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Case report

Coexistence of anti-NMDAR and anti-IgLON5 antibodies in an autoimmune encephalitis patient: The first case report

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ABSTRACT

Background: The coexistence of autoimmune encephalitis (AE) with multiple neural auto-antibodies is of great clinical significance because overlying antibodies may cause super-position or variation of clinical syndrome, which increases the difficulty of diagnosis and treatment of the disease. To the best of our knowledge, the coexistence of anti-N-methyl D-aspartate Receptor (NMDAR) and anti-IgLON5 antibodies in AE has not been published previously.

Case presentation: A 38-year-old female patient presented to our hospital due to headache and abnormal psychiatric behavior. Based on her clinical manifestations (psychiatric and behavioral abnormalities, involuntary limb movements, and sleep disorders) and laboratory assessment results (positive human leukocyte antigen (HLA)-DQB1*05:01 haplotype, anti-NMDAR, and anti-IgLON5 antibodies), she was diagnosed as AE with coexisting anti-NMDAR and anti-IgLON5 antibodies. After treatment with intravenous methylprednisolone and immunoglobulin, as well as plasmapheresis, her symptoms gradually improved with exception for the sleep disorders. Although oral prednisone acetate and mycophenolate mofetil were continued after discharge, her symptoms of sleep disorders did not improve at 6-month follow-up.

Conclusion: This is the first case of AE co-existing with anti-NMDAR and anti-IgLON5 antibodies. Co-existence of neural auto-antibodies should be considered when patients present with overlapping or atypical symptoms. Special attention should be paid to the treatment of these patients as some anti-IgLON5 encephalitis patients may not benefit from immunotherapy treatment.

1. Introduction

Autoimmune encephalitis (AE) accounts for approximately 10–20% of encephalitis, and is a group of immune-mediated inflammatory brain diseases. Until now, anti-N-methyl D-aspartate Receptor (NMDAR) encephalitis, characterized by the presence of neurological and psychiatric symptoms, was the most common type of AE, accounting for 54–80% of all AE cases [1]. Other

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antibody-mediated encephalitides, such as anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) encephalitis, anti-Gamma-aminobutyric acid-α-receptor ($GABA_AR$), anti-Gamma-aminobutyric acid-β-receptor ($GABA_BR$) encephalitis, anti-Metabotropic glutamate receptor 5 (mGluR5) encephalitis, and anti-Leucine-rich glioma inactivated 1 (LGI1) encephalitis, have also been reported.

Anti-IgLON5 encephalitis is a rare neurological entity that combines autoimmunization with neurodegeneration, which has heterogenous manifestations such as sleep disorder, gait abnormality, bulbar symptoms, as well as cognitive impairment, with or without chorea [2,3]. Most commonly, this disease is diagnosed among elderly patients with no sex predominance [4]. The detection of anti-IgLON5 antibodies in serum or cerebrospinal fluid (CSF) is the necessary element of the diagnosis of this disease.

Co-existing anti-IgLON5 with other neural auto-antibodies in AE is rare. Herein, we report the first case of AE with coexistence of anti-NMDAR and anti-IgLON5 antibodies.

2. Case report

A 38-year-old female patient was admitted to our hospital due to "headache for 20 days and abnormal psychiatric behavior for 8 days". 20 days before admission, the patient developed headache without obvious inducement, accompanied by nausea and vomiting. 8 days before admission, she had a temperature of 39.0 °C, and developed psychiatric and behavioral abnormalities, mainly manifesting as incomprehensible speech, yelling, orthocolosis, and binocular gaze, lasting approximately 40 minutes. Her head computed tomography (CT) and cerebrospinal fluid (CSF) examination results at a local hospital showed no abnormalities. Gram-positive cocci were revealed on blood culture. After treatment with ceftriaxone and vancomycin, the patient's symptoms did not improve, and she was then transferred to our hospital.

On admission, the patient was unable to speak and execute commands. When stimulated by sound and light, the patient began to yell and shout, expressing intermittent repetitive language, fumbling with her right hand and apathetic facial expression, and was unable to respond to verbal commands. She had no previous psychiatric history prior to the illness except a history of insomnia in the previous week. Physical examination of nervous system showed blurred consciousness, frightened expression, voluntary eye opening, without response to verbal commands, and without cooperation to advanced cognitive function tests. Glasgow score was 9 (eye opening 4, verbal response 1, motor response 4); besides, increased muscle tone of four extremities, voluntary movement of the upper limbs (not the lower limbs), retractions of the lower limbs after stimulation, as well as nuchal rigidity were observed. Physical examinations of heart, lung, and abdomen were unremarkable.

Auxiliary examinations were then performed. Lung CT revealed inflammation in both lungs. Cranial magnetic resonance imaging (MRI) (plain scan + enhanced) showed subtle swelling of the left frontal lobe parenchyma on plain T2WI-FLAIR sequence, slight enhancement of the left frontoparietal leptomeningeal membrane on enhanced T2WI-FLAIR sequence (Fig. 1A–C). Her intracranial pressure was 290 mmH_2O. CSF analysis showed normal cell count (red cell 0×10^{6}/L, nucleated cells 14×10^{6}/L), protein, glucose, chloride, lactate, and adenosine deaminase. CSF culture and acid-fast staining were all negative. The CSF next generation sequencing (NGS) examination excluded the intracranial infection (Kingmed, Diagnostics Co, Ltd). Anti-NMDAR antibodies were positive in both CSF and serum (titer of 1:10, cell-based assay, Kingmed Diagnostics Co., Ltd, HEK 293T cells were co-transfected with full-length

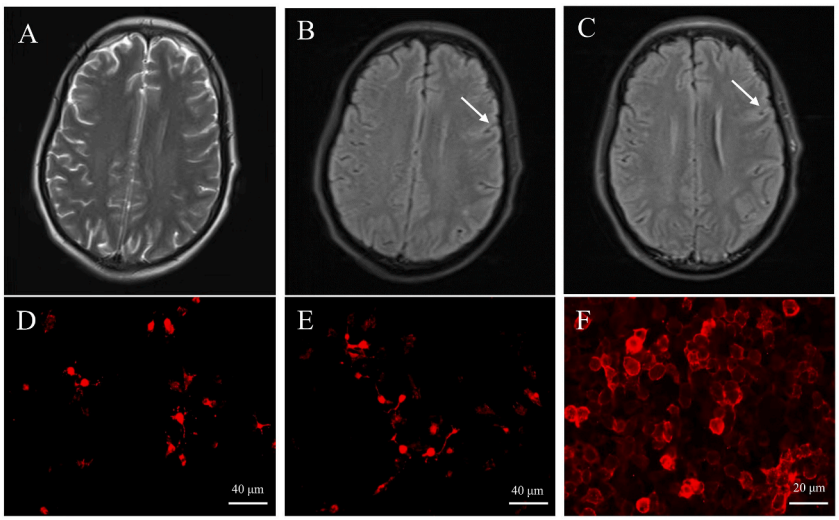

Fig. 1. Cranial magnetic resonance imaging (plain scan + enhanced) and detection of Anti-NMDAR and Anti-IgLON5 antibodies at admission: A. plain T2WI sequence, B. plain T2WI-FLAIR sequence: shows slight swelling of the left frontal lobe parenchyma (white arrow). C. enhanced T2WI-FLAIR sequence: slight enhancement of the left frontoparietal leptomeningeal membrane (white arrow); D. Anti-NMDAR antibody in serum (titer 1:10), Scale bars = 40 μm; E. Anti-NMDAR antibody in CSF (titer 1:10), Scale bars = 40 μm; F. Anti-IgLON5 antibody in serum (titer 1:30), Scale bars = 20 μm.

human NR1A and pcDNA3.1-EGFP using Lipofectamine 2000. The cells transfected 36 h, and were then fixed with 4% paraformaldehyde for 20 min, blocked in 10% goat serum. Patient sample was serially diluted and incubated with the cells for 1 hour at room temperature. Cells incubated with Alexa Fluor 546-conjugated goat anti-human IgG) (Fig. 1D and E); whereas anti-IgLON5 antibodies were found positive in serum only (titer of 1:30, cell-based assay, Kingmed Diagnostics Co., Ltd, HEK 293T cells were co-transfected with a full-length human IgLON5 and pcDNA3.1-EGFP using Lipofectamine 2000. The cells transfected 36 h, and were then fixed with 4% paraformaldehyde for 20 min, blocked in 10% goat serum. Patient sample was serially diluted and incubated with the cells for 1 hour at room temperature. Cells incubated with Alexa Fluor 546-conjugated goat anti-human IgG) (Fig. 1F). Anti-IgLON5 disease associated human leukocyte antigen (HLA)-DQB1*05:01 haplotype was identified in this patient. Mild sleep apnea hypopnea syndrome was diagnosed after sleep monitoring. In addition, high levels of carcino-embryonic antigen (CEA) (5.8ng/ml; normal range: 0–5 ng/ml), carbohydrate antigen 125 (CA125) (40.8U/ml; normal range: 0–35 U/ml) and human epididymis protein 4 (HE4) (79.3 pml/L; normal range: ≤60.5 pml/L) were presented. Other examinations were all unremarkable.

Based on the previous blood culture results obtained from the local hospital, vancomycin and ganciclovir were given for anti-infection and anti-viral treatment, respectively. After being diagnosed as AE with coexisting anti-NMDAR and anti-IgLON5 antibodies, the patient was treated with intravenous methylprednisolone at dose of 1000mg/d, 500mg/d, 250mg/d, and 125mg/d for 3 respectively days, immunoglobulin (0.4/kg/d) for 5 consecutive days, as well as plasmapheresis 2000ml/d for another 5 days. Her symptoms, such as psychiatric and behavioral abnormalities and consciousness disturbance, gradually improved during treatment. No cognitive decline was found after evaluation with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Repeat cranial enhanced MRI suggested that the left frontoparietal leptomeningeal enhancement was alleviated after treatment (Fig. 2A–C).

At discharge, her anti-NMDAR antibodies were negative in both CSF and serum (Fig. 3A and B); whereas anti-IgLON5 antibodies were positive in serum (titer of 1:10) (Fig. 3C). Oral prednisone acetate tablets at dose of 1mg/kg/d, reduced 5 mg per 2 weeks and mycophenolate mofetil 0.75g twice a day were continued. At her 6-month follow-up, the patient's symptoms continued to improve; however, repeat sleep monitoring showed that the total sleep time at night was reduced, sleep efficiency was low, the number of sleep cycles was severely insufficient, the sleep architecture were disorder, and there were involuntary limb movements in the rapid eye movement and non-rapid eye movement stages (Fig. 3D–F). Her serum anti-IgLON5 antibodies were still positive (titer: 1:30).

3. Discussion

Anti-NMDAR encephalitis, commonly seen in children and young adults, is a potentially treatable condition with clinical manifestations such as psychiatric and behavioral abnormalities, involuntary movement, and consciousness decline. Most anti-NMDAR encephalitis patients have prodromal symptoms, such as headache and fever. Currently, the diagnostic criteria of anti-NMDAR encephalitis mainly include the following three points: 1) rapid onset of major symptoms such as abnormal behavior, cognitive dysfunction, speech dysfunction, seizures, movement disorder, consciousness disorder, and autonomic dysfunction; 2) anti-NMDAR antibodies positive in CSF or serum; 3) exclusion of other diseases, such as herpes simplex virus encephalitis and Japanese B encephalitis, that might result in immune-mediated neurologic impairment [5]. Anti-IgLON5 encephalitis is an extremely rare neurological disorder that has complex clinical features, such as sleep disorder, bulbar syndrome, progressive supranuclear palsy-like syndrome, and cognitive impairment with or without chorea. Among these, sleep disorder is the most prominent and important clinical manifestation, which can manifest as insomnia, excessive diurnal hypersomnia, and sleep apnea [6]. Detection of anti-IgLON5 antibodies in serum or CSF is an important diagnostic basis of anti-IgLON5 encephalitis. In addition, anti-IgLON5 encephalitis typically shows a strong association with HLA-DRB1*10:01 and HLA-DQB1*05:01 haplotypes. Unlike anti-NMDAR antibodies, anti-IgLON5 antibodies were more commonly found in serum than in CSF [6–8]. This case had rapid onset of psychiatric and behavioral abnormalities and involuntary movements of the limbs. The patient presented with sleep disorders before and after admission, and she had HLA-DQB1*05:01 haplotype; besides, anti-NMDAR antibodies and anti-IgLON5 antibodies were found in her CSF and/or serum. Therefore, she was diagnosed as AE with coexistence of anti-NMDAR and anti-IgLON5 antibodies.

In recent years, increasing cases with multiple co-existing neural auto-antibodies in AE have been reported, which deserve special

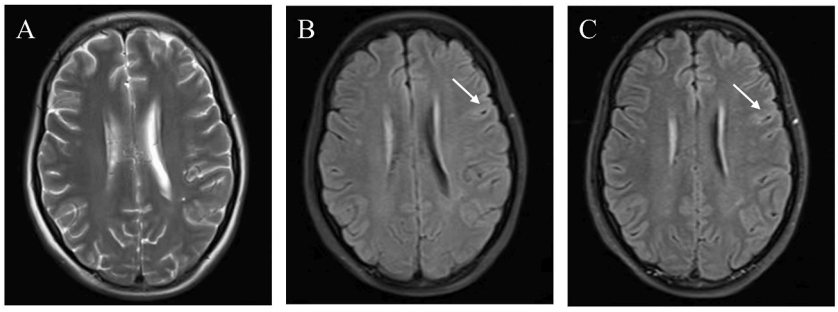

Fig. 2. Cranial magnetic resonance imaging (plain scan + enhanced) at discharge: A. plain T2WI sequence, B. plain T2WI-FLAIR sequence: shows that the swelling of the brain parenchyma in the left frontal lobe is reduced (white arrow). C. enhanced T2WI-FLAIR sequence: shows that the degree of leptomeningitis in the left frontoparietal lobe is reduced (white arrow).

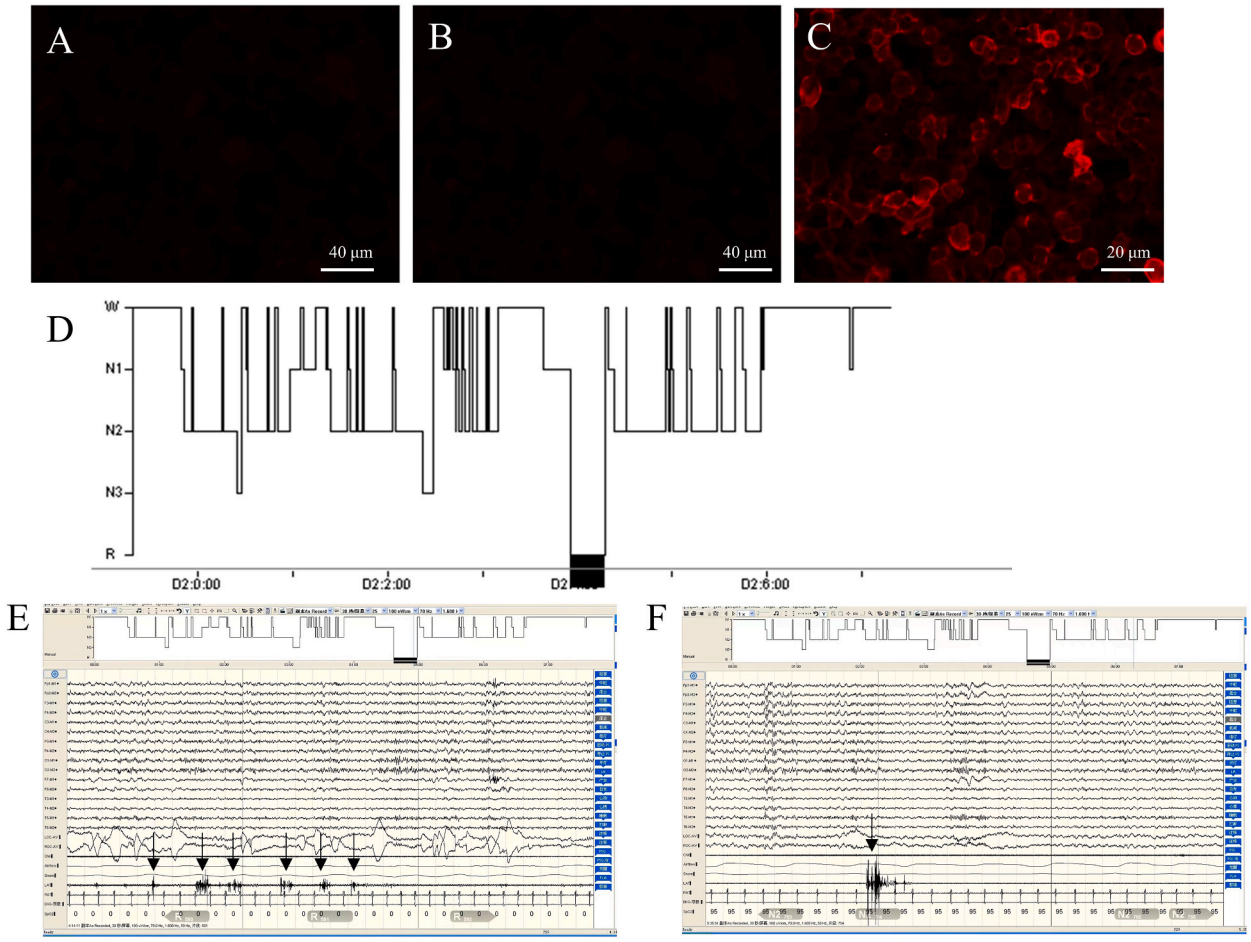

Fig. 3. Detection of anti-NMDAR and Anti-IgLON5 antibodies at discharge, and Hypnogram and Polysomnograhic epochs illustrating each sleep state: A, B. anti-NMDAR antibodies were negative in both CSF and serum, Scale bars = 40 μm; C. Anti-IgLON5 antibody in serum (titer 1:10), Scale bars = 20 μm; D. Hypnogram: sleep structure disorder; E, F : Polysomnograhic epochs illustrating each sleep state: sleep with leg movements that were particularly prominent at the left AT EMG channel (arrows).

attention because the overlying neuronal auto-antibodies may cause superposition or variation of clinical syndrome. Evidences have suggested that there was antibody overlap in 4–7.5% of anti-NMDAR encephalitis patients, and anti-NMDAR antibodies were commonly coexisted with antibodies such as aquaporin 4 antibodies, myelin oligodendrocyte glycoprotein (MOG), antibodies, and anti-glial fibrillary acidic protein antibodies [9,10]. Nevertheless, anti-IgLON5 antibodies coexisting with other antibodies is very rare. Very few cases have been described. For instance, in a multicenter retrospective study, Ni et al. reported two cases of co-existing anti-IgLON5 with other antibodies, one with anti-MOG antibodies and another with anti-LGI1 antibodies [7]. Chung et al. reported one case of AE with co-existing anti-IgLON5 and anti-$GABA_B$ antibodies [11].

Currently, the first-line treatment of AE is the combination regimen of corticosteroids, human immunoglobulin, and plasmapheresis. If failed, second-line treatment, such as rituximab and cyclophosphamide can be used. The effect of immunotherapy is well established in anti-NMDAR encephalitis, but remains inconsistent in anti-IgLON5 encephalitis [7]. In a systematic review, Cabezudo-García et al. reported that only 43.4% of anti-IgLON5 disease patients responded to immunotherapy [12]. Other studies have shown that, when compared with corticosteroids alone or no immunotherapy, the combination of multiple immunotherapy can improve the long-term prognosis and reduce the mortality of anti-IgLON5 disease patients, which was more obvious in patients with HLA-DRB1*05:01 allele [2,13,14]. In this case, the patient received a combination regimen of methylprednisolone sodium succinate, human immunoglobulin, and plasmapheresis during her hospitalization. Except for sleep disorders (the classical symptoms of anti-IgLON5 disease), her symptoms including psychiatric and behavioral abnormalities and involuntary movements of the limbs (common clinical manifestations of anti-NMDAR encephalitis) gradually improved after treatment, which was consistent with her antibody changes (anti-NMDAR antibodies from positive to negative, titer of serum anti-IgLON5 antibodies decreased from 1:30 to 1:10). Although oral prednisone acetate and mycophenolate mofetil were continued after discharge, her symptoms of sleep disorders did not improve, and her titer of serum anti-IgLON5 antibodies increased to 1:30 at her 6-month follow-up, indicating that her anti-IgLON5-antibody-related symptoms may not benefit from short-term immunotherapy treatment. The patient's sleep monitoring

showed sleep architecture were disorder and repetitive leg movements failure to criteria of periodic leg movements, but the anti-IgLON5 encephalitis is a rare and heterogeneity disease, more and more clinical manifestations and auxiliary examination results are being reported, research indicated that polysomnography shows a complex sleep pattern with rapid repetitive leg movements which also do not fit criteria of periodic leg movements. The relationship between anti-IgLON5 encephalitis and sleep disorder is still unclear.

In particular, special attention should be paid to AE patients with multiple co-existing neural auto-antibodies because of the increased risk of developing malignant tumors [15]. Although imaging tests showed no tumor in this case, she had high levels of CEA, CA125, and HE4, indicating a necessity for long-term follow-up for malignant tumors.

4. Conclusion

Herein, we describe the first case of AE with co-existing anti-NMDAR and anti-IgLON5 antibodies. Co-existence of neural auto-antibodies should be considered when patients present with overlapping or atypical symptoms.

Consent for publication

This case report obtained written informed patient consent.

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Data availability

Data are available from the Yu Tian and Lu Wang upon reasonable request and with permission of Guizhou Provincial People's Hospital.

CRediT authorship contribution statement

Yu Tian: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Lu Han:** Writing – review & editing, Writing – original draft, Data curation. **Cameron Lenahan:** Visualization, Validation, Supervision, Project administration. **Tao Wang:** Writing – original draft, Data curation. **Tian Tian:** Visualization, Validation. **Rui Liu:** Writing – review & editing, Validation, Funding acquisition. **Lijuan Liu:** Visualization, Validation, Funding acquisition. **Jian Huang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Lu Wang:** Validation, Project administration, Funding acquisition. **Xiao Hu:** Visualization, Validation, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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