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Case report

Repeated anti-N-methyl-D-aspartate receptor encephalitis coexisting with anti-myelin oligodendrocyte glycoprotein antibody-associated diseases: A case report

Shingo Aoe[a], Yohei Kokudo[a], Tadayuki Takata[b], Hideki Kobara[a], Mitsutoshi Yamamoto[c], Tetsuo Touge[d], Kazushi Deguchi[a,*], Tsutomu Masaki[a]

[a] Department of Gastroenterology and Neurology, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan
[b] Department of General Medicine, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan
[c] Department of Neurology, Takamatsu Neurology Clinic, 4-10 Konya-machi, Takamatsu-shi, Kagawa, Japan
[d] Department of Health Sciences, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan

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ABSTRACT

The coexistence of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and anti-myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated diseases has been reported. We report the case of a 36-year-old woman who presented with repeated typical anti-NMDAR encephalitis coexisting with unusual symptoms not consistent with anti-NMDAR encephalitis. Apart from the anti-NMDAR encephalitis, her first episode was characterized by balance disability with bilateral medial frontal cortical lesions, suggesting the involvement of the cortico-reticular projections and the basal ganglia-brainstem projections. The second episode presented with Broca's aphasia caused by involvement of the Broca's area and lower part of the precentral gyrus. The detection of MOG-Ab in both episodes suggested the coexistence of MOG-Ab-associated diseases. Thus, an evaluation of MOG-Ab should be considered when anti-NMDAR encephalitis presenting with atypical symptoms is encountered.

1. Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rapidly progressive encephalopathy characterized by abnormal behavior, cognitive dysfunction, speech dysfunction, seizures, movement disorders, decreased level of consciousness, autonomic dysfunction, and central hypoventilation (Titulaer et al., 2013). On the other hand, anti-myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease is an acute central nervous system (CNS) demyelination with optic neuritis, myelitis, brain stem encephalitis, and acute disseminated encephalomyelitis (ADEM)-like presentations (Jarius et al., 2018). In addition, the development of cortical encephalitis has been reported in several MOG-Ab-positive cases (Fujimori et al., 2017). Both anti-NMDAR and MOG-Ab could coexist as simultaneous or isolated episodes (Titulaer et al., 2014). In such cases, anti-NMDAR encephalitis shows typical symptoms, whereas MOG-Ab-associated disease might present diverse symptoms depending on the site of demyelination. We present here a patient who had repeated typical anti-NMDAR encephalitis immediately after developing a balance disability associated with cortical encephalitis and Broca's aphasia due to left frontotemporal lesions, which suggested MOG-Ab involvement. This case suggests that MOG-Ab should be evaluated if atypical symptoms and magnetic resonance imaging (MRI) findings not consistent with anti-NMDAR encephalitis are noted in cases of anti-NMDAR encephalitis.

2. Case presentation

A 36-year-old right-handed woman with a past history of depression developed a headache with fever. Five days later, she walked unsteadily, and after 11 days she needed assistance with walking. Brain MRI fluid-attenuated inversion recovery (FLAIR) imaging showed high-intensity lesions involving the medial aspect of the bilateral frontal lobes (Fig. 1). At admission to our hospital, her body temperature was 38.2 °C. She was awake and alert. Her Mini Mental State Examination (MMSE) score was 29/30 (1 point was deducted for delayed recall). Neurological examination showed severe truncal ataxia with difficulty in sitting. Other neurological abnormalities were not observed. Cerebrospinal fluid (CSF) findings were as follows: protein 40 mg/dL,

* Corresponding author.
E-mail address: kdeguchi@med.kagawa-u.ac.jp (K. Deguchi).

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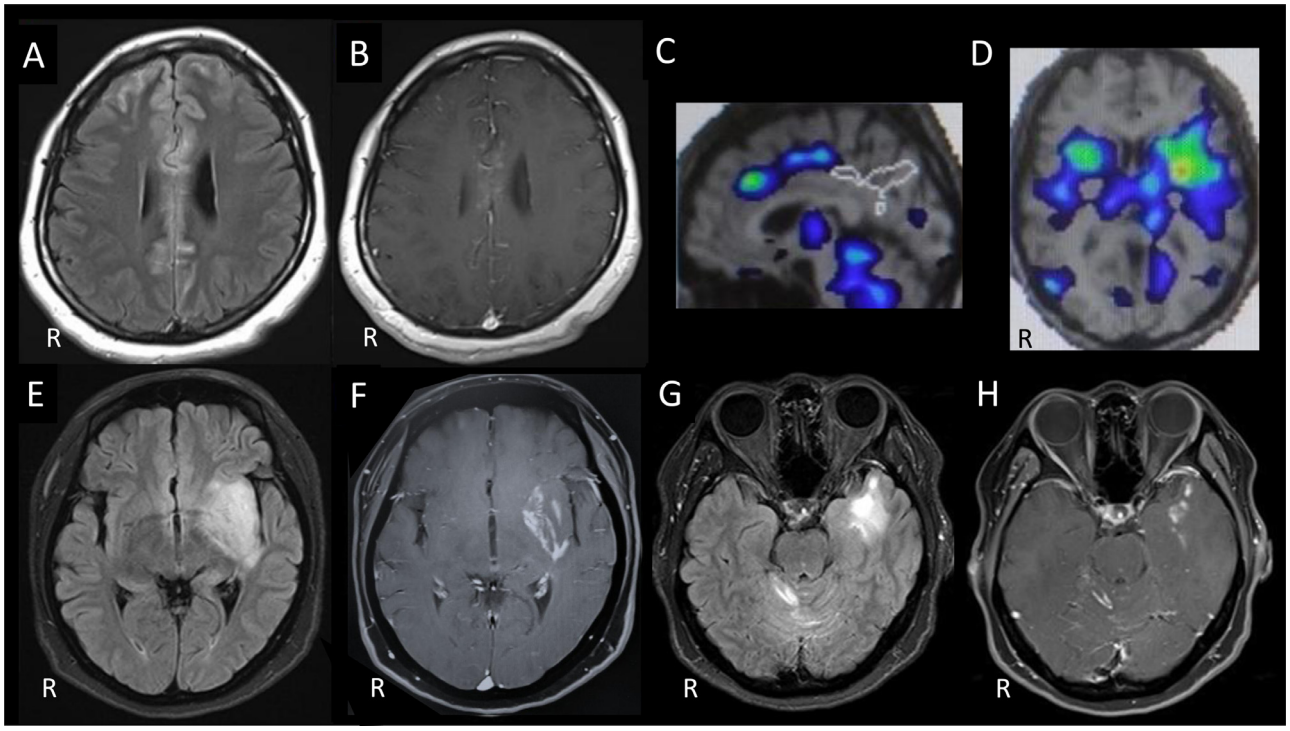

Fig. 1. Cranial MRI images taken in the first (A, B) and second (E–H) episodes and brain single photon emission computed tomography (SPECT) performed in the first episode (C, D). A fluid-attenuated inversion recovery (FLAIR) image demonstrates a lesion involving the medial aspect of the bilateral frontal lobes (A). A gadolinium-enhanced T1-weighted image (Gd-T1WI) shows enhancement in parts of the lesions (B). SPECT shows reduced technetium-99 m ethyl cysteinate dimer uptake in the medial aspect of the frontal lobe (C), and also in the brainstem (C) and basal ganglia (D). A FLAIR image revealed hyperintense lesions in the left basal ganglia (E), left temporal lobe, and right cerebellar hemisphere (G). Gd-T1WI shows enhancement in parts of the lesions (F, H). R,right side.

glucose 64 mg/dL, and cell count 128/μL (mononuclear cell count 116/μL). Brain single photon emission computed tomography (SPECT) showed reduced technetium-99m ethyl cysteinate dimer (99mTc-ECD) uptake in the basal ganglia and brainstem as well as in the medial aspect of the frontal lobe (Fig. 1). A certain type of encephalitis was suspected. Therefore, acyclovir and methylprednisolone (1 course: 1000 mg/day for 3 days) were started, and the truncal ataxia improved. After 23 days, however, she exhibited depression, followed by disorientation, delusions, and fluctuation in her consciousness level. On the 33rd day, oral dyskinesia and twitching of the right hand were observed. She could not be aroused by a loud voice, but intravenous injection of diazepam restored her response. Urinary retention was also observed, and central hypoventilation at night. These symptoms gradually improved with the combination of 3 courses of methylprednisolone and 1 course (0.4 g/kg for 5 days) of intravenous immunoglobulins (IVIg). On the 81st day, she was discharged without sequelae. She was diagnosed with anti-NMDAR encephalitis based on the NMDAR-Ab positivity of a CSF sample collected on admission (cell-based assays: CBAs).

At 3.5 years after the first episode, headache without fever appeared. Ten days later, she became aware of difficulties with word-finding, reading, and writing, and felt that she was not herself. Brain MRI FLAIR images revealed hyperintense lesions in the left basal ganglia, temporal lobe, and right cerebellar hemisphere, some of which showed gadolinium enhancement (Fig. 1). At admission to our hospital, she was awake and alert, but showed pressured speech. MMSE was 27/30 (2 points deducted for delayed recall, 1 for naming of objects). Except mild cognitive decline and speech dysfunction, neurological abnormalities were not observed. The CSF findings were as follows: protein 51 mg/dL, glucose 61 mg/dL, and cell count 93/μL (mononuclear cell count 85/μL). The myelin basic protein (MBP) in the CSF was elevated (192 pg/mL; standard value, <102). Oligoclonal IgG bands were detected. One course of methylprednisolone followed by plasma exchange was performed immediately, but her impaired speech was exacerbated by the addition of agrammatism, phonological paraphasia, failure of repetition, dysgraphia and dyslexia. On the 31st day, hallucinations, restlessness, tachycardia, hyperhidrosis, tachypnea, and central apnea developed. Following the administration of one course of IVIg and one course of methylprednisolone in combination, the psychiatric, autonomic, and respiratory problems disappeared. Although her conversation gradually normalized from the 38th day, impaired attention remained on the 74th day, when she was transferred to a rehabilitation hospital. NMDAR-Ab in the CSF was positive (1:20) even during the second episode. In addition, the large, confluent lesion and elevated MBP level suggesting demyelination prompted the measurement of MOG-Ab (CBAs) in serum, and MOG-Ab qualitative testing was positive. MOG-Ab positivity was also confirmed in the archived serum sample from the first episode. On the other hand, serum anti-AQP4 antibody (CBAs) was negative in all episodes. No ovarian teratoma was found on pelvic MRI throughout the entire course.

3. Discussion

This patient met the diagnostic criteria for “definite NMDAR encephalitis” during both the first and second episodes (Graus et al., 2016). In the first episode, while the patient exhibited the typical NMDAR encephalitis symptoms, she also showed a balance disability, which is unusual in NMDAR encephalitis in adults (Titulaer et al., 2013). Brain MRI showed lesions in the bilateral medial frontal lobe involving the motor cortical areas, while SPECT also revealed decreased blood flow in the basal ganglia and the brainstem reticular formation, which have neural connections with the motor cortical areas (Takakusaki, 2009). Since posture is controlled by the cortico-reticular projections and the basal ganglia-brainstem projections (Takakusaki, 2009), the impairment of these neural circuits demonstrated by SPECT might have been responsible for the balance disability

in this case.

In the second episode, her impaired speech progressed from anomia to Broca's aphasia, which was caused by a left frontotemporal lobe lesion involving the Broca's area and lower part of the precentral gyrus. This language difficulty was not consistent with the speech disorders that are major symptoms of NMDAR encephalitis (Titulaer et al., 2013). The large, confluent lesion and elevated MBP level in the CSF prompted MOG-Ab testing (Jarius et al., 2018), and thereby MOG-Ab positivity was revealed. It was also demonstrated that MOG-Ab was involved in the unusual first episode. The pathogenetic involvement of MOG-Ab in bilateral parasagittal cortical lesions remains unclear, as neither elevated MOG-Ab in the CSF nor demyelination has been reported in these lesions. However, in addition to the present case, other MOG-Ab-positive cases with unilateral and bilateral cortical lesions have also been reported; in these previous cases, the condition evolved into an ADEM-like illness with optic neuritis (Fujimori et al., 2017), again suggesting the involvement of MOG-Ab.

Cases of overlapping NMDAR encephalitis and MOG-Ab-associated diseases are classified into three types based on the clinical presentation of the first episode: NMDAR encephalitis (44%), MOG-Ab-associated diseases (31%), and concurrent onset (28%) (Fan et al., 2018). With respect to concurrent onset, repeated concurrent onset such as seen in this case has been reported only once before, to our knowledge (Fan et al., 2018). However, in that report, the symptoms and MRI findings involving MOG-Ab were clearly different in each episode. The clinical presentation of a great variety of symptoms might make an early diagnosis of coexisting MOG-Ab-associated diseases difficult, particularly in cases with a concurrent onset of NMDAR encephalitis.

Although an ovarian teratoma that contains nervous tissue and expresses NMDAR is a common pathogenetic finding in female NMDAR encephalitis patients (Titulaer et al., 2013), we could not detect an ovarian teratoma in this case over the entire 4-year clinical course. Unexpectedly, ovarian teratoma has been extremely rare in overlapping cases, even if the first episode involved NMDAR encephalitis alone (Fan et al., 2018; Titulaer et al., 2014). Thus, an ovarian teratoma might not be directly involved in the coexistence of both disorders. Under these circumstances, it has been suggested that autoimmunity to oligodendrocytes containing NMDAR and MOG might play an important role (Titulaer et al., 2014).

In summary, NMDAR encephalitis and MOG-Ab-associated diseases are indeed coexisting clinical conditions. In contrast to the more restricted typical clinical manifestations of NMDAR encephalitis, the broad clinical spectrum associated with MOG-Ab could delay the correct diagnosis of coexisting MOG-Ab-associated diseases, particularly with the simultaneous progression of both disorders. To ensure adequate treatment and meet prognostic expectations, differences from the typical clinical presentation of NMDAR encephalitis should be a focus, including rapid MOG-Ab testing.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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