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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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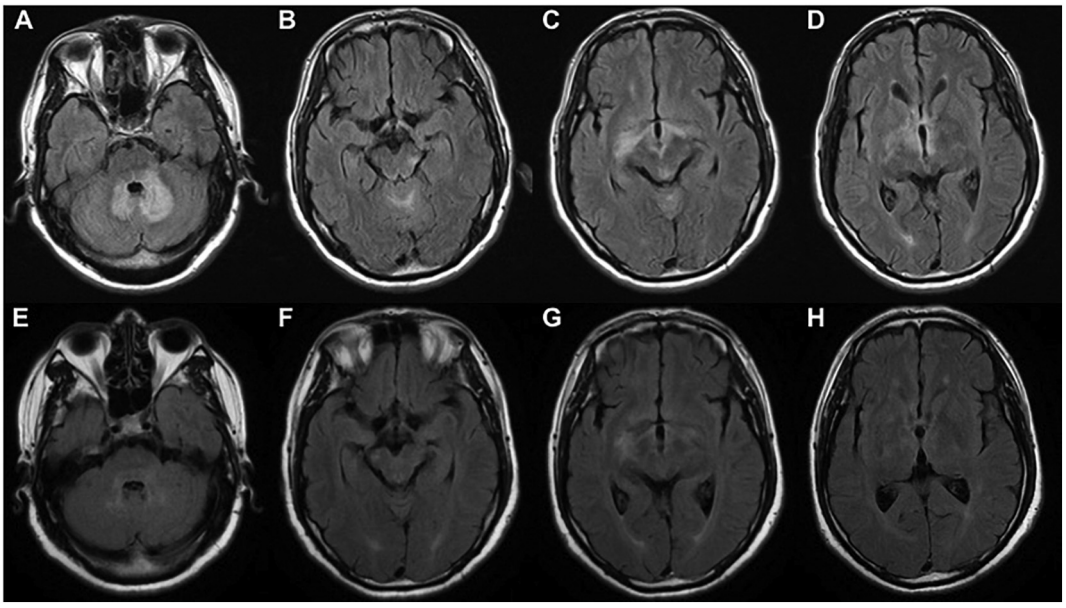

Fig. 1. Brain magnetic resonance imaging of the patient. The upper row (A–D) showed patient's T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging of the brain before the immunosuppressant treatment. There were multi-lesions in the brain, including extensive dorsal brainstem lesion involving 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.,

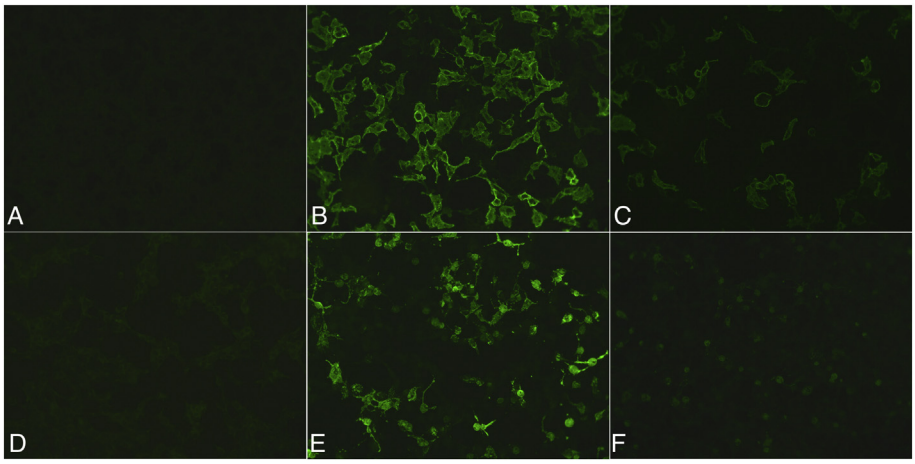

Fig. 2. Anti-MOG in serum and anti-NMDAR antibodies in CSF validated by transfected cell based indirect immune-fluorescence test. A and D were the photos of control-transfected cells. MOG antibodies in serum (B, 1:320) and anti-NMDAR antibodies in CSF (E, 1:32) were positive prior to the initiation of the immunosuppressant treatment. Half a month after the immunosuppressant treatment, the MOG antibodies in serum (1:320) and anti-NMDAR antibodies in CSF (1:10) remained positive, as showed in C and F, respectively.

2014). Extensive optic nerve lesions with anterior enhancement and peri-neural soft tissue enhancement are also common in MOG antibody-positive patients (Zhou et al., 2017b). Our patient initially manifested with unsteadiness followed by progressive narcolepsy which indicated cerebellar and diencephalic involvement. Brain MRI showed diencephalic lesions surrounding the third ventricles and dorsal brainstem lesions involving the cerebellar peduncle, adjacent to the fourth ventricles, without optic nerve involvement. Therefore, a presumptive diagnosis of AQP4-antibody mediated NMOSD was made upon admission. However, serum analysis was negative for AQP4-antibody but positive for MOG-Abs. A diagnosis of MOG antibody disease was established because he did not fulfill the definitive criteria for NMOSD. The intracranial lesions in anti-MOG related diseases are often heterogeneous, with both supra-and infra-tentorial involvement. They can be divided into 3 types: 1) juxtacortical white matter lesions, usually “fluffy” and scattered; 2) midline structure or deep gray matter lesions, commonly located in thalamus, midbrain, pons, around the third ventricle, diencephalon or callosum; and 3) large, edematous white matter lesion (Kim et al., 2015; Zhou et al., 2017b). Lesions that are located at the pontine tegmentum, thalamus or around the third ventricle may be indistinguishable from that of anti-AQP4 NMO/NMOSD lesions, as observed with our patient. The distribution of brain lesions does not reliably distinguish between NMO/NMOSD associated AQP4 and a MOG-antibody mediated disease.

Aside from a positive serum for MOG antibody, anti-NMDAR antibody was also found in the patient's CSF. Most patients with anti-NMDAR encephalitis have normal or nonspecific cortical or subcortical FLAIR/T2 MRI brain abnormalities, but in a few cases, patients can present with extensive demyelinating abnormalities (Titulaer et al., 2014). Symptoms of CNS demyelination such as ataxia, dizziness, tremor, tend to be over-shadowed by protracted unconsciousness, which is a common feature of anti-NMDAR encephalitis. Our patient first manifested with symptoms of CNS demyelination followed by psychosis and behavioral changes that were thought to be symptoms of anti-NMDAR encephalitis. The presence of both serum MOG antibody and CSF anti-NMDAR antibodies indicates that the two diseases can occur simultaneously. Sporadic reports have shown that anti-NMDAR encephalitis might occur with MOG antibody disease sequentially or simultaneously (Titulaer et al., 2014; Ran et al., 2017; Fan et al., 2018). Zhou and co-workers reported one case presenting with cerebral cortical encephalitis followed by recurrent CNS demyelination and a positive serum MOG antibody. Subsequently low titer anti-NMDAR antibody appeared in the CSF without the typical symptoms of anti-NMDAR encephalitis (Zhou et al., 2017a). In Fan et al.'s most recent case series, 2 patients presented with anti-NMDAR encephalitis and MOG antibody disease, with the initial symptoms related to the anti-NMDAR encephalitis rather than MOG antibody disease (Fan et al., 2018). Our patient manifested with an acute brainstem and diencephalic syndrome due to MOG antibody and anti-NMDAR encephalitis simultaneously, clarifying the clinical phenotype of the overlapping demyelinating syndromes with anti-NMDAR encephalitis. The frequency of coexistence of these two types of antibodies might be underestimated, especially in patients with anti-NMDAR encephalitis accompanied by CNS demyelinating lesions, given that these two conditions are not routinely screened or considered by clinicians. A higher incidence might be found if a routine demyelinating antibody test were to be performed in all patients with anti-NMDAR encephalitis and especially in those with CNS demyelinating lesions. Methodology in the detection of MOG antibody should be taken into consideration when interpreting our case. Although we think a false-positive MOG-Abs result was unlikely, we cannot fully exclude that possibility for the following reasons. First, the cell-based assay used by our group employs formalin-fixed cells. Which might result in the formation of neoepitopes. Unfortunately, live-cell assays are currently not commercially available in China. Second, the patient had neither signs of optic neuritis or myelitis as often seen in MOG encephalomyelitis. Third, an association of NMDAR encephalitis and MOG encephalomyelitis has only very rarely been reported, and MOG antibody seropositivity was not confirmed using a second assay in any of the previous cases. While we consider it important to report such rare associations, we agree that more studies are needed before providing definite recommendations regarding routine testing for MOG-IgG in patient with NMDAR encephalitis and vice versa.

It is not clear why both MOG-Abs and anti-NMDAR antibodies were present in our patient. Early viral infections may have played a role in inducing the production of the different types of antibodies. It should also be noted that oligodendrocytes have been reported to contain NMDAR. The immune response that targets myelin proteins may also involve NMDAR at the same time (Lipton, 2006).

The mainstay of treatment of anti-NMDAR encephalitis consists of the use of immunosuppressants, IVIG, and plasmapheresis, either alone or in combination. Corticosteroids, IVIG and plasmapheresis are considered as the first-line therapy, while rituximab and cyclophosphamide are thought to be the second-line agents. Approximately 50% of the patients respond well to first-line immunotherapies while the other 50% of the patients required second-line therapies (Titulaer et al., 2013). Early treatment with rituximab and/or cyclophosphamide seems to be beneficial in both paraneoplastic and non-paraneoplastic anti-NMDAR encephalitis. Furthermore, these patients are less likely to relapse than those who only receive first-line immunosuppressive treatment (Titulaer et al., 2013; Newman et al., 2016). MOG antibody-positive patients appear to have a quicker response to steroids and plasma exchange (Jarius et al., 2016). The effect of second-line therapy including mycophenolate, azathioprine and rituximab in MOG antibody

disease is unknown. Given that anti-NMDAR encephalitis may be associated with catastrophic clinical outcomes, our patient was treated with rituximab after treatment with IVMP and IVIG to prevent disease progression. Seizures, dyskinesias or autonomic dysregulation were not present in our patient, and he fully recovered. It is not known if the mild symptoms related to anti-NMDAR encephalitis in this patient were due to the effect of rituximab or due to the coexistence of MOG-Abs diseases. Therefore, further studies are necessary to investigate the treatment of double-antibody positive patients.

4. Conclusion

The current case suggests that it is crucial for clinicians to be aware that MOG antibody disease and anti-NMDAR encephalitis can occur simultaneously. Thus, it is necessary to evaluate the presence of NMDAR antibodies in patients with typical NMOSD in appropriate patient. More studies are needed to determine the exact relationship between these two diseases.

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Conflicting interest

None.

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