Anti-Leucine-rich glioma-inactivated Protein 1 antibody-associated encephalitis complicated by minimal change nephrotic syndrome: a case report

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Abstract. – BACKGROUND: The aim of the study was to summarize the clinical features, diagnosis and treatment of leucine-rich glioma inactivation protein 1 (LGI-1) antibody-associated encephalitis coexistence of minimal change nephrotic syndrome (MCNS), moreover, to strengthen the awareness of the disease. Increasing number of studies describe coexistence of autoimmune encephalitis and other systemic autoimmune diseases.

CASE REPORT: Here we report a case of a patient with anti-LGI1 antibody-associated encephalitis, who presented with cognitive dysfunction, faciobrachial dystonic seizures (FBDS), sleep disturbance, and hyponatremia. Treatment with immunoglobulins, corticosteroids, levetiracetam and oxcarbazepine was proven effective for this patient. The patient had a history of MCNS diagnosed by renal biopsy and responded to treatment with low dose of oral corticosteroids.

CONCLUSIONS: This case expanded the spectrum of autoimmune comorbidities in patients with anti-LGI1 encephalitis.

Key Words: LGI1, Autoimmune encephalitis, Nephrotic syndrome, MCNS, Case report.

Background

Anti-leucine-rich glioma inactivated-1 protein (LGI1) antibody-associated encephalitis is a type of autoimmune encephalitis that was first reported in 2010 by Lai et al1. It generally presents with faciobrachial dystonic seizures (FBDS), cognitive disorders and abnormal mental behavior. According to previous reports2, anti-LGI1 antibody-associated encephalitis accounts for 11.2% of all kinds of autoimmune encephalitis2, with an estimated incidence of 0.83 per 1 million population. Minimal change nephrotic syndrome (MCNS) is characterized by massive proteinuria and extensive podocyte foot fusion revealed by transmission electron microscopy3. Although anti-LGI1 antibody-associated encephalitis is an autoimmune disease (AD), its predisposing factors are still not very clear. There are only very few reports about the relationship between the nephrotic syndrome and the abnormalities of the central nervous system3. Here we reported a patient with anti-LGI1 antibody-associated encephalitis who has a history of MCNS.

Case Presentation

A 64-year-old man presented with a 2-months history of paroxysmal symptoms and one-month history of cognitive impairment. In September 2019, the patient started experiencing paroxysmal numbness in the left limb without obvious inducement. The symptom could appear several times a day for a few minutes each time and relieve spontaneously. The patient also experienced sleepiness during the same period, with no change in sleep duration. About two weeks later, he de-
developed typical signs of FBDS, involving right corner of the mouth and the right upper limb, which occurred more than 100 times per day and was more prone to occur during the activities. The patient developed lethargy in October 2019, and his sleep time increased significantly to more than 20 hours/day. There were no obvious abnormalities on the electroencephalogram (EEG) and head MRI (Figure 1) that were performed in October 2019. The symptoms did not improve after anti-epileptic therapy, and the patient gradually developed cognitive declination and short-term memory impairment. In November 2019, the patient started suffering from decreased sleep (only slept 2-3 hours per day), he could suddenly get up from a prone position, and sometimes walked unconsciously.

The patient had a history of systemic edema and proteinuria (PRO 3+), and in 2003, the minimal change nephrotic syndrome (MCNS) was diagnosed by renal biopsy. The patient took 50 mg prednisone for 1.5 years. In 2009, he started taking 20 mg dose of prednisolone again for one year because of the elevated urine protein (PRO 1+).

On physical examination, the patient’s mental state was blurred. The scores of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were 13/30 and 10/30, respectively. Frequent paroxysmal symptoms could be seen during the examination and included short right side of face and right upper limb twitching, and a sudden rise from a prone position that lasted for a few minutes. Patient exhibited signs of short-term memory deterioration and decline in the count and executing skills and orientation in time and space. Cranial nerve examination was normal. The muscle strength of all limbs was Medical Research Council’s (MRC) grade 5/5. The muscle tone and tendon reflexes of all the extremities, bilateral Babinski signs and the examination of sensory ataxia were normal.

Re-examination of EEG in November showed full-conducted medium-high amplitude slow wave. No positive epilepsy-like waves were seen. MRI showed mild brain atrophy. Lumbar puncture demonstrated elevated CSF protein of 0.64 g/L without pleocytosis. The LGI1 antibody of CSF and serum was positive (1:32 and 1:100, respectively), and the NMDA-R-Ab, CASPR2-Ab, GABA2-R-Ab and GAD65-Ab of CSF were all negative. The patient was then diagnosed with anti-LGI1 antibody-associated encephalitis. IVIG (0.4 g/Kg/d) was given for 5 days, followed by intravenous drip of methylprednisolone (80 mg for 7 days and 40 mg for another 7 days). Then the immunotherapy was changed to 45 mg of prednisone orally once a day and 0.25 g of mycophenolate mofetil dispersible tablets orally twice a day. Levetiracetam and oxcarbazepine were given to control the paroxysmal symptoms. The patient’s paroxysmal symptoms were significantly reduced after the treatment, time and space orientation and memory were significantly improved, and computing abilities returned to normal. Repeated MMSE was 22/30. After the discharge from the hospital, the patient received oral administration of mycophenolate mofetil dispersible tablets and prednisone.

**Conclusions**

According to previous studies, the peak age of onset of anti-LGI1 antibody-associated encephalitis is between 61 and 64 years, and men account for 55-66% of the total number of patients. FBDS is one of the characteristic manifestations of anti-LGI1 antibody-associated encephalitis, mainly characterized by involuntary contraction of the face and the upper or lower extremity, which lasts for several seconds and may occur up to 100 times a day. These symptoms often occur before the onset of cognitive impairment.
Timely start of immunotherapy may prevent the development of borderline encephalitis. Thompson et al. found that only 10% of all patients used antiepileptic drugs to control the onset of FBDS despite the fact that in up to 51% of the patients FBDS onset was stopped 30 days after starting immunotherapy.

Hyponatremia is present in 60% of patients with anti-LGI1 antibody-associated encephalitis. Brain MRI showed that two-thirds of patients present with T2 hyperintensity in the middle temporal lobe. FBDS and hyponatremia were both consistent with the performance of the patient in the case described in our study. The patient received oral sodium valproate and levetiracetam before hospitalization with a negative effect. After the hospitalization, IVIG and hormone levels of the patient had significantly improved.

Severe sleep disturbance is a rare manifestation of anti-LGI1 antibody-associated encephalitis and is characterized by the difficulty falling asleep or maintaining a normal sleep. It is currently believed that the disruption of physiological regulation of arousal sleep may be related to abnormal changes in the potassium channels. The patient in our study started experiencing a reduction in sleep half a month before admission, sleeping only 2-3 hours a day. Patient's clinical symptoms, blood and cerebrospinal fluid analysis confirmed the diagnosis of the anti-LGI1 antibody-associated encephalitis.

The exact pathogenic mechanism of anti-LGI1 antibody-associated encephalitis is still unclear. Unlike most AEs, such as anti-NMDA receptor encephalitis, where the main antibody subtype is IgG1, the main antibody of the anti-LGI1 antibody-associated encephalitis is IgG4. IgG4 cannot activate complement and is not as effective as IgG1 when cross-linking and internalizing target antigens.

Previous studies have shown that the presence of one AD increases the chance of another AD occurrence in patients. Other studies reported the coexistence of AE and other AD, such as Hashimoto’s thyroiditis (HT), systemic lupus erythematosus (SLE), allergic purpura, vitiligo, Sjogren’s syndrome (SS), chronic urticaria, bullous pemphigus, Uveitis, myasthenia gravis (MG).

MCNS is a common cause of primary nephrotic syndrome and is an autoimmune disease. However, it is rare for nephrotic syndrome to be related to abnormalities of the central nervous system. Differential diagnosis of MCNS includes PEHO syndrome (Progressive encephalopathy with Edema, Hypsarrhythmia and Optic atrophy), ARC syndrome (arthrogryposis, renal tubular dysfunction, cholestasis), Senior-Loken Syndrome (SLS), CDG syndrome (congenital disorders of glycosylation) and Galloway-Mowat Syndrome (GMS).

The kidney is one of the most frequently affected organs in IgG4-related disease. In a previous case, an elderly patient was diagnosed with thymoma-associated MG and anti-LGI1 antibody-associated encephalitis accompanied by muscle rigidity, and MCNS after thymectomy. Another case reported a patient with IgG4-related disease who developed MCNS. This case is the first report of a male patient that had a history of MCNS and was diagnosed with LGI1 antibody-associated encephalitis, which raises several questions. Does our observation indicate that LGI1 encephalitis is associated with MCNS? Is IgG4 the possible link between LGI1 encephalitis and MCNS? Since MCNS affects the glomeruli rather than the tubules, does this suggest possible LGI1 protein distribution in the glomeruli?

In summary, LGI1 antibody-associated encephalitis is rare, and its cause is still unknown. We report a case of a patient with a clear previous diagnosis of MCNS that was treated for anti-LGI1 antibody-associated encephalitis. The patient has clinical characteristics of FBDS, hyponatremia and was blood- and cerebrospinal fluid- anti-LGI1 positive. The treatment with IVIG, prednisone and mycophenolate mofetil achieved an obvious short-term effect. Continuous long-term follow-up of this patient is needed to assess the long-term prognosis and a risk of recurrence. More similar cases will need to be studied to better define the association between MCNS and anti-LGI1 antibody-associated encephalitis.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Ethics Approval
The study was approved by the Institutional Ethical Committee of The First Hospital of Yulin City.
Informed Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of Data and Materials
All data generated and analyzed during this study are included in this article.

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Authors’ Contribution
NG examined, evaluated the patient and drafted the manuscript. WJZ and NG analyzed the neuroimages. WJZ participated in the design of the case report and helped to draft the manuscript. All authors read and approved the final manuscript.

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