Anti-Myelin Oligodendrocyte Glycoprotein Antibody-Associated Meningitis with Psychotic Symptoms

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Abstract

Introduction: Anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated encephalitis is a demyelinating central nervous system disease, whose most common clinical manifestations are optic neuritis, myelitis and acute disseminated encephalitis. However, data on psychotic symptoms in anti-MOG antibody-associated meningitis are still limited.

Case description: A 31-year-old female presented with headache, fever, thinking rupture, and dissociative amnesia. Enhancement of the pia mater was found in her magnetic resonance imaging. With antiviral therapies and anti-psychotic treatment, her symptoms didn't disappear until positive anti-MOG IgG antibody was found in the serum and she received steroid therapy.

Conclusion: Psychotic symptoms may be the main manifestation of anti-MOG antibody-associated meningitis. Besides being caused by anti-neuronal antibodies against cell-surface antigens (such as anti-N-methyl-D-aspartate receptor antibodies) and intracellular antigens (such as anti-Hu antibodies), autoimmune psychosis could also occur due to anti-myelin antibodies against MOG. These findings may expand the understanding of this newly described autoimmune disease.

Introduction

The acute onset of psychotic symptoms are common in various disorders such as schizophrenia, acute and transient psychotic disorder, and viral or bacterial encephalitis. Meanwhile, immunological causes have been detected to play an important role in psychosis, which were recently classified under autoimmune psychosis (AP). Significant findings were observed in AP cases: anti-neuronal antibodies against intracellular antigens (e.g. anti-Hu

antibodies) and cell-surface antigens (e.g. anti-N-methyl-D-aspartate receptor [NMDA-R])[2]. MOG antibodies are reported present in 4.0%–7.5% of patients with NMDA-R encephalitis [3]. In such cases, psychotic symptoms can be accounted for by anti-NMDA-R encephalitis, in the context of which paranoid-hallucinatory symptoms are often the presenting complaint [4]. However, the role of anti-MOG antibodies remained unclear, and they were usually not routine examination of patients with psychosis [1].

MOG is a membrane protein that is located on the surface of oligodendrocytes and in myelin sheaths [5]. Anti-MOG antibody-associated encephalitis is an immune-mediated inflammatory disease targeting MOG antigens in the central nervous system leading to demyelination.

Psychotic symptoms have been well studied in other demyelinating diseases. However, MOG-associated demyelinating disease may be distinct from acute disseminated encephalomyelitis, multiple sclerosis and neuromyelitis optica spectrum disorder [6], which has certain particular characteristics such as: (1) clinical manifestations of acute disseminated encephalomyelitis, optic neuritis, myelitis, and brainstem syndrome in most cases [7]; (2) imaging feature such as cortical lesions' hyper-intensity in fluid-attenuated inversion recovery (FLAIR) [8]; (3) cerebrospinal fluid (CSF): white blood cell count has been elevated in more than 50% of CSF samples, and dysfunction of blood-CSF barrier was detected in 48% of the patients [9]; (4) electroencephalography (EEG): non-specific slow waves consistent with the location of cortical lesions; (5)electrophysiological investigations may reveal altered visually evoked potentials (VEPs) in patients with optic neuritis [10]; and (6) pathology: early lesions of demyelination, such as inflammatory changes present in the cortex and subcortex with microglial proliferation in subcortical white matter and peripheral vascular regions [11]. Consequently, anti-MOG

antibody-associated disorders must be identified as a separate disease entity. In 2018, the term MOG encephalomyelitis has been established by Jarius et al.[10], which is characterized by symptoms such as acute optic neuritis, myelitis, (brainstem) encephalitis, or any combination of them. Recently, its symptom spectrum has been expanded, including epileptic seizures, disturbance of consciousness, behavioral changes [10], as well as prolonged fever, which is an important component of the pediatric symptom complex [12]. It has now been described as MOG antibody-associated demyelinating disorders (MOGAD). However, the relationship of psychotic symptoms and MOGAD remains unknown.

We report one case of MOGAD with psychotic symptoms, aiming to discuss the possible relationship between them.

Case description

A 31-year-old female presented with headache and paroxysmal clouding of consciousness, as well as fever with 37.6 ℃ as the highest temperature for 3 days. She also lacked appetite and sleep, talking to herself at random. She underwent lumbar puncture in a local hospital, and her CSF nucleated leukocyte count was 17 × 10^6/L (reference range: 0 – 8 × 10^6/L) without any other significant abnormal result, including magnetic resonance imaging (MRI). Thus, she was diagnosed with viral encephalitis and treated with antiviral therapy for 7 days. She regained consciousness; however, she developed new symptoms of splitting of thought (i.e., irrelevant and intricate answers for the physician’s questions and thinking rupture, such as saying that the ozone layer has been totally destroyed) and dissociative amnesia (i.e., she could identify her parents, son, friends and physicians except for her husband) before admitted to our hospital. At neurological

examination, she showed features of meningeal irritation (particularly stiff neck), while other pathological signs were negative. Lumbar puncture was performed for the second time after admission. Her CSF pressure was 200/165 mmH_2O. CSF analysis showed the nucleated leukocyte count decreased to 2 × 10^6/L, while other biochemistry indicators and routine CSF test results were still normal. Antibodies associated with autoimmune encephalitis in both CSF and serum were was also detected: anti-NMDA-R, anti-leucine-rich glioma-inactivated protein 1, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 and 2, anti- γ -aminobutyric acid-B receptor, anti-contactin-associated protein 2, anti-dipeptidyl-peptidase-like protein 6, and anti-IgLON family protein 5 antibodies. However, all the tests results were normal. Moreover, serological identification showed that her electrolyte, glycosylated hemoglobin, estrogen, cortisol, and thyroid, liver and kidney function were normal. Only pachymeningeal enhancement was observed on T2-weighted FLAIR MRI after gadolinium enhancement (Fig. 1A), with a disorganized alpha rhythm on EEG. She was treated with acyclovir (an antiviral drug) 500 mg every eight hours and paliperidone 6mg qd (once daily) for one week without any significant remission of psychotic symptoms. Subsequently, paliperidone was increased to 9 mg, and acyclovir was used in the next two weeks. Afterwards, she was discharged after totally recovering from dissociative amnesia but only partial remission of splitting of thought. Paliperidone 12 mg qd was continued. However, at the two-month follow-up, she still manifested splitting of thought and talking to herself. Clozapine (maximum dose of 100 mg) was prescribed for more than one month with paliperidone 12 mg qd; however, she had no significant improvements. The patient was readmitted, and lumbar puncture was performed for the third time. She was tested again for antibodies associated with autoimmune encephalitis and demyelinating disease in the central

nervous system and serum (anti-MOG antibodies, anti-aquaporin-1, anti-aquaporin-4, anti-myelin basic protein, anti-glial fibrillary acidic protein, and anti-flotillin-1/2), along with oligoclonal bands. The results showed no obvious abnormalities; however, anti-MOG IgG antibodies were positive in serum, with a titer of 1:10 (reference range: negative), as detected by live cell-based assays. Enhanced MRI showed no increase in the degree of meningeal enhancement compared with the previous one (Fig. 1B). Thus, she was diagnosed with anti-MOG antibody-associated meningitis and treated with intravenous methylprednisolone therapy at a dose of 20 mg/kg for 6 consecutive days. Afterwards, prednisone acetate 55 mg was given to the patient orally with gradual dosage reduction. Clozapine 50 mg qn (every night) was also prescribed for 1 week, decreased to 25 mg qn for the next week, and then withdrawn. After the treatment, her thinking rupture remitted partly for 6 days; however, she recovered totally during the subsequent visit after two weeks. Enhanced MRI showed reduction in pachymeningeal enhancement in the third-month of follow-up (Fig. 1C). She did not present any symptoms and didn't relapse after the 4th month of follow-up. All important clinical events are showed in table 1.

Discussion and conclusions

In this report, we present the case of a patient diagnosed with anti-MOG antibody-associated meningitis, whose main clinical manifestation is thinking rupture. This is the third detailed case report of the patient with psychotic symptoms as well as anti-MOG antibodies (without comorbid anti-NMDA-R encephalitis) [1] and the first wherein immunotherapy was performed according to our literature search.

Previous studies reported that patients with anti-MOG antibodies encephalitis often presented

with comorbid anti-NMDA-R encephalitis [3]; moreover, approximately 9% of patients that had positive serum MOG-IgG antibodies were also positive for CSF anti-NMDAR-IgG antibodies [13]. Patients with anti-NMDA-R encephalitis was reported to have psychotic symptoms. However, patients with psychotic symptoms and have abnormal anti-MOG antibodies were rarely reported. To our knowledge, in previous studies, one case reported a patient with psychotic symptoms (intermittent visual hallucinations and paranoia), positive anti-MOG antibodies and anti-NMDA-R encephalitis [14]. The other two studies respectively reported two patients with anti-MOG antibody-associated psychosis, that were negative for anti-NMDA-R antibodies in both CSF and serum [1,15]. Two patients in the former study presented with acute-onset or chronic paranoid-hallucinatory syndrome [1]. While the latter study reported two pediatric patients with psychiatric disorders before or concomitant with recurrent alternating ON, which is the typical clinical manifestation of MOGAD [15]. Meanwhile, the patient in this case report was characterized with splitting of thought and dissociative amnesia (i.e., she could identify everyone except for her husband, which may be related to the fact that she accidentally found out that her husband was having an affair two weeks before she was became ill). This suggested the diversity of psychotic symptoms of anti-MOG antibody-associated encephalitis or meningitis. It also implied the importance of taking a detailed history of patients with acute-onset psychotic symptoms, especially including fever, headache, and unconsciousness.

The patient, who has symptoms such as splitting of thought and dissociative amnesia, didn’t achieve complete remission with adequate doses of antipsychotic treatment, until she was treated with steroid pulse therapy. This implied the importance of immunotherapy in the treatment of anti-MOG antibody-associated encephalitis or meningitis with psychotic symptoms [16]. However,

the previous case which reported two patients with anti-MOG autoantibody-associated schizophreniform psychosis partly recovered due to treatment with risperidone, olanzapine, and valproate [1]. In that case, MRI analyses revealed no inflammatory lesions, but with pronounced intermittent rhythmic theta activity or disorganised alpha rhythm on EEG. However, one patient experienced recurring auditory hallucinations in stressful situations, while the other's negative symptoms persisted. Accordingly, patients with MOGAD seems to exhibit a rapid response to steroid therapy. Thus, we suggest that immunotherapy should be prescribed as soon as anti-MOG antibody encephalitis or meningitis with psychotic symptoms was confirmed.

Brain nervous system lesions related to MOG antibodies in previous cases mostly involved the brain parenchyma (including cerebral peduncles, pons, medulla oblongata, cerebellar hemispheres, and cerebellar peduncles), optic nerve, or spinal cord [17]. The main radiological sign was enhanced FLAIR signal in the cortical in patients with positive MOG antibody cortical encephalitis [18]. However, the patient in this case showed pachymeningeal enhancement instead of brain parenchymal lesions, with few focal neurological symptoms, which was rarely reported. This is similar to the case reported by Lin S et al. [19], in which brain MRIs revealed no parenchymal abnormality but slight enhancement of the leptomeninges. The usual reported prominent clinical manifestations of these patients include fever, headache, vomiting, and seizures. Nevertheless, the patient in this case showed psychotic symptoms except fever, as well as headache without seizures, which was unusual in MOG antibody-associated aseptic meningitis. Due to the atypical clinical features and CSF/MRI changes, MOG antibody-associated aseptic meningitis may be misdiagnosed as infectious encephalitis in the early stage (such as viral encephalitis), as seen in many cases. Therefore, this rare kind of MOGAD must be considered

especially when the patient presents with fever, headache, and mental disorders with meningitis-like image changes.

From a pathophysiological point of view, anti-MOG antibodies are considered to be pathogenic given their extracellular target being the myelin sheaths [20]. Furthermore, they cause experimental autoimmune encephalitis in animal models [21]. Moreover, the expression of MOG gene appears to be down-regulated in schizophrenia, which resides within a high-susceptibility locus for schizophrenia within the major histocompatibility complex (MHC) locus on chromosome 6p21.3 [22]. These findings may illustrate that anti-MOG antibodies may be responsible for some psychotic symptoms, or schizophrenia may be related to immunity in pathogenesis. However, these results should still be viewed with caution since there was no pathological evidence for demyelination, which leads to the uncertainty of whether encephalitis is caused by MOG antibodies or complications associated with other immune-mediated disease mechanisms.

Our findings prove the complexity of the clinical manifestations of anti-MOG antibody-associated diseases in patients with psychotic symptoms as the primary or main symptom. Thus, this report may expand our understanding of autoimmune psychosis. Besides being caused by anti-neuronal antibodies against cell-surface and intracellular antigens, autoimmune psychosis could also occur due to anti-myelin antibodies against MOG. More research is needed to understand the impact of anti-MOG antibody on psychosis.

Abbreviations

MOG: myelin oligodendrocyte glycoprotein; NMDA-R: N-methyl-D-aspartate receptor; AP:

autoimmune psychosis; FLAIR: fluid- attenuated inversion recovery; CSF: cerebrospinal fluid; EEG: electroencephalography; MRI: magnetic resonance imaging; MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated demyelinating disorders.

Declarations

Data availability statement

The raw data is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from the patient and her husband for the case report. This study protocol was reviewed and approved by West China Hospital Ethics Committee, approval number 941.

Consent for publication

The patient and her husband received a complete description of the report and provided written informed consent to publish. A copy of the signed consent form is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

XFC wrote the first draft of the manuscript. XFC, QY, LYS and ZWS collected the patient data. LML made the contribution to the conception and revised the manuscript. All authors read and approved the final manuscript.

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