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

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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 immunoglobin; 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

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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 immunoglobin; MELAS: mitochondrial encephalomyopathywith lactic acidosis and stroke-like episodes; mRS: modified Rankin scale; NMOSD: neuromyelitis optica spectrum disorders; RTX: intravenous rituximab; PLEX: plasma exchange; WM: white matter.