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Research article

Repeated misdiagnosis of a relapsed atypical anti-NMDA receptor encephalitis without an associated ovarian teratoma

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HIGHLIGHTS

- The differential diagnosis of anti-NMDAR encephalitis is broad and difficult.
- Repeated misdiagnosis can lead to serious sequelae.
- Non-organ specific antibodies may be byproducts of the autoimmune reaction in anti-NMDAR encephalitis.
- Mitochondrial encephalomyopathy should be highlighted as a differential diagnosis of anti-NMDAR encephalitis.

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ABSTRACT

We present an atypical case of relapsed anti-NMDAR encephalitis in a young female patient without an associated ovarian teratoma. She presented with recurrent seizure attacks with muscle weakness, psychosis, dyskinesia, autonomic failure and insomnia. She was first misdiagnosed as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) then Hashimoto's encephalopathy due to diffuse cerebral lesions, elevated serum lactic acid concentration, increased amount of thyroid peroxidase and thyroglobulin antibodies in serum and diffuse lesions of the thyroid gland. Her final diagnosis was delayed for 6 months with the detection of anti-NMDAR antibodies in her CSF. After treatment, she had poor recovery with serious sequelae at 10-month follow-up. Noteworthy, MELAS should be highlighted as a differential diagnosis of anti-NMDAR encephalitis.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis [1] is a new category of treatment-responsive autoimmune synaptic encephalitis, which commonly occurs in young women with an ovarian teratoma, and is characterized by the presence of anti-NMDAR antibodies in serum and cerebrospinal fluid [2]. The differential diagnosis of anti-NMDAR encephalitis is broad and difficult [3], leading to misdiagnosis and delay in the treatment, therefore compromising the treatment efficacy and causing serious sequelae. Herein, we describe a case of relapsed anti-NMDAR encephalitis in a young woman who underwent successive misdiagnosis and showed poor recovery.

1. Case presentation

An 18 year old female experienced transient spasm in the right leg and aphasia with eyes closed for one minute (**day 0**). Approximately 30 min later, she experienced another attack with residual muscle weakness. Three days later, she experienced a third attack followed by immediate numbness of the left toe. Eight days later, she was admitted to a hospital (**day 8**). Babinski signs were positive in her both legs. Sustained-release tablet of valproate (500 mg, twice daily) was administered for controlling the seizure.

Her cerebrospinal fluid (CSF) had normal protein concentration and cell count. Cerebral magnetic resonance imaging (MRI) detected diffuse lesions of hyperintense T_2-weighed signals in bilateral hippocampus, cingulate gyrus and corpus callosum (Fig. 1A/B). Thoracic MRI revealed no evidence of acute myelitis. Digital subtraction angiography detected no cerebrovascular thrombosis. Laboratory test showed elevated serum lactic acid concentration (4.6 mmol/L; reference range: 0.4-2.2 mmol/L). Magnetic resonance spectroscopy (MRS) (TR = 1700 ms, TE = 135 ms) showed bimodal inversion lactate peak, reduced NAA peak and

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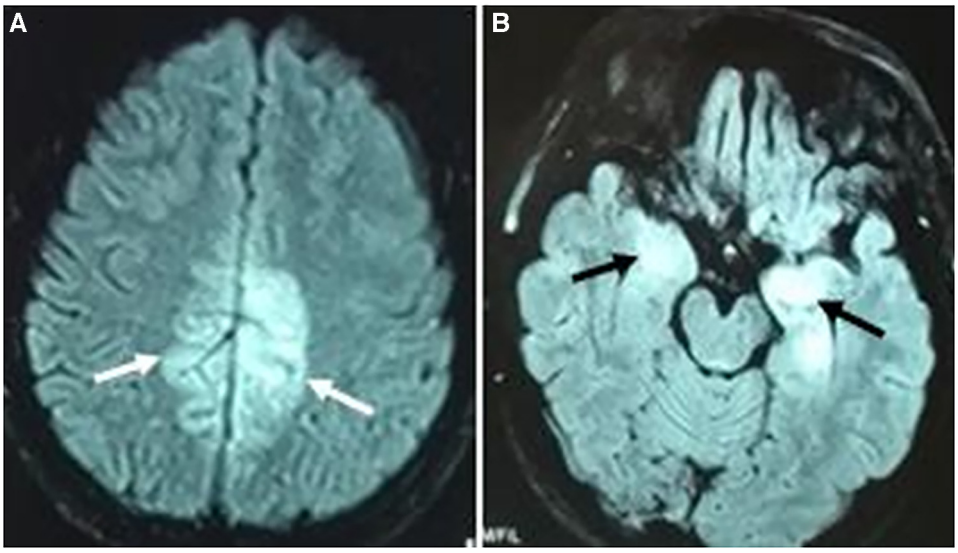

Fig. 1. (A/B) Initial T_2-MRI showing hyerintense lesions in bilateral cingulate gyrus (white arrows) and hippocampus (black arrows).

elevated Cho peak. The diagnosis of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) was suspected (**day 22**). Intravenous adenosine triphosphate with added coenzyme Q10 was administrated. The antiepileptic drug was changed to oxcarbazepine tablet (150 mg, twice daily). However, subsequent genetic testing and muscle biopsy provided no evidence of ME.

Further investigations showed elevated thyroid peroxidase antibodies (TPO, 58.43 IU/mL; reference range: 0–12 IU/mL) and thyroglobulin antibodies (TG, 920.33 IU/mL; reference range: 0–34 IU/mL) levels in serum. Ultrasonography revealed diffuse lesions in the thyroid gland. Therefore, the diagnosis was converted to Hashimoto's encephalopathy (**day 39**). Immunosuppressive therapy (methylprednisolone, 500 mg per day) was administrated intravenously for 5 days, but showed no effect. Immunoglobin (0.4 g/kg per day) was subsequently administered intravenously for 5 days, and the general condition of the patient gradually improved. She was transferred to a rehabilitation center, where she underwent relapse with lower limb weakness (**day 120**), became increasingly restless, agitated and anxious within one week, and experienced insomnia, hyperhidrosis and sphincter disorders. During the next week, she presented stereotypical oro-facial dyskinesias, dystonia and choreoathetosis movements, followed by decreasing verbal output that progressed to complete mutism (**day 134**). Levodopa (250 mg, twice daily) and clonazepam (2 mg, twice daily) for treating dystonia were administered for two months but did not show any effects.

She was transferred to our hospital with a modified Rankin Scale (mRS) score of 5 (∼**day 180**). Anti-NMDAR antibodies were positive in CSF and negative in serum; anti-Ma2 antibody was positive in serum. Diffuse slow activity was observed in a long-term electroencephalogram (EEG) test. Anti-NMDAR encephalitis was diagnosed (**day 184**). No ovarian teratoma was detected. She was treated with 5 sessions of plasma exchange (PE) and 5 days of intravenous methylprednisolone injection (500 mg per day) for immunosuppression. To prevent relapse, azathioprine tablet (50 mg, twice daily) was administered after she obtained normal thiopurine methyltransferase activity. Three months later (**day 260**), the patient showed alleviation of clinical symptoms, diffuse brain atrophy on MRI, no signs of anti-NMDAR antibodies in CSF, and no signs of tumor on pelvic ultrasonography. The dose of azathioprine was increased to 50 mg, three times a day. Ten months later (∼**day 560**), the patient showed complete elimination of movement disorders, autonomic failure and insomnia, and partial recovery of psychological and behavioral disorders with a mRS score of 4.

2. Discussion

Unlike conventional limbic encephalitis, anti-NMDAR encephalitis has unpredictable MRI findings. According to previous reports, brain MRI had been reported as normal in approximately 50% of the patients with anti-NMDAR encephalitis. Patients whose MRI are abnormal have nonspecific cortical or subcortical T1/T2-weighted signal abnormalities, sometimes involving the limbic system (medial temporal regions, cingulate gyrus, etc.) [4]. These MRI signal abnormalities are not strongly correlated (if any) with the symptoms in patients. Our patient showed FLAIR/T2 lesions in limbic lobes, which could explain the symptoms of epilepsy, mental and cognitive disturbances, or even autonomic dysfunction, but were not associated with the dystonia and movement disorders during the relapse. Besides, limbic system abnormalities are not specific features of anti-NMDAR encephalitis and can be seen in other autoimmune encephalitis, metabolic encephalopathy or even vascular diseases.

Our patient initially exhibited atypical clinical symptoms of anti-NMDAR encephalitis and multiple cerebral lesions which were concomitant with elevated serum lactic acid concentration and appearance of large lactate peak on MR spectrum, leading to the misdiagnosis of MELAS. The similarities and differences between MELAS and anti-NMDAR encephalitis are summarized in Table 1. MELAS has not been listed as a routine differential diagnosis of anti-NMDAR encephalitis [3], because MELAS patients often present with characteristic clinical appearances associated with mitochondrial energy metabolism abnormalities [5]. Currently, there is no effective treatment for MELAS [5]. Besides, in tumors [6], ischemia [7], and some times during ictal phase or the immediate period following the seizure, large and deep lactate peak may also appear on MR spectrum because of increased anaerobic glycolysis. Hence, diagnosis of MELAS should be made with caution basing on the observation of lactate elevation.

Hashimoto's encephalopathy (HE) refers to a syndrome of encephalopathy with high serum anti-thyroid antibody concentrations that is typically responsive to glucocorticoid therapy [8].

Table 1
Differential diagnosis among MELAS, HE and anti-NMDAR encephalitis.

	MELAS	HE	Anti-NMDAR encephalitis
Sex	Similar	Female	Female
Age of onset (y.)	<20	bimodal (20–30 and 50–70)	2–40
Onset form	acute	subactute/chonic	acute/subacute
Cognition/psychiatrics	mental-retardation	rapid/chronic progressive	rapid progressive
Epilepsy	multi-forms	multi-forms (myoclonic seizure)	multi-forms
Characteristics	migrainous headache, lactic acidemia	none	oro-facial dyskinesias, choreoathetosis movements
CSF	none	inflammatory, 14-3-3 protean (+)	mild inflammatory
EEG	nonspecific	nonspecific	30% extreme delta brush
MR Imaging	occipital/parietal "cortical ribbon signs"; lactate accumulation	nonspecific lesions	50% nonspecific or limbic lesions
Antibodies	none	TPO/TG, NAE	NMDAR
Associated tumors	none	none	ovarian teratoma
Genetics/myology	m.3243A > G/RRF	none	none
Effect to GC	none	effective	effective but tardive

CSF: cerebrospinal fluid; EEG: electroencephalogram; GC: glucocorticoid; HE: Hashimoto encephalopathy; MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MR: magnetic resonance; NAE: the amino-terminal of alpha-enolase antibodies; RRF: Ragged-red fibers; TPO: thyroid peroxidase antibodies; TG: thyroglobulin antibodies.

The differential diagnosis between HE and anti-NMDAR encephalitis can be difficult if anti-NMDAR antibody screening is not available [9]. The similarities and differences between MELAS and anti-NMDAR encephalitis are summarized in Table 1. According to Graus' recommendations, the term HE should only be used when rigorous clinical assessment and comprehensive testing for well characterized neuronal antibodies exclude other potential causes of encephalopathy [3]. In our patient, the association of elevated TPO/TG antibodies with clinical appearances supported the diagnosis of HE, whereas the absence of overt thyroid disease and poor effectiveness of intravenous glucocorticoid therapy strongly suggested an alternative diagnosis [3]. Furthermore, the unspecific TPO/TG antibodies, as well as other non-organ specific antibodies such as antinuclear antibodies, are known to increase in healthy individuals and patients with other autoimmune encephalitis [3,10,11]. Our patient also exhibited seropositive anti-Ma2 antibody, a well-recognized onconeural antibody, but she did not develop any tumor until now. These antibodies are possibly just byproducts during the autoimmune reaction.

There is ongoing controversy as to whether serum or CSF screening is better for testing anti-NMDAR antibody levels. Dalmau's study showed that not all patients with anti-NMDAR encephalitis have detectable antibodies in serum [4]; Irani reported that the absolute levels of anti-NMDAR antibodies in serum were higher than in CSF, and many patients were diagnosed on the basis of the serum antibody alone [12]. To avoid the risk of false-negative diagnosis, antibody studies should include both serum and CSF analysis in the recent recommendation [3]. The anti-NMDAR antibodies were examined in both serum and CSF in our patient during relapse, but were only detected in the CSF, one of the reason may be that the previous administration of immunotherapies may diminish the titer of the antibody in the blood [13].

Although anti-NMDAR encephalitis is often associated with neoplasms, specifically, an ovarian teratoma [4], about 40% of the patients remain non-paraneoplastic and carry no tumor at the time of diagnosis, especially in children, adolescents, and male patients [4,12]. Slow recovery and relapses were more common in these non-paraneoplastic patients than in those with tumors who were treated with early resection [4,14]. Consistently, our young female patient, who had no detectable tumor and underwent repeated delay in diagnosis, experienced retardant recovery although proper and extreme immunotherapies were administered during relapse.

In conclusion, our case suggests that the clinical manifestations of anti-NMDAR encephalitis can be very heterogeneous, and highlight anti-NMDAR encephalitis as a differential diagnosis of ME. CSF anti-NMDAR antibody test is highly recommended for atypical autoimmune encephalopathy patients.

Conflict of interest

None.

Authors contribution

Collection of data and drafting of manuscript: Weihe Zhang.
Data of case provide: Li Yan.
Revision of the manuscript: Jinsong Jiao.

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