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Case report

Cerebral cortical encephalitis followed by recurrent CNS demyelination in a patient with concomitant anti-MOG and anti-NMDA receptor antibodies

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ABSTRACT

We report the case of a patient who initially presented with fever, headache and seizure. MRI revealed a fluid attenuation inversion recovery (FLAIR) high-intensity lesion involving the right temporal, parietal and occipital cortex. Afterwards, the patient developed three recurrent episodes, manifested as brainstem encephalitis, optic neuritis and ADEM-like illness successively, indicating demyelination. Both of his serum anti-MOG and CSF anti-NMDAR antibodies were proved positive by transfected cell based assays. We consider our case to have cortical encephalitis due to certain autoimmune mechanism initially, and then developed MOG-antibody mediated recurrent demyelination in the following episodes.

1. Introduction

With the introduction of highly specific cell-based assays (CBA), conformation-sensitive antibodies to myelin oligodendrocyte glycoprotein (MOG) are detected in a distinct spectrum of central nervous system (CNS) inflammatory demyelinating diseases (IDDs), with clinical phenotype partly overlapping neuromyelitis optica spectrum disorders (NMOSD) or acute disseminated encephalomyelitis (ADEM) (Jarius et al., 2016). Different types of brain lesions have been described in Chinese Han patients with MOG antibody (Zhou et al., 2017). Recently, unique cortical encephalitis was reported in 5 Japanese cases with MOG antibody, which appeared distinct from the brain involvement previously observed (Ogawa et al., 2017; Fujimori et al., 2017). However, no autoimmune encephalitis (AIE) associated antibody was detected in these 5 cases, leaving the relationship between MOG antibody and the cerebral cortical encephalitis undefined. Herein we report another case manifested as antecedent cortical encephalitis followed by recurrent CNS demyelination and optic neuritis with concomitant anti-MOG and anti-N-methyl-D-aspartate receptor (NMDAR) antibodies.

2. Case report

A 31-year-old man developed fever, headache in early March, 2016. Ten days later, his temperature rose to 39 °C and he experienced a generalized seizure and loss of consciousness lasting for 5 min (Fig. 1). MRI revealed a fluid attenuation inversion recovery (FLAIR) high-intensity lesion involving the right temporal, parietal and occipital cortex (Fig. 2A, B). An electroencephalogram revealed epileptic discharges in the right hemisphere. A cerebrospinal fluid (CSF) examination revealed elevated leucocytes (142 * 10^6/L; 80% mononuclear) and protein (66.9 mg/dL, normal range < 40 mg/dL). CSF antibodies to herpes simplex virus (HSV) I, II, epstein-barr virus, cytomegalovirus (CMV) and rubella virus (RV) were tested, only IgG antibody to HSV I, CMV and RV were positive. He was treated empirically with intravenous acyclovir and dexamethasone (10 mg/d) in the hospital he first visited. The headache and fever relieved quickly and seizure didn't occur again. After discharge, oral prednisone was tapered off quickly within two weeks. Soon the fever and headache flared up in April 2016. CBAs for anti-NMDAR antibodies, anti-voltage-gated potassium channel (VGKC) antibodies, anti-alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptor (AMPAR) antibodies and anti-γ-aminobutyric acid-B receptor (GABA(B)R) antibodies in the CSF and serum were tested and all were negative (Fig. 1). After treatment with methylpredisolone (80 mg/d) for 2 weeks, his symptoms relieved again. However, due to the upper gastrointestinal bleeding caused by duodenal ulcer, he had to stop the steroid treatment. Two months later, the

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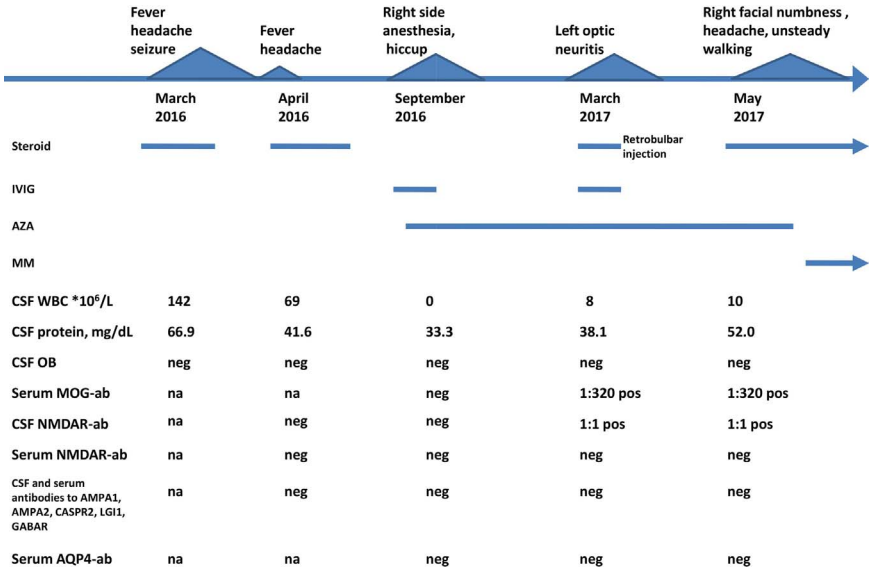

CSF WBC *10^6/L	142	69	0	8	10
CSF protein, mg/dL	66.9	41.6	33.3	38.1	52.0
CSF OB	neg	neg	neg	neg	neg
Serum MOG-ab	na	na	neg	1:320 pos	1:320 pos
CSF NMDAR-ab	na	neg	neg	1:1 pos	1:1 pos
Serum NMDAR-ab	na	neg	neg	neg	neg
CSF and serum antibodies to AMPA1, AMPA2, CASPR2, LGI1, GABAR	na	neg	neg	neg	neg
Serum AQP4-ab	na	na	neg	neg	neg

Fig. 1. The summary of clinical episodes, treatments and immunological examination outcomes. MOG: myelin oligodendrocyte glycoprotein; AQP4: aquaporin 4; NMDAR: N-methyl-D-aspartate receptor; CASPR2: contactin associated protein 2; LGI1: leucine-rich glioma-inactivated 1; AMPAR: anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABAR: anti-γ-aminobutyric acid receptor; CSF: cerebrospinal fluid; IVIG: intravenous immunoglobulin; AZA: azathioprine; MM: mycofenolate mofetil; WBC: white blood cell; OB: oligoclonal band; neg: negative; pos: positive; na: not applicable.

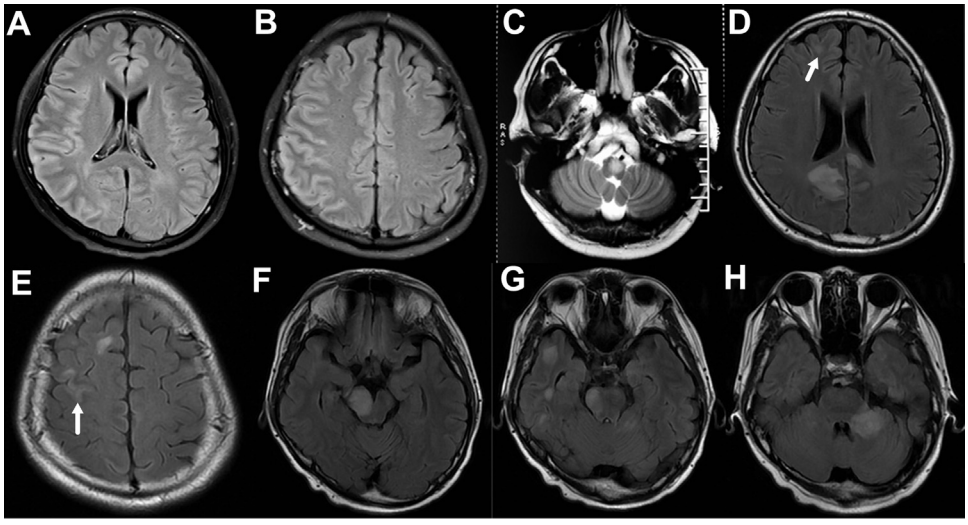

Fig. 2. MRI presentations during different episodes. (A, B) MRI-Flair images showed the right temporal, parietal and occipital cortical lesion in the first episode; (C) Left medulla oblongata lesion on T2WI developed during the second episode; (D–H) MRI-Flair images during the fourth episode: (D) MRI-Flair images showed juxtacortical white matter lesion in frontal and occipital lobe; (E) Focal serpentine cortical lesion as well as juxtacortical white matter lesion in the right parietal lobe; (F–H) Lesions located at right mid brain, pons, left brachium pontis and temporal lobe.

cortical lesion diminished significantly in follow-up MRI.

In September 2016, the patient developed right side anesthesia and continuous hiccup. MRI discovered a new lesion in left medulla oblongata (Fig. 2C). Repeated examinations of CSF and serum NMDAR, VGKC, AMPAR, GABA(B)R antibodies were still unremarkable. Meanwhile, serum anti-MOG and anti-AQP4 antibodies were tested negative. He was treated with IVIG (0.4 g/kg/d) alone for 5 days and azathioprine was initiated.

In early March 2017, the patient felt movement pain and blurred vision in his left eye. His high contrast visual acuity (HCVA) decreased to 0.03 and left optic disc edema was observed. The above mentioned auto-antibodies were re-tested, and this time serum anti-MOG (1:320) and CSF NMDAR (1:1) antibodies were proved positive (Figs. 1, 3). He was treated with IVIG and methylprednisolone retrobulbar injection, and the HCVA improved quickly to 1.0 within 2 weeks.

It was not until May 2017 that the patient came to NMO clinic of Huashan Hospital, when he gradually developed right facial numbness, headache and unsteady while walking. Neurological examination revealed decreased right facial perception, left sided ataxia and nystagmus. MRI revealed ADEM-like multiple lesions located in right mid brain, pons, left brachium pontis and juxtacortical white matter (Fig. 2D–H). Focal serpentine lesion was also observed in the left parietal cortex (Fig. 2E). The serum MOG antibody and CSF NMDAR antibody were re-examined in the same laboratory as previous tests, both were positive (Fig. 1). Blood tests for other systematic autoimmune diseases, vasculitis or sarcoidosis were unremarkable. After reviewing his medical history, we speculated this patient to have autoimmune cortical encephalitis initially, and then developed MOG antibody mediated recurrent demyelination in the following episodes. High dose methylprednisolone pulse therapy (HDMT) was initiated, his symptoms relieved gradually and he was on mycofenolate mofetil (2000 mg/d) now (Fig. 1).

The multiple examinations for MOG, AQP4 and AIE related antibodies in this patient were all performed by the China branch of Euroimmun Medical Diagnostic Laboratory through a fixed cell based indirect immune-fluorescence test (IIFT). (EUROIMMUN AG, Lüebeck, Germany). We obtained written informed consent from the patient. The study was approved by the Medical Ethics Committee of Huashan Hospital.

3. Discussion

MOG antibody was once considered to predict the early conversion of clinically isolated syndrome to definite MS. However, this finding was not further verified. Other early investigations were also questioned as they applied western blot or enzyme-linked immunosorbent

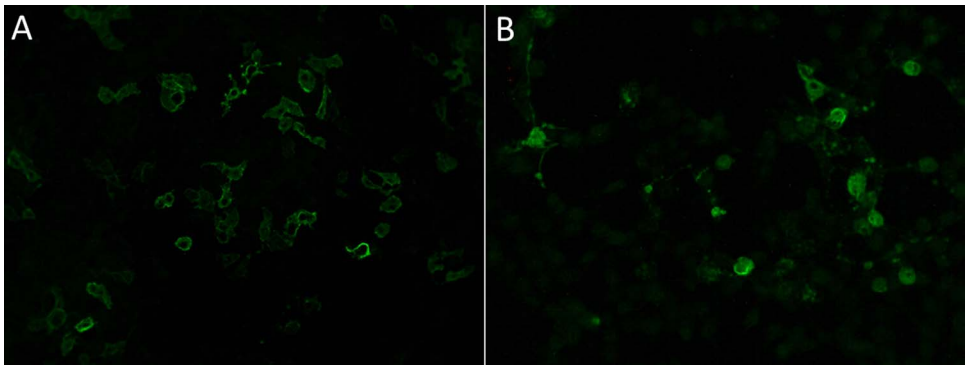

Fig. 3. Positive anti-MOG and anti-NMDAR antibodies validated by transfected cell based indirect immune-fluorescence test. (A) HEK293 cells transfected with full length MOG were stained with the serum of the patient; (B) The patient's CSF was positive for anti-NMDAR antibodies.

assay (ELISA), which actually identified antibodies to denaturated MOG. Recently, several groups using advanced CBA uncovered MOG antibody in pediatric patients with ADEM and adult patients with NMOSD or optic neuritis who were AQP4-ab seronegative. Data from the two largest MOG antibody-positive adult cohorts so far indicate that the majority of patients develop a recurrent disease course with optic neuritis as the most frequent symptom, and the clinical spectrum of MOG-IDDs seems to be broader as previously anticipated, only partly overlapping with NMOSD and multiple sclerosis (Aktas, 2015; Reindl et al., 2017).

The clinical diagnosis of the patient reported here posed substantial difficulties. The initial serpentine cortical lesion was typical of that in AIE, but the anti-NMDAR antibody was not identified until one year later. The CSF positivity of IgG antibodies to HSV I, CMV and RV were not sufficient for the diagnosis of virus encephalitis, although AIE was reported to occur in patients with HSV encephalitis (Prüss et al., 2012). The subsequent episode of brainstem encephalitis indicated a demyelinating event, which leaded to diagnostic challenge based on the negative results of all antibody tests at that time. Diagnostic confusion arose as the cortex encephalitis and the following brainstem encephalitis seemed not to be explained by a single disease. The following attack of optic neuritis provided further evidence of demyelination, and repeated examinations of auto-antibodies at this time point revealed positive anti-MOG and NMDAR antibodies. In the latest episode, the multiple ADEM-like lesions were similar to those reported in MOG antibody positive cases. Taken together, we consider our case to have cortical encephalitis due to certain autoimmune mechanism at first, and then developed typical MOG antibody mediated demyelination in the following three episodes (brainstem encephalitis, optic neuritis and ADEM-like attack).

The diagnosis of MOG-IDDs is definite. However, whether the patient had anti-NMDAR antibody mediated AIE is controversial, as the NMDAR antibody was negative during the episode of headache, fever and epilepsy. Besides, patients with MOG antibody alone can develop cortical encephalitis: recently, Ogawa et al. (2017) described 4 MOG antibody positive cases with benign, unilateral, cerebral cortical encephalitis. Fujimori et al. (2017) reported a MOG antibody positive case with steroid-responsive bilateral frontal cortical encephalitis, and subsequently evolved into an ADEM-like illness and optic neuritis. None of the five Japanese cases had AIE associated autoantibodies. Furthermore, widespread cortical demyelination can be induced in MOG immunized rats following intracerebral injection of TNF-alpha and IFN-gamma (Üçal et al., 2017).

So, how to explain the NMDAR antibody positivity in this patient? It is noteworthy that NMDAR and MOG antibodies became positive simultaneously from the third episode of optic neuritis. Considering that oligodendrocytes do contain NMDAR, it is reasonable to speculate the immune attack targeting myelin may involve NMDAR at the same time (Lipton, 2006). As the patient hadn't presented any AIE related symptoms since the anti-NMDAR antibody turned positive, this antibody might just be an accompanying phenomenon. Further investigations are needed to establish the frequency of cortical encephalitis in anti-MOG antibody positive cases combined with comprehensive antibody testing.

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Conflicts of interest

The authors have no financial conflicts of interest.

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