Letter to the Editor

Rare autoimmune encephalitis presenting as fluid-attenuated inversion recovery-hyperintense lesions in anti-Myelin oligodendrocyte glycoprotein-associated encephalitis and seizures accompanied with anti-IgLON5 antibody

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Introduction

Autoimmune encephalitis (AE) was first described as a form of encephalopathy mediated by an autoimmune mechanism by Dalmau *et al.* in 2007 (1). Anti-IgLON5 antibody-related encephalopathy is a rare type of AE characterized by sleep disorder, bulbar paralysis, and oculomotor nerve disorder (2). However, this newly described disease presents without any remarkable or specific features in brain magnetic resonance imaging (MRI). Due to the diversity of autoantibodies, the MRI findings of AE are relatively complex and easily lead to misdiagnosis. Myelin oligodendrocyte glycoprotein (MOG) is a myelin glycoprotein specifically expressed in oligodendrocytes of the central nervous system. It mediates inflammatory demyelinating disease known as MOG-immunoglobulin G (IgG)-associated encephalomyelitis (MOG-EM) (3). These two antibodies contribute to an overlapping disease, however, imaging findings of the overlapping disease have not been reported. Here, we report a case that presented with cortical fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in anti-MOG encephalitis and seizures (FLAMES), accompanied with anti-IgLON5 antibody (4).

Case presentation

A 33-year-old male presented with paroxysmal loss of consciousness which had started 17 days ago without definite cause. During the episodes, his head deviated to the right, he had no speech, and he exhibited jerking of the extremities which lasted for 3 minutes and then spontaneously subsided. Throughout the past two years, the patient had experienced sluggish reflexes, significant hypomnesis, difficulty falling asleep, and involuntary movements of the limbs after sleep. He had no history of similar complaints. Neurological examination showed that the patient was awake, alert and had clear speech. His memory and calculation skills were decreased, although his orientation was in the normal range. The tendon reflexes of four of his extremities were all increased, and the pathological signs were negative. The Montreal Cognitive Assessment (MoCA) score was 15 points (a normal score is at least 26 points), which indicated cognitive dysfunction. Polysomnography (PSG) revealed decreased sleep efficiency at 18.8%, disturbed sleep structure, and absence of the rapid eye movement (REM) phase, but the patient did not have obstructive sleep apnea and periodic leg movements. The electroencephalogram (EEG) showed

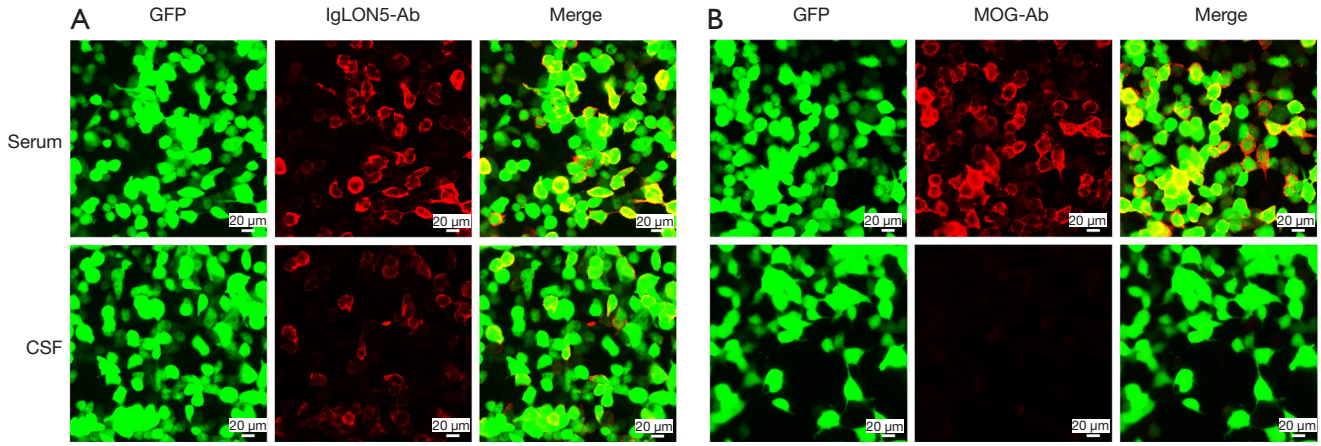

Figure 1 Anti-IgLON5 and anti-MOG antibodies as shown in immunofluorescence tests using fixed cell-based assay. (A) Anti-IgLON5 antibodies 1:30 in the serum; Anti-IgLON5 antibodies 1:10 in the CSF. (B) Anti-MOG antibodies 1:32 in the serum. Scale bar =20 μm. GFP, green fluorescent protein; MOG, Myelin oligodendrocyte glycoprotein; CSF, cerebrospinal fluid.

slow wave emission in the right central, parietal, and middle temporal regions, as well as a sharp wave, sharp and slow wave from the right central parietal region. Lumbar puncture showed a cerebrospinal fluid (CSF) pressure of 140 mmH_2O (normal, 80–180 mmH_2O). No abnormality was found in the routine biochemical tests (color, cell count, glucose, chlorine, and protein) or in the pathogenic microorganism examination of CSF. Antibody testing was performed using a commercial fixed cell-based assay and evaluated using immunofluorescence microscopy (KingMed Diagnostics Reference Laboratory, Shenyang, Liaoning, China). Autoantibody screening showed the presence of IgLON5 antibodies in the serum (1:30) and the CSF (1:10) (*Figure 1A*). This screening also showed the presence of MOG antibodies in the serum (1:32) but not in the CSF (*Figure 1B*). Other antibodies in the CSF (NMDA, AMPA1, AMPA2, LGI1, GABAB, CASPR2, DPPX, GIyR1, DRD2, GAD65, and mGluR5) were all negative.

The brain MRI showed swelling in the bilateral frontal and cingulate gyrus region cortex with a hyperintense lesion on the T2-weighted image (T2WI) and FLAIR (*Figure 2A-2D*). The lesion had a mild hyperintensity on the axial diffusion-weighted imaging (DWI) with a decreased apparent diffusion coefficient (ADC) value (*Figure 2E,2F*). After the contrast medium was injected, the bilateral frontal pia meninges displayed contrast enhancements (*Figure 2G*). Perfusion weighted imaging (PWI) showed decreased cerebral blood flow (CBF) and cerebral blood volume (CBV) in the bilateral frontal and cingulate gyrus (*Figure 2H,2I*). Magnetic resonance spectroscopy (MRS) showed a lower peak for the N-acetyl aspartate (NAA) signal and higher peaks of choline-containing compounds (Cho) and creatine derivatives (Cr) signal (Cho/Cr: 1.38; Cho/NAA: 1.17; NAA/Cr: 1.17) (*Figure 2J*).

Treatment and discharge follow-up involved the following: The patient was treated with high-dose intravenous methylprednisolone (1 g/d for 3 days, halved every three days, and changed to oral administration when reduced to 60 mg) and immunoglobulins (27.5 g/d for 5 days), which led to a rapid improvement over a few days. His seizures completely recovered. However, at discharge, his reflexes remained delayed, and he still had hypomnesis. The patient continued treatment with prednisone acetate tablets by regular oral administration. At present, nearly 1 year after the onset of symptoms, his sleep disorder and cognitive impairment are persisting, but the other conditions are stable and no new aggravation has been reported. The patient did not undergo imaging examination after discharge.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Based on the positive antibodies, AE is divided into

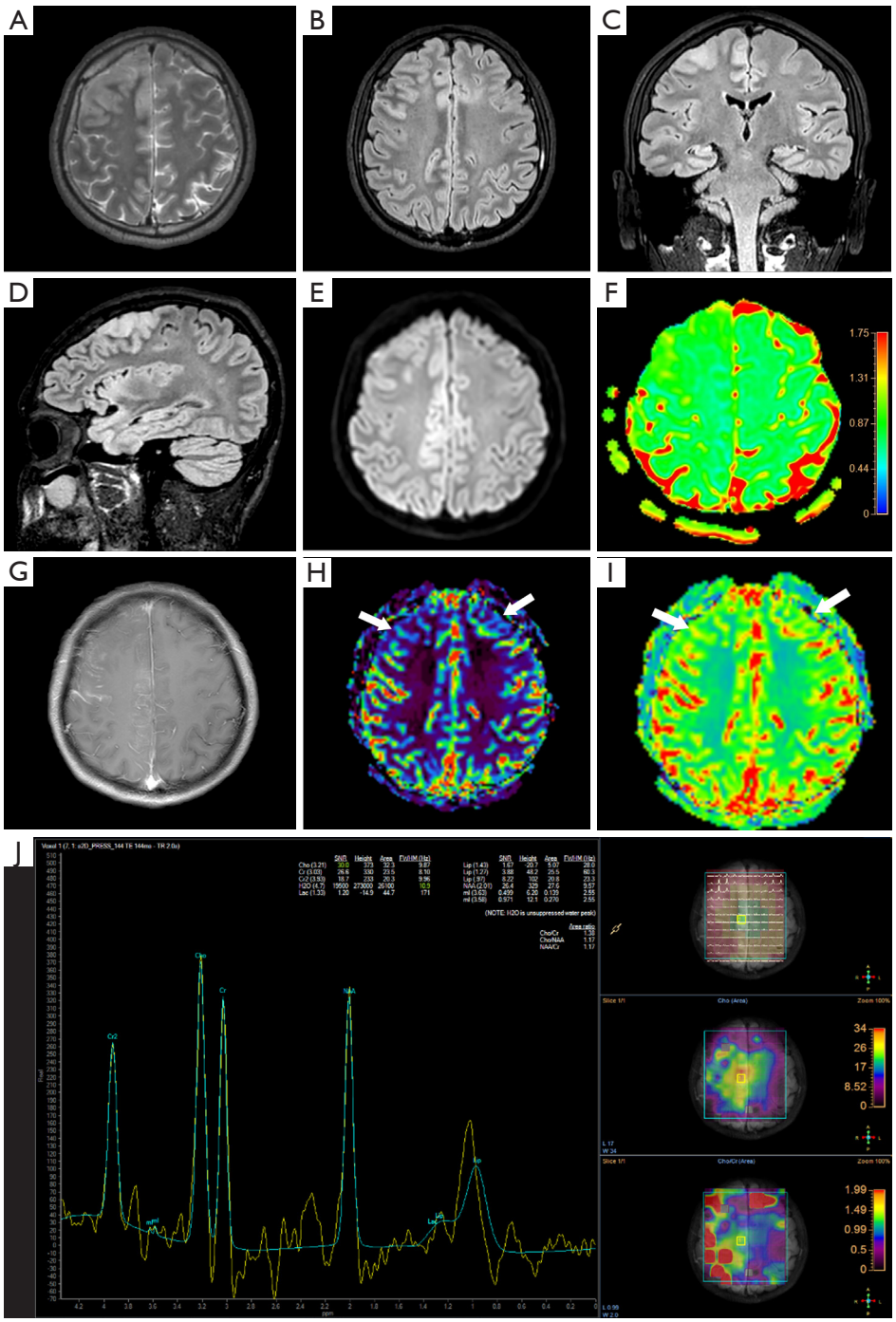

Figure 2 MRI findings of the lesion. Brain MRI demonstrated cortex swelling and a hyperintense lesion on axial T2WI (A) and FLAIR (B-D) on the bilateral frontal and cingulate gyrus region. Mild hyperintensity on the axial DWI (E) and ADC (F) value decreased, bilateral frontal pia meninges showed contrast enhancement (G). CBF (H) and CBV (I) showed decreased blood flow in the bilateral frontal and cingulate gyrus (white arrows). MRS (J) demonstrated a lower peak of the NAA signal and higher peaks of the Cho and Cr signal (Cho/Cr: 1.38; Cho/NAA: 1.17; NAA/Cr: 1.17). MRI, magnetic resonance imaging; T2WI, T2-weigted image; FLAIR, fluid attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; CBF, cerebral blood flow; CBV, cerebral blood volume; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; Cho, choline-containing compounds; Cr, creatine derivatives.

many subtypes, and each subtype has its own clinical characteristics and imaging findings. Clinically, AE patients are mainly positive for a single antibody, and only a few cases have two or more antibodies (5). As far as we know, this is the first report of an AE case that was positive for both anti-IgLON5 antibody and anti-MOG antibody. Anti-IgLON5 antibody-related encephalopathy has the neuropathological features of tau protein disease and is considered a bridge between autoimmune diseases and neurodegenerative diseases of the nervous system. Anti-IgLON5 antibody is considered to cause neurodegeneration in specific central nervous system areas involved in the brainstem, hypothalamus, and hippocampus. In addition, neuropathological findings revealed tau phosphorylation and deposition in these areas (6). The MOG antibody is a subtype of immunoglobulin IgG1. Studies have shown that MOG antibody can cause damage to the integrity of the blood-brain barrier, neuron loss, and gliosis (7). However, the pathogenic mechanism of MOG antibody disease is not clear at present.

The symptoms of Anti-IgLON5 antibody-related encephalopathy are heterogeneous. The most prominent characteristic is sleep dysfunction (REM and non-REM sleep parasomnia), obstructive sleep apnea syndrome, gait instability, and bulbar dysfunction (8). Sleep disturbance is a prominent clinical manifestation of anti-IgLON5 antibody encephalopathy. However, this case only showed an absence of the REM phase, and no obvious sleep disturbance was observed. This case did not show extrapyramidal symptoms that are characteristic of IgLON5 antibody encephalopathy. This may be related to the short onset time of the patient, because some reports show that IglON5 has a slow onset and a longer course of disease (9). Initially, MOG-EM was linked to manifestations similar to acute disseminated encephalomyelitis (ADEM) in children (10). Recent research has proposed a wide clinical spectrum for MOG-EM, including optic neuritis, transverse myelitis, and brainstem and cerebellar lesions (11,12). Eventually, MOG-EM may cause seizures (13). In our case, the seizures were consistent with the symptoms of MOG-EM. Cognitive impairment is the common clinical manifestation of both diseases (8,14).

According to reports, most cases of anti-IgLON5 antibody-related encephalopathy show no obvious or non-specific MRI results, and only a few cases have mild to moderate brain stem, bilateral hippocampus, and cerebellar atrophy (8). However, this patient did not exhibit imaging findings that were typical of anti-IgLON5 antibody encephalopathy. Radiographically, patients with MOG mainly present with cortical and subcortical lesions with T2WI and hyperintense FLAIR that may involve the brainstem (15). Some reports have shown that lesions are mainly distributed in the deep white matter, cortex, subcortical region, deep gray matter nucleus, and brain stem (16). Furthermore, a study found that the cingulate gyrus is the most affected area, and cortical involvement is a marker for the diagnosis of MOG-EM. Part of the MOG-EM brain lesions appears as contrast enhancement in imaging and presents as "flame-like" enhancement, gyrus, and leptomeningeal enhancement (7). Recently, a novel clinico-radiological sub-entity was named FLAMES. The FLAMES sub-entity is characterized by FLAIR imaging, hyperintense cortical lesions, and seizures in cases of MOG-EM. The case in this report presented with epileptic seizures and FLAIR hyperintense lesions in the bilateral frontal and cingulate gyrus region, leading to a diagnosis of cortical FLAMES. In addition, this case showed that the frontal lobe was extensively affected, and the frontal lobe is involved in the sleep disorder mechanism (17). This suggests that it was consistent with the patient's clinical manifestations. Hansen *et al.* (18) speculated that the potential autoimmune process of IgLON5 antibody infiltration can cause destruction of the blood-brain barrier and lead to changes in cortical hyperintensity. Therefore, the imaging manifestations of IgLON5 cannot be completely ruled out and further research is still needed.

The perfusion of AE varies according to the course of the disease. In the acute stage, high perfusion is present because of inflammation and vasodilation in the AE lesions, which may be related to the onset of acute seizures. In the chronic stage, the blood perfusion of the lesions decreases due to local tissue edema and relative vasoconstriction. The case in this report underwent MRI examination 17 days after the onset of seizures and hormone and immunosuppressive therapy. The PWI method is used to quantitatively evaluate blood flow changes, which may be helpful to monitor the evolution of the disease (19). In this patient, NAA reduction suggested that the patient had neuronal damage or loss. The slightly increased Cho peak may have been due to the infiltration of inflammatory cells. The changes of MRS are also dynamic and related to the course of disease and treatment.

A number of diseases should be considered and differentiated based on cortical abnormalities shown in imaging. First, in acute arterial occlusive infarction,

the lesion often involves the cortex and white matter with hyperintensity on DWI, which is consistent with the blood supply area of the responsible artery. Second, diffuse astrocytoma mainly affects white matter with the space-occupying effect. Both DWI and MRS can provide more clues for differential diagnosis, but there are often overlapping areas. Third, viral encephalitis or neuromyelitis optica spectrum disorders (NMOSD) are also considered, which often have similar clinical and imaging findings to AE. Standardized serological and CSF examination is necessary. In addition to the above diseases, hypoxic encephalopathy, Creutzfeldt-Jakob disease (CJD) (20), mitochondrial encephalomyopathies (21), and others also need attention. In summary, we report a case that featured cortical FLAMES with overlapping anti-IgLON5 and anti-MOG antibodies. When multiple cortical lesions that are suspected of inflammatory disease are present, the co-existence of two antibodies needs to be considered. In addition to conventional sequences, PWI and MRS may be helpful to differentiate the diagnosis of different diseases that have similar imaging results and can enable the disease evolution to be monitored.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1213/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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