

Cortical encephalitis with overlapping anti-*N*-methyl-D-aspartate receptor and anti-myelin oligodendrocyte glycoprotein antibodies: report of two cases

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To the Editor: Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis (NMDARE) is a potentially lethal autoimmune disease. Anti-myelin oligodendrocyte glycoprotein (MOG) antibody (Ab) could represent a diagnostic biomarker for a distinct spectrum of central nervous system (CNS) inflammatory demyelinating diseases (IDDs). Herein, we report two cases, positive for both NMDAR-Ab and MOG-Ab, which was presented with cortical encephalitis and subsequent demyelination.

A 32-year-old Chinese man was admitted to our hospital with acute headache, fever, and seizure. He had no previous medical history or hereditary diseases. Brain magnetic resonance imaging (MRI) at admission revealed high-intensity lesions in the right temporal, parietal, and occipital cortex without enhancement [Figure 1A–1C]. Cerebral spinal fluid (CSF) analysis showed elevated pressure (250 mmH₂O) and presence of leukocytes (142 cells/mm³) and protein (66.9 mg/dL). Oligonucleotide band was negative. CSF was positive for immunoglobulin (Ig)G but not IgM to rubella virus, herpes simplex types I and II, cytomegalovirus and Epstein-Barr virus. Electroencephalograms showed slow and sharp wave activity in the right hemisphere. The patient was treated with intravenous acyclovir and dexamethasone. Pressure, leukocytes, and protein in the CSF had improved at the time of discharge, but his headache and fever recurred 3 weeks later. Cell-based assays for all serum/CSF Abs associated with autoimmune encephalitis (AIE), demyelinating disease, and paraneoplastic neurologic syndrome were negative. Blood tests for systematic autoimmune diseases and cancer screening were also negative. Methylprednisolone (MP) (80 mg/d for 5 days) therapy ameliorated elevated CSF protein and leukocytes and his MRI returned to normal.

Six months later, the patient returned to the hospital because of right hemianesthesia and left upper limb numbness. MRI showed new lesions in the left medulla oblongata and right

temporal lobe [Figure 1D and 1E]. Follow-up MRI revealed enlargement of the lesions and new enhanced lesion [Figure 1F and 1G]. The serum/CSF Abs listed above were again negative. The patient was treated with intravenous immunoglobulin G (IVIG) (0.4 g/kg daily for 5 days) for 3 consecutive months combined with azathioprine.

A stable phase was reached for 6 months until the patient developed orbital pain and decreased visual acuity in the left eye. New enhanced lesions in the brainstem and the left optic nerve were detected [Figure 1H–1J]. He was re-tested and found positive for serum/CSF MOG-Ab (1:320/1:32) and NMDAR Ab (negative/1:1). No lesion was identified on spinal cord MRI. Tumor markers were still undetectable. Despite treatment with IVIG and MP via retrobulbar injection, his visual acuity recovered incompletely over 1-year follow-up (from counting fingers at 30 cm to 0.6). He experienced no seizures or adverse events.

A 50-year-old Chinese man had a history of headache, fever, and seizures. He had been diagnosed with viral encephalitis 15 years previously by a different hospital, but the clinical data had been lost. His seizures were well-controlled until February 2011, when he was sent to our hospital for recurrence of seizures with normal CSF. He had no previous medical history or family history of seizure. Fluid attenuation inversion recovery imaging revealed high-intensity lesions in the left insula and parietal cortex [Figure 1K–1N]. Electroencephalograms showed multiple sharp and slow waves in the left central and parietal regions. A diagnosis of gray matter heterotopia was considered during neurosurgical consultation and he underwent a parietal lobotomy. During hospitalization, the patient experienced paroxysmal visual and auditory hallucinations. Following administration of carbamazepine and levetiracetam, his symptoms disappeared.

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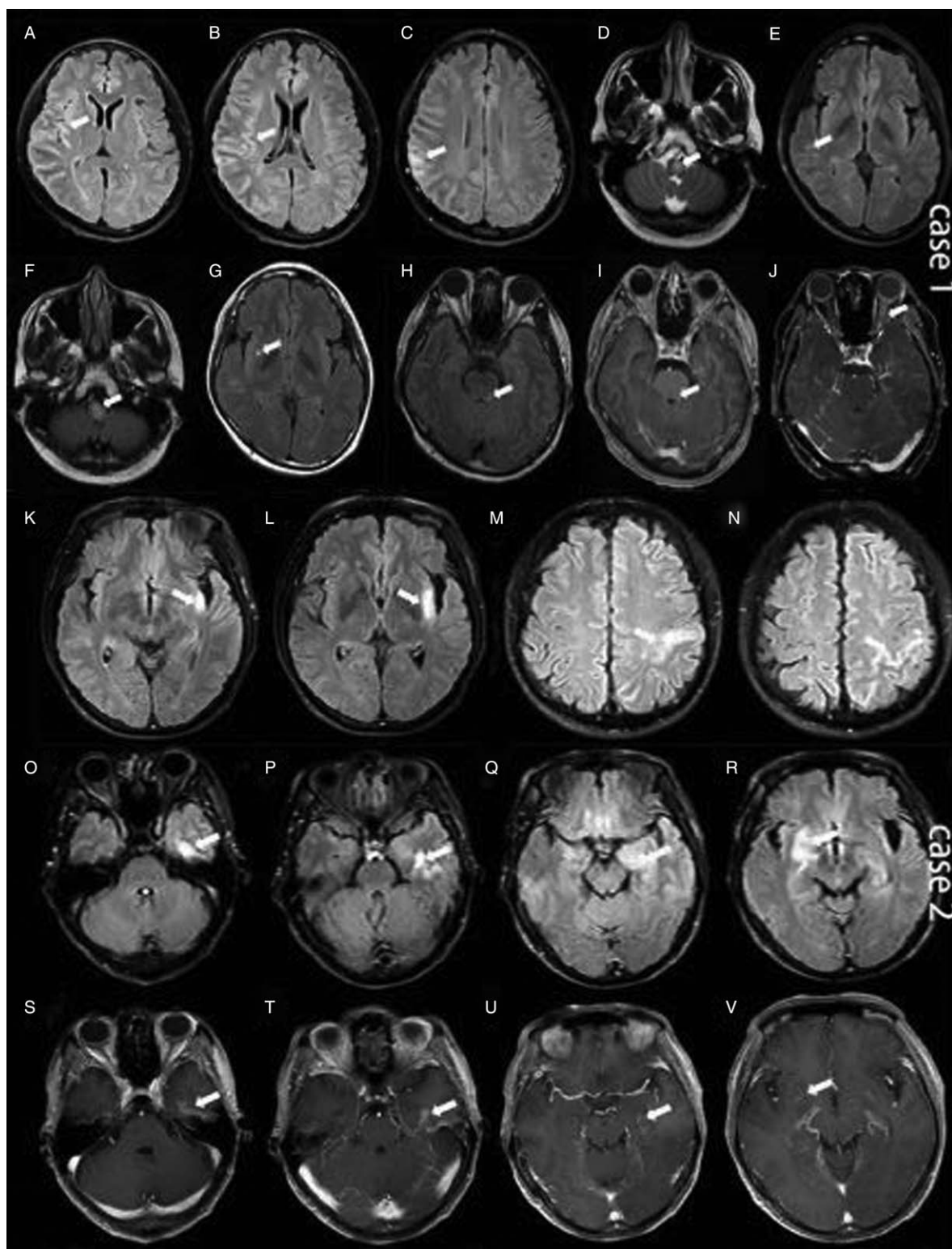


Figure 1: Brain magnetic resonance imaging (MRI) of patient 1 (A–J) and patient 2 (K–V). (A–C) Brain MRI showed hyperintensity on FLAIR imaging in the right temporal, parietal, and occipital gyri. Images obtained with the left medulla oblongata (D) and the right medial temporal lobe (E). Follow-up brain MRI showed lesion enlargement in the medulla oblongata (F) and a new lesion in the right basal ganglia (G). New lesions of the left margin of brain stem (H) with patchy enhancement (I). (J) Orbital MRI showed the left optic nerve flexion and enhancement on gadolinium-enhanced T1WI. (K–N) Imaging features of the cortical lesions of the left insula and parietal cortex. Brain MRI showed cortical lesions of the left temporal lobe (O, P), hippocampus (Q), and right basal ganglia (R) with mild enhancement (S–V).

In October 2017, the patient was admitted to the CNS demyelinating disease registry because he had been suffering from progressive cognitive decline, somnolence, visual hallucinations, and abnormal behavior. MRI revealed

multiple lesions with mild enhancement [Figure 1O–1V]. He had no abnormal findings on spinal MRI and CSF examination except for positive serum/CSF NMDAR-Ab (1:100/1:32) and MOG-Ab (1:32/1:10). His CSF was

positive for IgG to cytomegalovirus and Epstein-Barr virus. Cancer screening and autoimmune disease-related indices were negative. After initial administration of pulse intravenous MP (1000 mg/d for 5 days) and IVIG (0.4 g/kg daily for 5 days) therapies, his symptoms improved gradually. He received maintenance therapy with oral prednisone, azathioprine, olanzapine, oxcarbazepine, and levetiracetam without adverse events.

NMDARE can mainly present with psychosis, memory deficits, dyskinesia, involuntary movements, decreased level of consciousness, and central hypoventilation. The clinical manifestation of NMDARE may be heterogeneous, ranging from complete to mild/partial forms. Some cases may be asymptomatic. Despite the initial typical manifestations of AIE in the two cases described here, there were substantial difficulties in diagnosing NMDARE because NMDAR-Abs were either not identified (patient 1) or available (patient 2). NMDARE has also been reported to be closely associated with viral infections. NMDAR-Abs were detected in approximately 30% of polymerase chain reaction-positive herpes simplex encephalitis patients without tumors,^[1] suggesting that the virus may have triggered CNS injury or autoimmunity by inducing production of the NMDAR-Abs. Further studies are needed to better understand the pathogenesis of this disorder.

NMDARE has been reported to be preceded or followed by demyelinating episodes,^[2] while MOG-IDDs can be associated with AIE Ab-negative cortical encephalitis.^[3] Adding an additional layer of complexity, MOG-IDDs can occur simultaneously with NMDARE.^[4] Differentiating the contributions of these two Abs is challenging, although it should be noted that oligodendrocytes express NMDAR. The clinical courses of the two patients studied here were quite different. Patient 1 experienced two demyelinating attacks without the typical symptoms of NMDARE. Patient 2 experienced 15 years of seizures until NMDARE-like symptoms presented in 2017. Given the earlier attacks (seizures, paroxysmal visual and auditory hallucinations, and cortical lesions) in 2011, we speculate that he might have suffered from AIE rather than gray matter heterotopia. However, the ability to detect AIE-associated Abs via cell-based assays only became available in 2014 in Shanghai. This patient had no typical demyelination events, and the demyelinating lesion located in the basal ganglia was only detected on MRI. Interestingly, we found that the most prominent symptoms of both patients seemed to be associated with the titers of NMDAR-Abs and MOG-Abs. Demyelinating events mainly occurred in patient 1, who had a higher titer of CSF MOG-Ab than NMDAR-Ab.

The low titer of NMDAR-Ab may lead to atypical symptoms; alternatively, immune responses against myelin may simultaneously involve NMDAR.^[5] By contrast, patient 2 had the opposite pattern of Ab titers. But whether the two Abs are related to the clinical phenotype, course, or prognosis are still controversial.

Herein, we report two Chinese patients with both positive MOG-Ab and NMDAR-Ab, but the clinical manifestations were different from pure MOG-IDDs or NMDARE. Clear description of atypical cases is crucial: accurate recognition of these conditions will enable prompt testing for Abs and help in diagnosing overlapping NMDAR-Ab and MOG-Ab-associated disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the article. The patients understand that their name and initials will not be published and due efforts will be made to conceal the identity of the patients, although anonymity cannot be guaranteed.

Conflicts of interest

None.

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