

# Early identification of anti-NMDA receptor encephalitis presenting cerebral lesions in unconventional locations on magnetic resonance imaging

Weihe Zhang\*, Lei Cui, Wei Wang, Yujuan Jiao, Yeqiong Zhang, Jinsong Jiao

Department of Neurology, China-Japan Friendship Hospital, Beijing 100029, China

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## ABSTRACT

To facilitate the diagnosis of anti-NMDAR encephalitis presenting with brain lesions in unconventional locations (BLUL) on MRI, we retrospectively analyzed forty-five Chinese patients. Eighteen (40.0%) of their MRI initially exhibited one or more BLUL. These locations predominantly included cerebral gray matter (cortex, basal ganglia and thalamus), as well as white matter and brainstem. Due to these BLUL, thirteen (72.2%) patients were originally misdiagnosed with other diseases and developed poor clinical and imaging outcomes. Therefore, anti-NMDAR encephalitis has unpredictable MRI findings that easily obscure its diagnosis and cause serious sequelae. Anti-NMDAR antibody tests are highly recommended in patients with BLUL.

## 1. Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a new category of treatment-responsive autoimmune synaptic encephalitis, which commonly occurs in young women and is characterized by the presence of anti-NMDAR antibodies in serum and cerebrospinal fluid (Vitaliani et al., 2005; Dalmau et al., 2007). In contrast to another predominant B-cell autoimmune disease called neuromyelitis optica spectrum disorder (NMOSD), which generally manifests with stereotypical clinical and imaging abnormalities and can be diagnosed without the detection of aquaporin-4 antibodies in serum (Wingerchuk et al., 2015), anti-NMDAR encephalitis is characterized by a kaleidoscopic clinical appearance and unremarkable MRI findings (Dalmau et al., 2008). According to previous reports, only 35% of patients with anti-NMDAR encephalitis have abnormal brain MRI results at the disease onset, and only 50% ever have an abnormal MRI result during the entire course of the disease (Titulaer et al., 2013). The MRI abnormalities sometimes involve the limbic system (medial temporal regions, cingulate gyrus, etc.) (Dalmau et al., 2008; Leypoldt et al., 2015), which could facilitate an early diagnosis of anti-NMDAR encephalitis. However, lesions in unconventional locations other than the limbic areas could confound the diagnosis, delay the treatment, and cause serious sequelae (Titulaer et al., 2013). Therefore, differentiation and determination of the imaging features of brain lesions in unconventional

locations (BLUL) is crucial for the early diagnosis of anti-NMDAR encephalitis. To the best of our knowledge, no previous studies have specifically assessed BLUL in anti-NMDAR encephalitis. Our study aims to determine the imaging features of BLUL and optimize the recognition of anti-NMDAR encephalitis via a retrospective analysis of a series of Chinese patients.

## 2. Material and methods

### 2.1. Patients and inclusion criteria

Forty-five patients with clinical signs and symptoms of encephalitis (fever and headache, acute onset psychosis, loss of short-term memory, abnormal movements or even hypoventilation), who visited the China-Japan Friendship Hospital (Beijing, China) between January 2013 and July 2017, were consecutively reviewed. According to the description by Dalmau in 2008 (Dalmau et al., 2008) and the 2016 diagnostic criteria (Graus et al., 2016), the diagnosis of anti-NMDAR encephalitis was made based on clinical symptoms and signs, cerebrospinal fluid (CSF) analysis, electroencephalogram, brain MRI scans, and detection of the anti-NMDA receptor and other antibodies. The present study used the eight core clinical symptoms initially described by Dalmau in 2008 (Dalmau et al., 2008), considering many of the patients were diagnosed before 2016. The selection criteria of candidates for evaluation

**Abbreviations:** ANA, antinuclear antibodies; AQP4-IgG, Aquaporin-4 antibodies; BLUL, brain lesions in unconventional locations; BG, basal ganglia; CSF, cerebrospinal fluid; CTX, intravenous cyclophosphamide; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; FU, follow-up; HE, Hashimoto encephalopathy; HSE, herpes simplex encephalitis; HT, Hashimoto thyroiditis; HLD, hepatolenticular degeneration; IVMP, intravenous methylprednisolone; IVIg, intravenous immunoglobulin; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NMOSD, neuromyelitis optica spectrum disorders; RTX, intravenous rituximab; PLEX, plasma exchange; TPO, thyroid peroxidase; TG, thyroglobulin; WM, white matter

\* Corresponding author at: Department of Neurology, China-Japan Friendship Hospital, 2 YinghuaDongjie, Hepingli, Beijing 100029, China.

E-mail address: [z\\_weihe@hotmail.com](mailto:z_weihe@hotmail.com) (W. Zhang).

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**Table 1**  
Demographic and clinical features of patients with anti-NMDAR encephalitis.

Case	Age at onset/sex	Initial symptoms	NMDAR-Abs (serum/CSF)	Comorbid	Lesion locations	Nadir mRs	Therapies	FU at 6 Mons	Misdiagnosis
1	33/F	Seizure	+/+	Preceded by HSE	Hippocampus, frontal cortex	3	Antivirus, IVMP + IVIg	1	HSE
2	19/F	Seizure	-/+	HT	Bilateral hippocampus, cingulate gyrus, frontal and parietal cortex	5	IVMP * 2 + IVIg + PLEX	4	HE/MELAS
3	26/F	Aphasia	+/+	-	Frontal and lateral temporal cortex	3	IVMP + IVIg	0	MELAS
4	30/F	Psychosis	+/+	-	Hippocampus, insular lobe, lateral temporal cortex	4	IVMP + IVIg	1	MELAS
5	21/F	Consciousness disorders	+/+	Ovarian teratoma	Bilateral thalamus	5	IVMP + IVIg * 3 + teratoma resection	3	-
6	17/F	Consciousness disorders	+/+	Ovarian teratoma	Frontal cortex	3	IVMP + IVIg + teratoma resection	1	-
7	29/F	Psychosis	-/+	Ovarian teratoma	Bilateral insular lobe, frontal, lateral temporal and parietal cortex, subcortical WM, BG and thalamus	5	IVMP + IVIg * 3 + teratoma resection	2	-
8	62/F	Psychosis	+/+	-	Hippocampus, parietal cortex	5	IVMP * 2 + IVIg * 2 + CTX	3	-
9	24/F	Headache, memory loss	+/+	-	Bilateral frontal, lateral temporal and parietal cortex	5	Antivirus, IVMP + IVIg * 2	2	HSE
10	31/F	Memory loss	+/+	HT	Bilateral hippocampus, insular lobe, frontal cortex	4	IVMP + IVIg	3	HE
11	55/F	Psychosis, memory loss	+/+	HT	Bilateral hippocampus, BG, thalamus and midbrain	5	IVMP + IVIg + PLEX	2	HE
12	32/M	Consciousness disorders	+/+	Alcoholism	Symmetrical frontal cortex and splenium of corpus callosum	5	IVMP + IVIg	dead	Wernicke encephalopathy
13	38/M	Psychosis, memory loss	+/+	-	Frontal and lateral parietal cortex	5	IVMP + PLEX + IVIg * 2 + RTX	3	-
14	29/M	Seizure	+/+	-	Bilateral frontal, lateral temporal and parietal cortex	3	Anti-virus, IVMP	1	HSE
15	55/M	Dyskinesia	-/+	Cardiac carcinoma	Bilateral hippocampus, symmetrical BG	4	IVIg * 3 + IVMP + anti-tumor	2	HLD
16	41/M	Headache, psychosis	+/+	-	Hippocampus, insular lobe, BG	4	PLEX + IVIg * 2	2	Parasitic encephalitis
17	15/M	Fever, dyskinesia	+/+	-	Hippocampus, insular lobe, frontal, lateral temporal and parietal cortex, thalamus	4	anti-virus + IVIg + CTX	1	HSE
18	27/M	Dysarthria	+/+	-	Hippocampus, frontal cortex, periventricular WM, BG and medulla	3	IVMP	0	NMOSD

Abs: antibodies; BG: basal ganglia; CSF: cerebrospinal fluid; CTX: intravenous cyclophosphamide; FU: follow-up; HE: Hashimoto encephalopathy; HSE: herpes simplex encephalitis; HT: Hashimoto thyroiditis; HLD: hepatolenticular degeneration; IVMP: intravenous methylprednisolone; IVIg: intravenous immunoglobulin; MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; mRS: modified Rankin scale; NMOSD: neuromyelitis optica spectrum disorders; RTX: intravenous rituximab; PLEX: plasma exchange; WM: white matter.

**Table 2**  
Comparison of clinical features in patients with BLUL and non-BLUL.

	Patients with BLUL (n = 18)	Patients with non-BLUL		
		Total (n = 27)	Limbic lesions (n = 6)	Normal imaging (n = 21)
Sex (female, %)	11 (61.1)	17 (62.9)	4 (66.7)	13 (61.9)
Median age at onset, year (IQR)	29.5 (15.5)	30.0 (15.0)	29.5 (25.5)	30.0 (16.0)
Ovarian teratoma, n (%)	3 (16.7)	4 (14.8)	1 (16.7)	3 (14.3)
Other tumors, <sup>†</sup> n (%)	1 (5.6)	1 (3.7)	0 (0.0)	1 (4.8)
Misdiagnosis, n (%)	13 (72.2) <sup>a,b</sup>	7 (25.9)	2 (33.3)	5 (23.8)
Median delay time, <sup>‡</sup> days (IQR)	26.5 (25.2) <sup>a,b,c</sup>	19.0 (11.0)	17.5 (10.2)	19.0 (11.5)
Initial symptoms				
Seizure, n (%)	3 (16.7)	7 (25.9)	0 (0.0)	7 (34.6)
Psychosis, n (%)	6 (33.3)	12 (44.4)	4 (66.6)	8 (38.1)
Conscious disorders, n (%)	3 (16.7)	1 (3.7)	0 (0.0)	1 (4.8)
Cognitive disorders, n (%)	4 (22.2)	5 (18.5)	1 (16.7)	4 (19.0)
Movement disorders, n (%)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Speech disorders, n (%)	2 (11.1)	1 (3.7)	1 (16.7)	0 (0.0)
No. core symptoms (IQR)	4.0 (2.2)	4.0 (2.0)	4.5 (1.7)	3.0 (1.5)
Median nadir MRs (IQR)	4.0 (2.0)	4.0 (1.0)	4.5 (1.0)	4.0 (2.0)
Median residual MRs (IQR)	2.0 (2.0) <sup>a,b</sup>	1.0 (1.0)	2.0 (2.0)	1.0 (0.5)
Mechanical ventilation, n (%)	5 (27.8)	8 (29.6)	2 (33.3)	6 (28.6)
Relapse, n (%)	3 (16.7)	3 (11.1)	0 (0.0)	3 (14.3)
Poor outcome, n (%)	6 (33.3) <sup>a,b</sup>	2 (7.4)	2 (33.3)	0 (0.0)

BLUL: brain lesions in unconventional locations; No.: number.

<sup>a</sup>  $p < 0.05$  compared with total patients with non-BLUL.

<sup>b</sup>  $p < 0.05$  compared with patients with normal imaging.

<sup>c</sup>  $p < 0.05$  compared with patients exhibited limbic lesions.

<sup>†</sup> Other tumors include one cardiac carcinoma in BLUL group and one pineal teratoma in non-BLUL group.

<sup>‡</sup> Median delay time means the delay time of confirmed diagnosis.

included: (1) definite anti-NMDAR encephalitis and (2) brain MRI scans exhibiting one or more lesions in unconventional locations other than the limbic system at disease onset. The limbic system was defined as the medial temporal regions, cingulate gyrus, anterior insular cortex, etc. The patients were divided into two groups: 1) those with unconventional lesions (BLUL group), and 2) those that either had no lesions or only had the typical limbic system lesions (non-BLUL group). This study was approved by the Institutional Review Board of the China-Japan Friendship Hospital, and the need for informed consent was waived by the committee due to the retrospective nature of the study.

## 2.2. Clinical evaluations

Neurological functions were evaluated, and the modified Rankin Scale (mRS) (van Swieten et al., 1988) was obtained at both disease nadir and a 6-month follow-up. A good outcome was defined as a complete or near complete resolution with a residual mRS score that declined to between 0 and 2 at the 6-month follow-up. A poor outcome had limited or no improvements in neurological functions and had a residual mRS score of 3 or higher (Titulaer et al., 2013). Other clinical parameters were also retrospectively analyzed as follows: demographic data, clinical features such as initial symptoms, number of core clinical symptoms, requirement of mechanical ventilator support, comorbidities (combined with ovarian teratoma or other tumors), the delay time of diagnosis and misdiagnosis rate.

## 2.3. Laboratory data

Serum and CSF antibodies against the NMDA receptor and other neuronal cell surface and synaptic proteins were performed using a cell-based assay by third-party medical testing agencies. Serum specimens were collected during the acute phase in all cases before the initiation of immunotherapies. Serum and/or CSF antibodies against herpes simplex virus, adenovirus, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and enterovirus were considered. We also recorded well-recognized serum and CSF onconeural antibodies [e.g., anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ri (ANNA-2), anti-CV2 (CRMP5), anti-

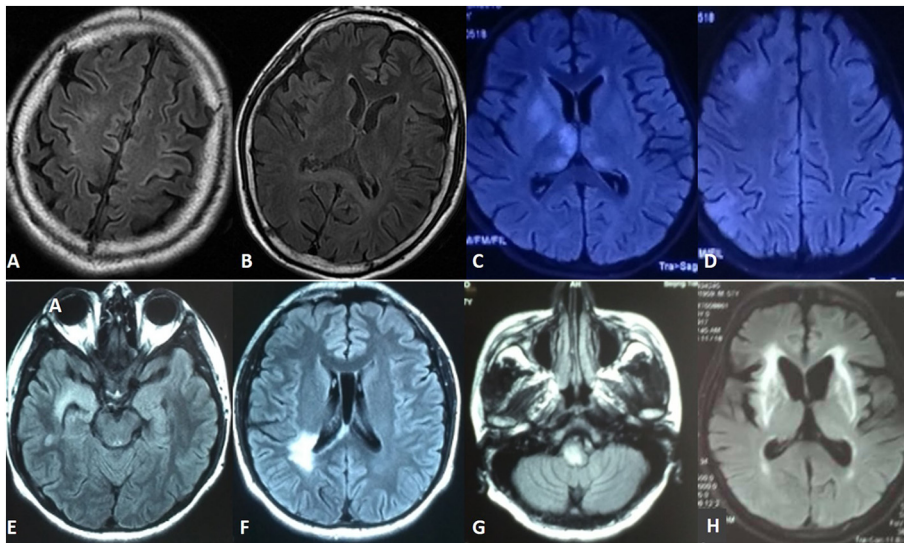
amphiphysin, and anti-Ta/Ma2] to rule out paraneoplastic limbic encephalitis. Other non-organ specific autoimmune antibodies, such as anti-nuclear antibody, anti-double stranded DNA antibody, SSA/SSB, anti-cardiolipin antibody, anti-neutrophil cytoplasmic antibodies and thyroid peroxidase (TPO)/thyroglobulin (TG) antibodies, were tested in most patients.

## 2.4. Imaging study

Since some patients had their initial and follow-up imaging completed at an outpatient department, we were unable to use the same MRI equipment. In the BLUL group, ten patients hospitalized in our hospital had their brain MRI scans completed in a SignaHDX-3.0T MR system (General Electric Co., Fairfield, CT, USA) or GYROSCAN-1.5T nuclear magnetic resonance scanner (PHILIPS Co., Amsterdam, Holland); the others (No. 5–9 and 14–16) were initially admitted to different hospitals and had their MRI scans done at the referring hospitals. The brain scanning included the T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). T2-weighted sequences were used to obtain axial and sagittal images. We delineated the locations of the brain lesions, including the limbic system and unconventional areas, as well as assessed chronological MRI changes at different follow-up intervals. Additionally, to detect insidious tumors, most patients received thoracic and abdominal-pelvic computed tomography scans (CT; Aquilion; Toshiba, Tokyo, Japan).

## 2.5. Statistical analysis

All statistical analyses were performed with SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Statistical significance was set at  $p < 0.05$ . The medians (interquartile range, IQR) of variables including age of onset, delay time of diagnosis, number of clinical core symptoms, nadir and residual mRS were analyzed using Mann-Whitney *U* tests. Differences in the other categorical parameters between the two groups were analyzed using Fisher's exact tests.



**Fig. 1.** Representative brain lesions in unconventional locations obtained from patients with anti-NMDAR encephalitis.

Case 12: a 32-year-old male alcohol abuser was initially misdiagnosed as having Wernicke encephalopathy as the brain FLAIR scan exhibited symmetrical “ribbon-like” frontal cortical and splenium lesions (A/B). Case 7: a 29-year-old woman associated with ovarian teratoma exhibited multiple lesions including bilateral frontal lobe, subcortical white matter, basal ganglia and thalamus (C/D). Case 18: a 27-year-old man who was initially misdiagnosed as having neuromyelitis optica spectrum disorder and exhibited multiple lesions at bilateral hippocampal, brainstem and periventricular white matter on the FLAIR scan (E/F/G). Case 15: a 55-year-old man manifested with dyskinesia as his initial symptom. The T2-weighted image exhibited symmetrical basal ganglia lesions that mimicked hepatolenticular degeneration (H).

### 3. Results

#### 3.1. Clinical characteristics

In our cohort, 18/45 (40.0%) patients with anti-NMDAR encephalitis exhibited one or more lesions in unconventional locations. The detailed clinical characteristics of the BLUL group are summarized in [Tables 1 and 2](#). Patients in the BLUL group were often female (61.1%) with a median age at onset of 29.5 (15.5) years. Numbers above and below in brackets are the interquartile values. Thirteen patients (72.2%) in the BLUL group were misdiagnosed for other diseases at the first visit or in the referring hospitals, which was significantly more prevalent compared to the non-BLUL group (7 [25.9%]) and its subgroup (5 [23.8%]),  $p < 0.05$ . One case in the BLUL group suffered from a repeated misdiagnosis of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), followed by a diagnosis of Hashimoto's encephalopathy (HE). The median delay time of diagnosis was 26.5 (25.2) days in the BLUL group, which was significantly greater than the non-BLUL group (19.0 [11.0]) and its subgroups (17.5 [10.2] and 19.0 [11.5]),  $p < 0.05$ .

Other clinical characteristics including sex ratio, age of onset, initial symptoms, number of core clinical symptoms and comorbidity (associated with ovarian teratoma or other tumors) were not different between the groups (see [Table 2](#)).

#### 3.2. Treatments and clinical outcome

The standard dose of first-line immunotherapies (e.g., intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIg), and plasma exchange (PLEX)) was administered in all patients. The specific therapies for the BLUL group are shown in [Table 1](#). Of the 18 patients, 2 received IVMP only, while others received repeated, multimodal immunotherapies. Of the 4 patients who did not respond to first-line therapies, 3 received intravenous cyclophosphamide or intravenous rituximab as second-line therapies. One of these patients passed away. Four patients found to have tumors received surgery at the disease nadir. One of these patients had a cardiac carcinoma and received radiotherapy and chemotherapies. Symptomatic treatments were administered to all patients, as needed. As shown in [Table 2](#), the median mRS score at disease nadir was 4.0 (2.0) in the BLUL group, which was similar to the non-BLUL group, while the median mRS score at a 6-month follow-up was significantly greater in the BLUL group (2.0 [2.0]) than those in the non-BLUL (1.0 [1.0]) and its subgroup (1.0 [0.5]),  $p < 0.05$ . At a 6-month follow-up, 6 (33.3%) patients in the BLUL

group had a poor clinical outcome, which was significantly more prevalent compared to the non-BLUL group (2 [7.4%]) and its subgroup (0 [0.0%]),  $p < 0.05$ . In the BLUL group, 5 patients (27.8%) required mechanical ventilation for 1–4 months, and 3 patients (16.7%) experienced symptom relapses during the follow-up, which were both similar to the non-BLUL groups.

#### 3.3. Imaging features of brain lesions in unconventional locations

At disease onset, among the 24/45 (53.3%) patients who exhibited brain lesions on their initial MRI evaluation, 6 (13.3%) exhibited brain lesions that were limited to the limbic system, and 18 (40%) exhibited one or more BLUL, ten of whom also had concomitant classical limbic system impairment, as shown in [Table 1](#). All of the limbic system lesions in BLUL group involved the medial temporal lobe (hippocampus for 10/18 [55.6%], insular lobe for 5 [27.8%] and cingulate gyrus for 1 [5.6%]). The unconventional locations in our cohort included cerebral gray matter (cortex, thalamus and basal ganglia) in all patients, white matter (periventricular, subcortical and corpus callosum) in 3 patients and brainstem (midbrain and medulla) in 2 patients. Thirteen (72.2%) patients manifested multiple lesions in the unconventional locations. There were no spinal cord lesions present in our cohort. More detailed information on the distribution of the brain lesions in unconventional locations is summarized in [Figs. 1 and 2](#).

#### 3.4. Neuroimaging outcomes for patients with BLUL

Of the 18 patients who exhibited BLUL, 12 underwent chronological MRI assessments between months 3 and 12 ([Fig. 3](#)). Two patients (cases 11 and 13) developed irreversible diffuse cerebral atrophy at the 6- and 12-month follow-up; two patients (case 2 and 10) developed bilateral medial temporal lobe (hippocampus) atrophy between 3 and 6 months after disease onset; and one patient (case 16) had a basal ganglia lesion that had partially resolved by the 3-month follow-up. The brain lesions of the remaining 7 patients had completely recovered, as determined via the brain MRI scans.

### 4. Discussion

In our cohort, approximately half of the patients with anti-NMDAR encephalitis exhibited brain lesions on their initial MRI scan, which corresponds with the previously reported anti-NMDAR encephalitis statistics ([Dalmau et al., 2008](#); [Titulaer et al., 2013](#)). Furthermore, our study demonstrated that more than one-third of the patients presented



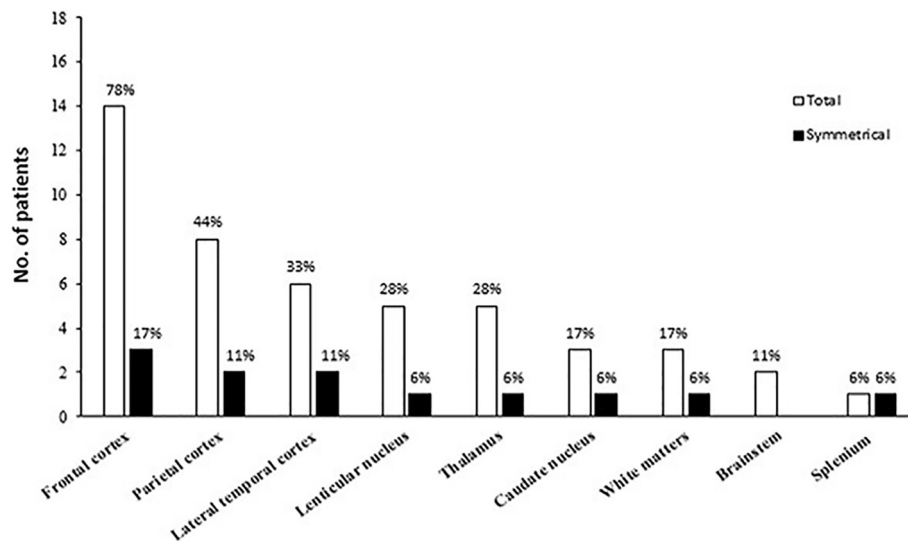


Fig. 2. Distribution of brain lesions in unconventional locations.

with BLUL that was not a part of the limbic system. These unconventional locations included the cortex, periventricular and subcortical white matter, splenium of corpus callosum, basal ganglia, thalamus and brainstem. The cerebral cortex, particularly the convexity of the frontotemporal cortex, is most prevalently afflicted. This is where NMDA receptors are present at a high density and is in line with the nature of this neuronotropic disease (Dalmau, 2016). More importantly, our study revealed that the rate of misdiagnosis significantly increased in patients with BLUL than in those with non-BLUL, which indicates that these chameleonic imaging appearances may easily be confused with other disorders.

In our study, a great proportion of patients exhibited cortical lesions that had a “ribbon-like” or “lacy-like” morphology on the FLAIR and DWI scans. Some of these patients were comorbid with Hashimoto's thyroiditis and were initially misdiagnosed as having HE. However, the unspecific TPO/TG antibodies are known to increase in both healthy individuals and patients with anti-NMDAR encephalitis (Mirabelli-Badenier et al., 2014; Graus et al., 2016; Zhang et al., 2017). This indicates that the term HE should be used cautiously unless the well-characterized neuronal antibodies have been rigorously evaluated. Other patients were misdiagnosed as having MELAS due to the appearance of a lactic (Lac) peak on the  $^1\text{H}$ -MR spectroscopy study. We eventually excluded the diagnosis MELAS using the normal methods of detection such as genetic testing and muscle biopsy, which delayed the optimal therapeutic time. Furthermore, large and deep Lac peaks may also appear on the MR spectroscopy results from increased anaerobic

glycolysis caused by other disorders (Shimizu et al., 1996; Gillard et al., 1996). Hence, the diagnosis of MELAS should be made with caution, particularly given the lack of effective treatment.

In addition to the cortex, deep gray nuclei such as the basal ganglia (BG) and thalamus were also involved as BLUL in our patients. The BG impairment is presumably associated with the characteristic involuntary movements, such as orofacial dyskinesias or choreoathetosis, which is seen in anti-NMDAR encephalitis patients. The decreased NAA peak in mRS (Kataoka et al., 2009) and the reduced metabolism in FDG-PET (Tobin et al., 2014) in the BG area support this functional correlation.

The NMDA receptor, which binds the neurotransmitter glutamate, is highly expressed by excitatory neurons throughout the brain (Cull-Candy and Leszkiewicz, 2004). The NMDAR antibody is thought to be pathogenic and directed against the neuron surface NMDA receptor, which causes gray matter damage (Martinez-Hernandez et al., 2011). However, the mechanisms for the white matter (WM) changes caused by NMDAR antibodies are unknown. In a large study with 691 anti-NMDAR encephalitis enrollees, 23 patients had clinical or MRI features suggesting WM demyelinating disorders like NMOSD (Titulaer et al., 2014). These overlapping syndromes may partially explain the WM involvement in anti-NMDAR encephalitis. Nevertheless, multiple isolated WM lesions (2 patients in our cohort) were also reported in two other patients with anti-NMDAR encephalitis (Chan et al., 2010; Wang et al., 2015). Taken together, this indicates that further research is necessary to discover the underlying mechanisms.

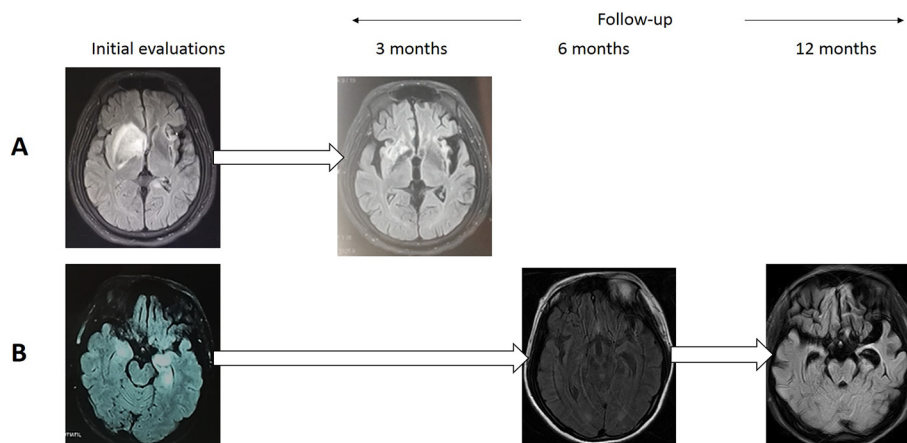


Fig. 3. Neuroimaging outcomes in representative patients with brain lesions in unconventional locations.

The unilateral basal ganglia lesion in a 41-year-old man (case 16) resolved partially at a 3-month follow-up (A). Case 2: a 19-year-old girl who experienced repeated misdiagnoses of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, then Hashimoto's encephalopathy, exhibited multiple brain lesions. These lesions included “ribbon-like” bilateral frontal and parietal cortical, hippocampal and cingulate gyrus lesions on her FLAIR scan at the initial neuroimaging evaluation. Her bilateral medial temporal lobe (hippocampus) progressively developed atrophy at her 6- and 12-month follow-up (B).

To date, few relevant reports of long-term neuroimaging outcomes in anti-NMDAR encephalitis have been published (Iizuka et al., 2010; Iizuka et al., 2016). These follow-up studies indicated that most patients who recovered or left with mild residual deficits had improved or normalized MRI results. Two of these patients developed transient frontotemporal atrophy at 9–14 months, which surprisingly became reversible 5–7 years after the disease onset (Iizuka et al., 2010). However, in contrast to these studies, nearly a quarter of our patients who exhibited BLUL developed diffuse or local cerebral atrophy across the 3- to 12-month follow-up. In addition, most of the patients with BLUL recovered more slowly (residual mRS  $\geq 3$ ) than those with non-BLUL, indicating that patients with BLUL may have worse clinical and imaging outcomes. This variable brain atrophy and serious sequelae require further long-term follow-up evaluations.

In conclusion, anti-NMDAR encephalitis has unpredictable and heterogeneous imaging features. Cerebral gray matter may represent the predominant unconventional location, as well as the WM and brainstem. Contributing to the dominant factor that obscures diagnosis and delays treatment, BLUL may also be associated with poor clinical and imaging outcomes at short-term follow-ups. Therefore, serum and CSF anti-NMDAR antibody tests are highly recommended for patients with atypical imaging abnormalities. There are some limitations in the present study. For example, patients were enrolled in a single hospital, diagnostic workups were heterogeneous, and this review was retrospective. Thus, a long-term, multi-center study that includes a larger sample of patients with anti-NMDAR encephalitis is warranted.

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## Competing interests

The authors declare that there are no potential competing interests among the authors and/or other organizations.

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