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Short communications

An unusual case of anti-MOG CNS demyelination with concomitant mild anti-NMDAR encephalitis

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ABSTRACT

We report the case of a patient who presented with progressive unsteadiness and narcoleptic attacks followed by behavioral change and psychosis, without visual disturbances or seizures. MRI revealed multiple areas of fluid attenuation inversion recovery (FLAIR) high-intensity lesions involving the cerebellum, brainstem, thalamus and third ventricular peri-ependymal region consistent with demyelination. Both the serum myelin oligodendrocyte glycoprotein-antibodies (MOG-Abs) and cerebral spinal fluid (CSF) anti-*N*-methyl-D-as-partate receptor (NMDAR) antibodies were positive using transfected cell based assays. The patient presented simultaneously with symptoms of MOG antibody disease and anti-NMDAR encephalitis, an unusual clinical scenario, indicating the co-existence of the two disorders.

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a protein expressed at the outermost lamellae of the myelin sheath in the central nervous system (CNS). Antibodies against MOG can be detected in a distinct spectrum of CNS inflammatory demyelinating diseases, with the clinical phenotype partly overlapping neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) or acute disseminated encephalomyelitis (ADEM) (Brunner et al., 1989; Jarius et al., 2016). Patients with MOG antibodies (MOG-Abs) often present with isolated optic neuritis (ON) (Kim et al., 2015). Anti-*N*-methyl-D-as-partate receptor (NMDAR) encephalitis is a severe autoimmune disorder associated with antibodies against the GluN1 subunit of the NMDAR (Dalmau et al., 2011). It typically begins as a fulminant encephalopathy with acute behavioral changes, psychosis, seizures, memory deficits, dyskinesias, speech problems, and breathing dysregulation (Dalmau et al., 2008). Anti-NMDAR encephalitis can occur with demyelinating diseases, especially in those with aquaporin-4 (AQP4)-immunoglobulin G (IgG) (Titulaer et al., 2014; Ran et al., 2017). The coexistence of MOG and NMDAR antibodies is an extremely rare scenario. We report a middle-aged man who initially presented with symptoms of CNS demyelination followed by acute mania that was thought to be due to anti-NMDAR encephalitis, as evidenced by a high concentration of anti-NMDAR antibody in the CSF.

2. Case report

A 54-year-old male was admitted to our hospital with progressive dizziness, unsteadiness and narcoleptic attacks in October 2017. He first complained of light-headedness and intermittent spinning sensations, without nausea or vomiting 2 weeks prior to hospitalization. Additionally, he had intermittent ataxia and unsteadiness. Ten days later, he developed drowsiness and became slow to respond. He was sent to an outside hospital where he was asked to minimize the use of alcohol due to the possibility of Wernicke encephalopathy. He was treated with oral thiamine and intravenous acyclovir, without improvement. He developed intermittent visual hallucinations, and paranoia. He was transferred to our hospital on November 16, 2017. On the fourth hospitalization day, he accused the medical staff of trying to kill him when an EEG was being performed. He verbally and physically attacked the EEG technician and required physical restraint. Seizure activity or abnormal movements, including orofacial dyskinesias, chorea, athetosis, ballismus stereotyped movements or rigidity were not present.

Abbreviations: FLAIR, fluid attenuation inversion recovery; MOG, anti-myelin oligodendrocyte glycoprotein; CSF, cerebral spinal fluid; NMDAR, *N*-methyl-D-as-partate receptor; CNS, central nervous system; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; ADEM, disseminated encephalomyelitis; ON, optic neuritis; AQP4, aquaporin-4; CBAs, Cell-based assays; IVMP, intravenous methyl-prednisolone pulse; IVIG, intravenous immunoglobulins; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LGI1, leucine-rich glioma-inactivated protein 1; CASPR2, contactin-associated protein-like 2; DPPX, dipeptidyl aminopeptidase-like protein 6; GABAR, anti-γ-aminobutyric acid-B receptor

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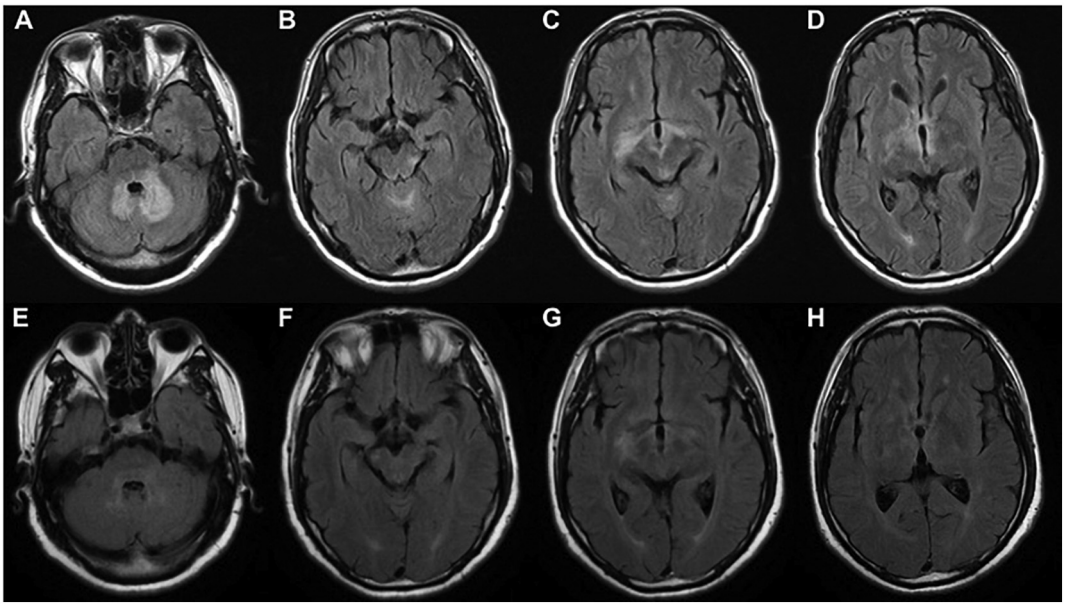

Fig. 1. Brain magnetic resonance imaging of the patient. The upper row (A–D) showed patient's T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging of the brain before the immunosuppressant treatment. There were multi-lesions in the brain, including extensive dorsal brainstem lesion involving the bilateral cerebellum, right cerebral peduncle and the brain parenchyma surrounding the third ventricle. The lower row (E–F) showed FLAIR imaging after one and half a month of immunosuppressant treatment. These slides suggested that lesions in brainstem, bilateral cerebellum and brain parenchyma surrounding the third ventricles have been almost resolved.

Past medical history was otherwise unremarkable. He smoked socially and denied ever using drugs. He was a heavy alcohol drinker, consuming approximately 500 mL of yellow rice or millet wine every day. On admission, a neurologic examination revealed drowsiness and decreased responsiveness. He was oriented to time and place. Cranial nerve examination was normal. Motor exam revealed normal muscle strength. Bilateral Babinski's signs were present. Finger-to-nose and heel-to-shin testing were normal. The gait was unsteady and he could not tandem walk. Romberg sign was positive.

Fluid attenuation inversion recovery (FLAIR) MR imaging revealed multiple lesions in the brain (Fig. 1A–D), without contrast enhancement. An electroencephalogram performed one month after the onset of disease revealed no abnormalities, such as diffuse slow activities or extreme delta brush. A cerebrospinal fluid (CSF) examination showed a normal opening pressure, with mild leukocytosis (28×10^6/L) and protein levels (0.58 g/L, normal range < 0.45 mg/dL). Oligoclonal band in CSF was negative. The IgG index in the CSF was 0.62. CSF cell-based assays (CBAs) for anti -alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1or 2 (AMPAR1/R2), leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein-like 2 receptor (CASPR2), dipeptidyl aminopeptidase-like protein 6 (DPPX) and anti-γ-aminobutyric acid-B receptor ($GABA_BR$) IgG antibodies were negative but positive for NMDAR-IgG (1:32) (Fig. 2C). Serum MOG-IgG tested positive (1:320) (Fig. 2B). Blood tests showed a cholesterol level of 6.76 mmol/L, triglyceride 3.65 mmol/L, and low density lipoprotein 4.01 mmol/L and the erythrocyte sedimentation rate was 16 mm/h. Hematological tests and studies for screening malignancy, including a chest-CT scan and liver, gallbladder, spleen, pancreas and testicle ultrasound, were unremarkable.

Treatment with intravenous benzodiazepines and thiamine was ineffective. A diagnosis of anti-MOG CNS demyelination and anti-NMDAR antibody encephalitis was made. He was treated with intravenous methyl-prednisolone pulse (IVMP) therapy 500 mg per day for 3 days, and intravenous immunoglobulins (IVIG) therapy, 0.4 g/kg per day for 5 days, followed by intravenous rituximab (600 mg (375 mg/m^2)) once a week for 3 weeks. Flow cytometry demonstrate serum levels of CD19 + B cells and CD27 + B cells at 0. Sodium valproate, olanzapine and memantine were given for treatment of mania. He was discharged home on the 21st hospitalization day, with a mild gait disturbance. MOG-Abs in serum (1:320) (Fig. 2E) and anti-NMDAR antibody in CSF (1:10) (Fig. 2F) remained positive. He continued taking low dose oral prednisone. A follow up brain MRI done 2 months after discharge showed significant resolution of most lesions (Fig. 1E–H) and he was symptom free.

Assays for serum and CSF MOG-IgG, AQP4-IgG, NMDAR-IgG, LGI1-IgG, CASPR2-IgG, AMPAR1/R2-IgG and $GABA_B$ R-IgG were carried out at EUROIMMUN Diagnostic Laboratory, China by cell-based indirect immune-fluorescence test(IIFT) employing BIOCHIPs (EUROIMMUN AG, Luebeck, Germany). Written informed consent for publication was obtained from the patient.

3. Discussion

NMOSD is a group of autoimmune inflammatory demyelinating disorders that affect the CNS. In most patients with NMO/NMOSD, AQP4 antibodies can be detected in peripheral serum. (Jarius and Wildemann, 2010) Patients often manifest a relapsing disease characterized by diffuse areas of myelitis and ON. The most characteristic brain MRI findings involve periependymal lesions surrounding the ventricular system, including diencephalic, dorsal brainstem and corpus callosum lesions. (Wingerchuk et al., 2015) However, AQP4 antibodies are not always found in patients with suspected NMO/NMOSD. For those patients, a new antigenic target, MOG, has been identified. The MOG-Abs can be detected by CBAs in patients with inflammatory demyelinating diseases, especially those with seronegative AQP4-antibody NMO/NMOSD. (Zhou et al., 2017b) Approximately 20% of AQP4-seronegative patients can have MOG-Abs. (de Sèze et al., 2016) In contrast to AQP4 antibody positive NMO/NMOSD, MOG-Abs related diseases seemed to have a stronger association with optic nerve dysfunction. The most common manifestations of the disease include ON with symptoms of retrobulbar pain and/or pain with eye movements, followed by myelitis and other symptoms attributable to brain or cerebellar lesions. Patients are more likely to have brain MRI features classified as ADEM-like with deep gray matter lesions (Kitley et al.,