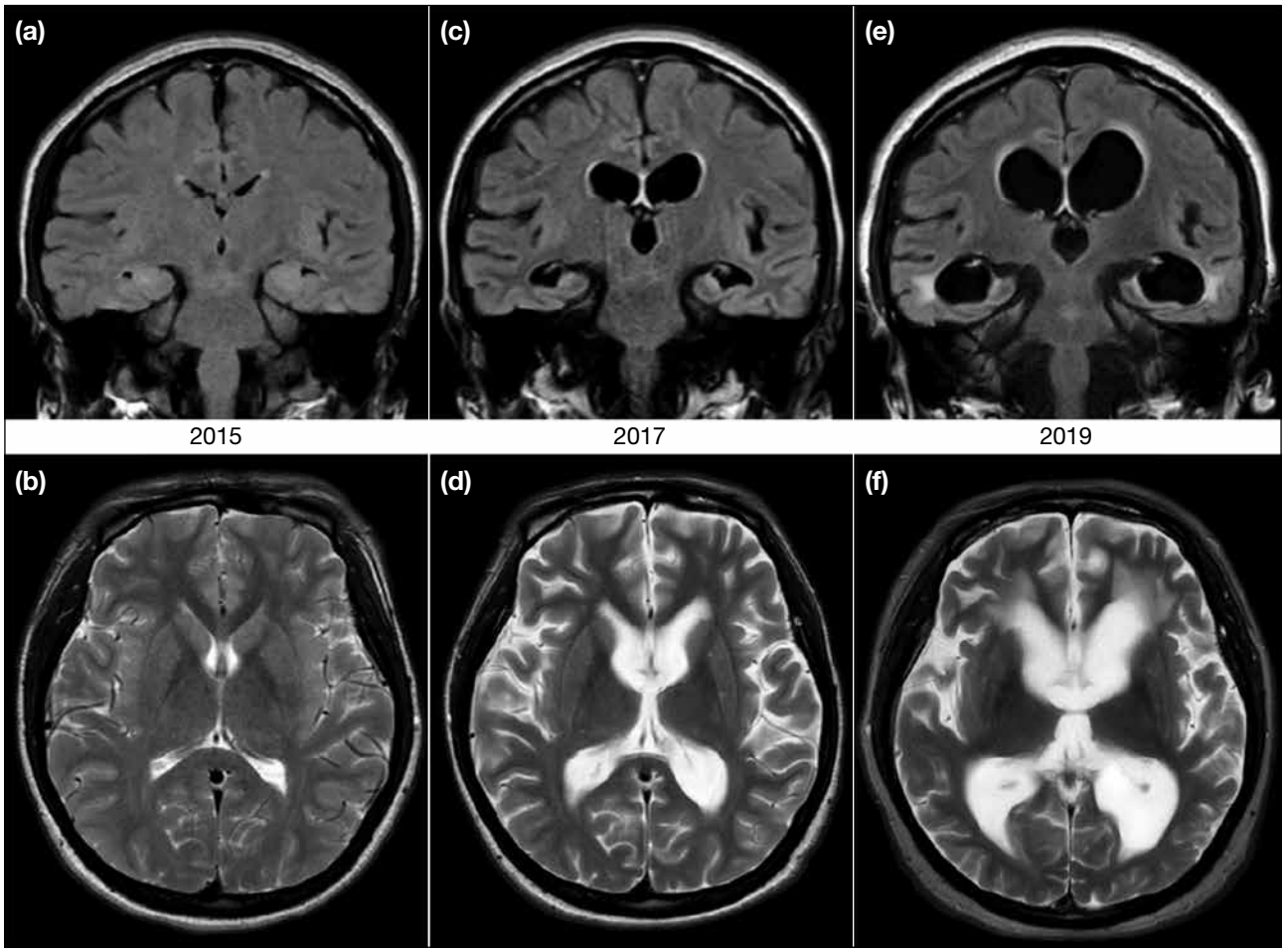

Figure 4. A patient with serial repeat magnetic resonance imaging (MRI) scans showing progressive global cerebral atrophy. Coronal fluid-attenuated inversion recovery (upper row) and axial T2-weighted (lower row) MRI scans of the brain of a patient done in (a, b) 2015, (c, d) 2017, and (e, f) 2019. Since diagnosis in 2015 at age 29 years, serial re-assessment MRI brain showed progressive global cerebral atrophy as evident by progressive dilatation of the ventricles and sulci. Patient suffered a poor functional outcome with a modified Rankin scale score of 5.

ganglia involvement could mimic Japanese encephalitis, metabolic/toxic encephalopathy, or and Creutzfeldt–Jakob disease, which are important diagnoses to exclude. Clinical information including history and presentation play an important role in diagnosis.

The age (range, 5-42 years) and sex (88% female) of our patients are similar to those in previous studies.[6,13,15] The rate of associated neoplasm varied greatly among previous studies (10%-60%); among our 17 patients, four (24%) had ovarian teratomas.[15,16]

Slightly more than 50% of our patients showed normal MRI findings at presentation, which is comparable to previous studies. However, in the seven patients presenting with abnormal MRI brain findings, the most commonly affected locations were the temporal lobe (excluding the hippocampus), followed by the hippocampus, and the insula. Only two of our patients had multifocal extrahippocampal lesions at presentation (Figures 1 and 2). This finding is different from previous studies in which the hippocampus was most commonly affected.[15,16] The small sample size of this study does not allow any conclusions to be made of this finding.

Although cerebral atrophy in repeat scans correlated with a worse functional outcome, as well as a lower rate of symptom-free recovery, not all of our patients had a follow-up MRI for a comprehensive and unbiased assessment. Indications and time interval for repeat imaging were also not standardised due to the retrospective nature of this study. Some patients had second MRIs

due to a clinical relapse, whereas some were completely asymptomatic at time of repeat scan. The time of repeat imaging ranged from as soon as 2 months after clinical recovery to as late as 2 years. Although cerebral atrophy was unlikely to be an acute process as delineated in the patient shown in Figure 4, there is reasonable suspicion of underestimation of the incidence of cerebral atrophy in this study given the short time interval of some follow-up scans. Cerebral and medial temporal atrophy were correlated with poorer clinical outcome and disease severity in previous studies.[15,16] The lack of correlation between abnormalities on the MRI at presentation and subsequent development of cerebral atrophy in repeat imaging implies that they are nonspecific. However, it could partly be attributed to a non-standardised analysis due to the intrinsic heterogeneity in MRI signal characteristics of multifocal lesions. Standardisation of repeat imaging schedules, quantitative assessment of the degree of cerebral atrophy, and subgroup analysis (global versus localised atrophy) may also shed light on the actual pathological process that determines the clinical outcome of the disease.

Despite extensive search for anti-NMDAR encephalitis patients in this multicentre study, only 19 patients were noted to be diagnosed with the disease since 2007, the year of the first description of the illness.[4] Comparing to a previous study of a similar ethnic population,[16] and with reference to data in a previous large-scale study,[6] there is a suggestion of underdiagnosis of the disease in this locality. Although the basic demographics of our patients and most of their clinical features appeared to be comparable to those of most of the previous publications,[6,15,17] small sample size of this study limits inferential statistical analysis. Grouping and categorisation of the highly variable imaging features of anti-NMDAR encephalitis for subgroup analysis, which may reveal implication on clinical outcome and prognosis,[16] was not feasible due to the small sample size.

A previous study investigating into more advanced MRI sequences (functional connectivity, diffusion tensor imaging, and voxel-based morphometry) revealed altered functional connectivity and white matter changes in anti-NMDAR encephalitis patients not identified on routine sequences.[14,18] This may explain some of the apparently paradoxical symptomatology in our cases and suggests the use of these sequences in anti-NMDAR encephalitis patients.

In conclusion, features of routine MRI sequences (T1-weighted spin-echo with and without contrast enhancement, T2-weighted spin-echo, DWI, T2-weighted gradient-echo or susceptibility-weighted imaging, and FLAIR) of patients with anti-NMDAR encephalitis are nonspecific, with more than half of our subjects showing normal findings at presentation. The temporal lobe (excluding the hippocampus) was the most commonly involved sites of abnormal MRI signal in our study. Interval development of cerebral atrophy was shown to be associated with worse functional outcome and lower rate of symptom-free recovery. Future studies of larger sample size, with more advanced MRI protocols, standardised repeat imaging, and subgroup analysis would be desirable, but the low incidence of the disease renders these measures problematic to carry out.

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