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Overlapping syndrome of recurrent anti-N-methyl-D-aspartate receptor encephalitis and anti-myelin oligodendrocyte glycoprotein demyelinating diseases: A case report

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Abstract

BACKGROUND

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARe) is capable of presenting a relapsing course and coexisting with myelin oligodendrocyte glycoprotein antibody (MOGAb) disease, whereas it has been relatively rare. We describe a man with no history of tumor who successively developed ³ anti-NMDAR encephalitis and anti-MOG antibody disease.

CASE SUMMARY

A 29-year-old man was initially admitted with headache, fever, intermittent abnormal behavior, decreased intelligence, limb twitching and loss of consciousness On July 16, 2018. On admission, examination reported no abnormality. During his presentation, he experienced the symptoms aggravated, and the reexamination of cranial MRI indicated punctate abnormal signals in the left parietal lobe. External examination of cerebrospinal fluid and serum results returned: serum NMDAR-Ab (-), cerebrospinal fluid NMDAR-Ab (+) 1:10, EBV virus capsid antigen antibody IgG (+). Due to the imaging findings, anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARe) was our primary consideration. The patient was administrated with methylprednisolone and gamma globulin pulse therapy, mannitol injection dehydration to reduce

intracranial pressure, sodium valproate sustained-release tablets for anti-epilepsy, olanzapine and risperidone to mitigate psychiatric symptoms.

The patient was admitted to the hospital for the second time for "abnormal mental behavior and increased limb movements" on December 14, 2018. Auxiliary examination: reexamination of EEG and cranial MRI showed no abnormality. The results of autoimmune encephalitis antibody returned: serum NMDAR-Ab was weakly positive, cerebrospinal fluid NMDAR-Ab was positive, considering comprehensive recurrent anti-NMDARe, the patient was administrated with propylene-hormone pulse combined with immunosuppressive agents (Mycophenolate mofetil), and the symptoms were relieved.

The patient was admitted for "hoarseness and double vision" for the third time on August 23, 2019. Reexamination of cranial MRI showed abnormal signals in the medulla oblongata and right frontal lobe, and synoptophore examination indicated concomitant esotropia. In such a period, the patient's visual acuity further decreased, and the reexamination of cranial MRI + enhancement reported multiple scattered speckled and patchy abnormal signals in the medulla oblongata, left pons arm, left cerebellum, midbrain, and right thalamus. The patient was recognized to be accompanied with demyelinating disease, and serum anti-myelin oligodendrocyte glycoprotein (MOG) (+) 1:10 and NMDAR antibody (+) 1:10 were examined. Diagnosis: MOG antibody-related inflammatory demyelinating disease of central nervous system complicated with anti-NMDARe overlap syndrome; the patient was administrated with methylprednisolone, gamma globulin pulse therapy and rituximab treatment, and he was ameliorated and discharged. The patient remained asymptomatic and follow-up MRI scan six months showed complete removal of the lesion.

CONCLUSION

We emphasize the rarity of this antibody combination in man and suggest these patients may require longer follow-up due to the risk of recurrence of two autoimmune disorders.

INTRODUCTION

In several individuals, anti-NMDAR encephalitis may occur with MOG antibody disease sequentially or simultaneously [2,4,13]. However, there have been rare reports on recurrent anti-NMDAR encephalitis with MOG antibody disease overlap syndrome worldwide. We present a case of a young man initially admitted with headache, fever, behavioral abnormalities and intellectual decline, followed by hoarseness, blurred vision, disturbance of consciousness, as well as seizures. MRI involved multiple regions (e.g., the parietal lobe, frontal lobe, midbrain, thalamus, cerebellum and medulla oblongata). This case highlights that for patients suspected of having central nervous system demyelinating disease or anti-NMDAR encephalitis, this paper recommends the simultaneous detection of viruses, autoimmune encephalitis-associated antibodies, and central nervous system demyelination-associated antibodies. The aim is to increase the understanding of autoimmune encephalitis overlap syndrome, ³ as their clinical and prognostic features may differ from those of single-antibody disease.

¹CASE PRESENTATION

Chief complaints

A 29-year-old man presented to the Neurology Department of our hospital complaining of headache, fever, intermittent abnormal behavior, decreased intelligence, limb twitching and loss of consciousness. During his presentation, he experienced the symptoms aggravated.

The patient was admitted to the hospital for the second time for the abnormal mental behavior and increased limb movements.

The patient was admitted for hoarseness and double vision for the third time. During his presentation, the patient's visual acuity further decreased.

History of present illness

The patient began to experience symptoms of headache, fever, nausea, and vomiting 7 days before admission, limb weakness, intermittent behavioral abnormalities, and decreased intelligence 4 days before admission, and limb twitching and loss of consciousness 2 days before admission.

History of past illness

The patient had a history of previous surgery for otitis media.

Personal and family history

The daughter of the uncle in the family suffered from lupus erythematosus.

Physical examination

First admission: Clear consciousness, poor orientation to time, place, personality, and poor numeracy, and unremarkable physical examination.

Second admission: Intermittent clear consciousness, uncooperative rest of nervous system.

Third admission: Horizontal movement of eyeball was limited, nystagmus to the left in left vision, nystagmus to the right in right vision, vertical nystagmus in upper and lower visions, decreased lateral acupuncture sensation in bilateral face, weak closure of left eyelid, less sensitive corneal reflex, left central facial paralysis, less powerful elevation of right soft palate, left deviation of uvula, left muscle strength grade 4, less stable finger and nose, decreased tendon reflexes in four extremities, and positive Barthel sign on the left side were identified.

Laboratory examinations

First admission: Immunoglobulin 5 items, mycobacterium tuberculosis antibody detection reported no abnormality. Cerebrospinal fluid (CSF): WBC $40 \times 10^6/L$, total protein 0.4 g/L, glucose 3.12 mol/L, chloride 126.9 mmol/L. External examination of cerebrospinal fluid and serum results returned: serum NMDAR-Ab (-), cerebrospinal

fluid NMDAR-Ab (+) 1:10, cerebrospinal fluid herpes simplex virus antibody (HSV1, II IgG, IgM), rubella virus antibody (RV IgG, IgM), cytomegalovirus (CMV IgG, IgM), EBV virus early antigen antibody IgG, IgM, IgA, EBV virus capsid antigen antibody IgM, IgA were negative, EBV virus capsid antigen antibody IgG (+).

Second admission: The results of autoimmune encephalitis antibody returned: serum NMDAR-Ab was weakly positive, cerebrospinal fluid NMDAR-Ab was positive.

Third admission: Serum anti-myelin oligodendrocyte glycoprotein (MOG) (+) 1:10 and NMDAR antibody (+) 1:10 were examined.

Imaging examinations

First admission: Head MRI, chest X-ray, EEG showed normality. Reexamination of cranial MRI showed punctate abnormal signals in the left parietal lobe(A).

Second admission: Examination of EEG and cranial MRI showed no abnormality (Figure B).

Third admission: Examination of cranial MRI showed abnormal signals in the medulla oblongata and right frontal lobe (Figure C), and synoptophore examination indicated concomitant esotropia. In such a period, the reexamination of cranial MRI + enhancement reported multiple scattered speckled and patchy abnormal signals in the medulla oblongata, left pons arm, left cerebellum, midbrain, and right thalamus (Figure D-F).

A Punctate abnormality in left parietal lobe (first episode) B Normal sagittal position

C High signal intensity was identified in the medulla oblongata in the T2 sagittal view

D High signal intensity shadows were identified in the cerebellum on T1 sagittal view

E High signal intensity was identified in the left medulla oblongata and cerebellum of Flair

F Flair showed hyperintensity in the left pontine arm and left cerebellum

MULTIDISCIPLINARY EXPERT CONSULTATION

Wang Lin, MD, Chief Physician, Department of Neurology, Beijing Xuanwu Hospital. The patient confirmed the diagnosis of anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARe) for first admission. The patient should undergo medical treatment with methylprednisolone and gamma globulin pulse therapy and olanzapine to improve sleep. In addition, this patient required regular re-examination of EEG.

Guan Zhihong, MD, Professor and Chief, Department of Central nervous system infection, Beijing Xiehe Hospital. The patient confirmed the diagnosis of recurrent anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARe) for second admission. The patient had psychiatric symptoms, language disorder, autonomic dysfunction and other symptoms in this attack, which were considered to be comprehensive recurrent type. First, the presence of tumors in the patient's body was assessed, gamma globulin and hormone pulse therapy were standardized in those without tumors, and the hormone dose was reduced to 75 mg, 1 tablet every 2 wk. At the same time, according to the consensus, immunosuppressant (mofetil) 1-2 mg/d, orally for at least one-year, antiepileptic treatment with sodium valproate, and olanzapine increased to 2 mg/time to control psychiatric symptoms.

FINAL DIAGNOSIS

The final diagnosis of the presented case is MOG antibody-related inflammatory demyelinating disease of central nervous system complicated with anti-NMDARe overlap syndrome.

TREATMENT

The patient underwent medical treatment with methylprednisolone and gamma globulin pulse therapy and olanzapine to improve sleep for first admission. The patient was assessed to be tumor-free for second admission and given standard gamma globulin and steroid pulse therapy with a steroid dose reduced to 75 mg, 1 tablet every 2 wk. At the same time, according to the consensus, immunosuppressive agents (mofetil) 1 – 2 mg/day, orally for at least one-year, antiepileptic treatment with sodium

valproate, and olanzapine increased to 2 mg/time to control psychiatric symptoms. Last admission, the patient was administrated with methylprednisolone, gamma globulin pulse therapy and rituximab treatment, and he was ameliorated and discharged.

¹ **OUTCOME AND FOLLOW-UP**

The patient had an uneventful clinical course, whilst dexamethasone was decreased progressively until its cessation. At follow-up visit, one years after ¹ hospital discharge, the patient was asymptomatic, and a MRI scan showed complete removal of the lesion. But we found scattered red rashes on both upper limbs and trunk. Since dermoscopy showed scattered red spots and plaque changes on the glans penis and ventral surface of the extremities, and a few scales, the diagnosis of psoriasis was considered, and halometasone ointment was applied externally.

DISCUSSION

The concept of anti-NMDAR encephalitis was first introduced in 2007 by Dalmau *et al*^[1,10]. MOG antibodies are related to demyelinating diseases of the central nervous system, so the concept of MOG antibody-related demyelinating diseases of the central nervous system (MOG antibody disease) was proposed ^[9,11]. Some patients suffering anti-NMDAR encephalitis have positive serum MOG antibody, and some patients suffering MOG antibody have positive cerebrospinal fluid anti-NMDAR antibody, which is called MOG antibody disease with anti-NMDAR encephalitis overlap syndrome (MNOS) ^[2,12,18]. In several individuals, anti-NMDAR encephalitis may occur with MOG antibody disease sequentially or simultaneously ^[2,4,13]. However, there have been rare reports on recurrent anti-NMDAR encephalitis with MOG antibody disease overlap syndrome worldwide.

Encephalitis is a neurological disorder caused by diffuse or multiple inflammatory lesions of the brain parenchyma. Among them, autoimmune encephalitis generally refers to a type of encephalitis mediated by autoimmune mechanisms^[21]. ⁴ At present, the

proportion of autoimmune encephalitis accounts for 10% -20% of encephalitis cases, of which anti-NMDAR encephalitis is the most common, accounting for about 80%^[16,20]. Autoimmune encephalitis should be differentiated from central nervous system infections caused by herpes simplex encephalitis, epidemic encephalitis B, neurosyphilis, bacteria, fungi, and parasites, Creutzfeldt-Jakob disease, and the presence or absence of opportunistic infectious diseases associated with immunosuppressive agents or anti-tumor^[15,17]. Cerebrospinal fluid antibodies were negative in the acute phase of the above infectious diseases^[14]. In this case, relevant examinations such as cerebrospinal fluid cytology, culture, virus, antibody, cranial MRI, electroencephalogram, tumor screening (tumor markers, chest CT, scrotum, both kidneys, hepatobiliary b-ultrasound), and PET-CT were perfected for differential significance^[18,19]. We report a young man who initially presented with headache, fever, and epilepsy as the first symptoms, followed by behavioral abnormalities, intellectual decline, dyskinesia, and decreased autonomic function, in accordance with the course of "bimodal encephalitis" reported in the literature^[3]. Combined with cerebrospinal fluid NMDAR antibody (+) 1:10, EBV viral capsid antigen antibody IgG (+), negative tumor screening program and other examinations, it was considered to be anti-NMDAR secondary to non-tumor viral encephalitis. The disadvantage of this case is that mNGS was not further refined to identify the presence of other bacterial or viral infections. Five months after improvement of treatment, the patient once again developed psychiatric symptoms and increased limb movements, and the cerebrospinal fluid NMDAR antibody (+) was 1:10. Given the definition of recurrent anti-NMDAR, i.e., new symptoms not able to be explained by other reasons or aggravation of original symptoms were identified 2 mo after the improvement of NMDAR treatment^[4,21], the diagnosis of recurrent anti-NMDAR could be confirmed. Subsequently, the patient developed hoarseness and double vision, and the reexamination of cranial MRI + enhancement indicated new lesions. On the whole, anti-NMDAR was not related to optic nerve damage and sensory disturbance in clinical practice, and patients suffering demyelinating diseases of the central nervous system are considered to be combined

with MRI and clinical manifestations. The detection of serum MOG antibody indicated MOG (+) 1:10, by complying with the diagnostic criteria of MOG antibody disease [5], and then diagnosed as anti-NMDAR encephalitis with MOG antibody disease overlap syndrome.

Characteristics of this case: (1) Etiology: It has been reported in the literature that anti-NMDARe is related to tumors, but the incidence of tumors detected in patients suffering MNOS is small, and the prognosis is good [4,6,21]. The present patient agreed with previous literature reports in which no tumor was detected during a two-year course. (2) Affected population: MOG antibody disease and anti-NMDARe are usually more common in women, and the incidence of MNOS in children is higher than that in adults [2,18]. Though the patient in this case was an adult male, it was relatively rare. (3) Clinical manifestations: The clinical symptoms of recurrent anti-NMDARe are mild, overall manifested as a single symptom, which is mild recurrent [7,21]. Nevertheless, this patient is inconsistent with existing literature reports, showing psychiatric symptoms, language impairment, autonomic dysfunction. At the time of recurrence, with considerable clinical symptoms, i.e., a comprehensive recurrent anti-NMDARe. (4) MRI findings: The cranial MRI of patients suffering anti-NMDARe may be unremarkable, or there may be only scattered cortical and subcortical dot-like abnormalities [1, 7], and the first two episodes in this patient are consistent with the findings in previous reports. All patients suffering MNOS will have supratentorial lesions and less infratentorial lesions [2], but both supratentorial and infratentorial cranial MRI were involved in this patient. (5) Prognosis: The optic nerve injury and encephalitis of this patient recovered completely, thereby not complying with the findings of Titulaer *et al*, who found that patients suffering MNOS had a delayed recovery from demyelinating disease and a more pronounced residual deficit [1]. (6) Complicated diseases: At present, anti-NMDARe secondary to EBV-related viral encephalitis has not been reported worldwide, and psoriasis was reported by dermatoscopy during the half-year follow-up of the patient. Psoriasis [8] is an immune-mediated polygenic genodermatosis, which may be the result of a combination of genetic, environmental and immunological

factors. To the best of the authors' knowledge, there have been no reported related cases worldwide.

CONCLUSION

In clinical practice, for patients suffering suspected central nervous system demyelinating disease or anti-NMDAR encephalitis, this paper recommends simultaneous detection of viruses, autoimmune encephalitis-related antibodies and central nervous system demyelination-related antibodies. First, when the patient has a typical course of "bimodal symptoms", i.e., the first peak has "fever, psycho-behavioral abnormalities, epilepsy" as the symptoms, and the second peak has "psycho-behavioral abnormalities, memory loss, dyskinesia, autonomic dysfunction" as the primary symptoms to consider autoimmune encephalitis secondary to viral encephalitis. Second, when anti-NMDAR patients are identified to develop symptoms involving the optic nerve and spinal cord (e.g., decreased visual acuity, limb motor or sensory impairment), the coexistence of MOG antibody disease should be considered. Third, when patients suffering MOG antibody disease develop encephalitis symptoms (e.g., psycho-behavioral abnormalities or cognitive impairment) and novel lesions seen on cranial MRI, the anti-NMDAR coexistence should be considered.

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