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Case report

Anti-IgLON5 disease with severe central sleep apnea-hypopnea syndrome: A case report

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ABSTRACT

Anti-IgLON family protein 5 (IgLON5) antibody-related encephalitis is a rare but increasingly recognized central nervous system autoimmune disease. It displays heterogeneity in clinical presentation. As the clinical case repository expands, our understanding of the disease's clinical phenotypes and therapeutic approaches continues to evolve. This report details a 73-year-old male's case, initially misdiagnosed with narcolepsy due to excessive daytime sleepiness and sleep-related involuntary behaviors, but later found to have severe respiratory disturbances, diverging from narcolepsy. During treatment, the patient's condition progressed to respiratory failure, necessitating further investigation. Diagnosis was confirmed through positive serum and cerebrospinal fluid (CSF) tests for anti-IgLON5 antibodies. Treatment with continuous positive airway pressure (CPAP), immunoglobulin pH4, and corticosteroids significantly improved his condition. This case underscores the critical need for awareness of anti-IgLON5 encephalitis within the differential diagnosis of complex sleep disorders, highlighting its potential for severe progression and the challenges associated with its diagnosis.

1. Introduction

Anti-IgLON5 antibody-type autoimmune encephalitis was first described and characterized by Sabater et al., in 2014 [1]. The disease is predominantly characterized by progressive sleep disorder, complemented by a spectrum of neurological manifestations, including bulbar dysfunction, abnormal gait, chorea, and cognitive decline, among other nonspecific symptoms [2]. The pathogenesis of this disease is still unclear. Some researchers suggest that the pathogenic mechanism may involve a pronounced inflammatory response driven by antibody activity leading to neurodegeneration or that a continuous pathological accumulation of tau protein may aggravate the autoimmune response. The disease is closely related to HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles, underscoring a complex interplay between genetic factors and immune responses in the disease's etiology [3]. Given the limited reports on this disease, there is a pressing need to augment the repository of case reports and studies to enrich our comprehension of this condition. In this context, we present a case encountered in our clinical practice, aiming to contribute to the broader understanding of anti-IgLON5 disease.

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2. Case report

A 73-year-old man presented recurrent episodes of twitching at the corners of his mouth and in his face, along with involuntary movements of his upper limbs during sleep for one year. His wife described him as prone to dozing off when alone and not talking, followed by involuntary facial twitching and upper limb movements. These manifestations included lip smacking, pouting of the mouth, chewing, and repeatedly waving his hands, sometimes accompanied by talking to himself. These symptoms spontaneously ceased upon awakening, and he was conscious but had no recollection of the preceding twitching. There was no intervention before he was admitted. He had a one-year history of coronary heart disease and no prior history of seizures.

No apparent abnormalities were found during the neurological examination. The chest CT scan revealed a minor infection in the upper lobe of the right lung and the lower lobe of both lungs (Fig. 1). Cranial magnetic resonance imaging (MRI) revealed multiple punctate signals, slightly hyperintense in T1 and T2 sequences, in the bilateral frontoparietal lobes, periventricular areas, and the deep white matter of the basal ganglia. Multiple dilated perivascular spaces are observed in the bilateral basal ganglia regions. Bilateral hippocampal signal intensity was slightly increased on T2-weighted imaging (T2WI) (Fig. 2). The electroencephalogram (EEG) indicated slight abnormalities without typical interictal epileptiform discharges. In the awake state, he exhibited intermittent involuntary movements of the lower jaw and both upper limbs. Synchronized EEG showed movement artifacts without typical abnormal wave discharges (Fig. 3). Initially diagnosed with narcolepsy, further assessment during hospitalization revealed severe respiratory disturbances. The polysomnography (PSG) revealed a total of 115 respiratory pause episodes, comprising 76 episodes of obstructive sleep apnea, 22 episodes of central sleep apnea, and 17 episodes of mixed-type sleep apnea. Additionally, there were 990 episodes of hypopnea, with 923 episodes of central hypopnea and none of obstructive hypopnea. The apnea-hypopnea index (AHI) was calculated at 133.1/hr (normal is less than 5/hr), with a corresponding respiratory disturbance index of 133.1/hr. The average oxygen saturation during sleep was 69 %, with a minimum oxygen saturation of 43 %. There was no significant periodic limb movement during sleep. Furthermore, analysis of sleep architecture indicated a reduction in both deep sleep and REM sleep stages. These findings are consistent with central sleep apnea-hypopnea syndrome (Fig. 4).

After admission, he was administered a comprehensive treatment regimen that included lipid-lowering therapy, plaque stabilization, nutritional support for nerve health, correction of electrolyte imbalances, and enhanced respiratory management. Based on his clinical presentation, cranial MRI, and PSG results, we cannot rule out the diagnosis of autoimmune encephalitis. We communicated with the patient's family about the necessity of a lumbar puncture, but the family did not agree. On the eighth day of hospitalization, he exhibited significant clinical deterioration, manifesting as a coma, disturbance of consciousness, and an exacerbation of pulmonary infection. Blood gas analysis showed a partial pressure of carbon dioxide (PCO_2) of 112 mmHg and a partial pressure of oxygen (PO_2) of 69 mmHg, indicative of type II respiratory failure. Given the severity of his condition, he was urgently transferred to the intensive care unit (ICU) for advanced support following endotracheal intubation.

He underwent a lumbar puncture in the ICU. The CSF routine analysis revealed normal cell counts, with both white blood cell and nucleated cell counts being zero. However, the CSF biochemical analysis showed a decreased chloride level of 117.5 mmol/L. Additionally, the CSF immunoglobulin profile indicated elevated levels of IgA and IgM, with IgM at 1.10 mg/L and IgA at 7.71 mg/L. Autoimmune encephalitis antibodies in the serum and CSF, detected by cell based assays (CBA), showed strong positivity for anti-IgLON5 antibodies. The titer of the antibodies in both serum and CSF was 1:300 (Fig. 5). This finding led to a definitive diagnosis of anti-IgLON5 disease. Given the significant titers of anti-IgLON5 antibodies detected in both serum and CSF, plasmapheresis was considered a therapeutic option. However, due to the severe mental disorder symptoms, he was unable to cooperate with catheterization and plasmapheresis therapy was not performed. Consequently, an alternative treatment regimen was initiated, consisting of

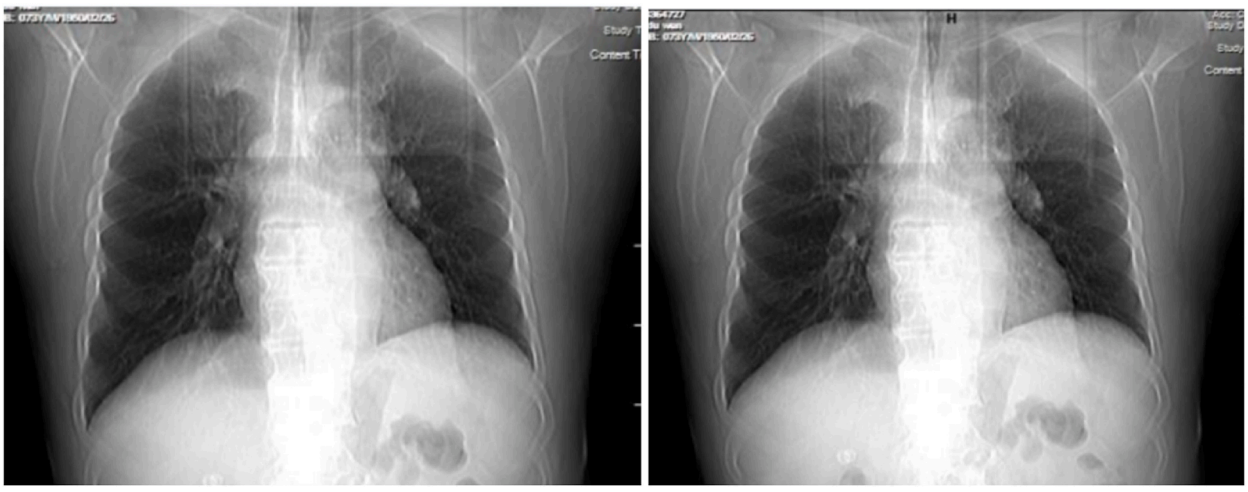

Fig. 1. Plain CT scan of the chest.
The plain chest CT scan reveals mild inflammation in the right upper lobe and both lower lobes of the lungs.

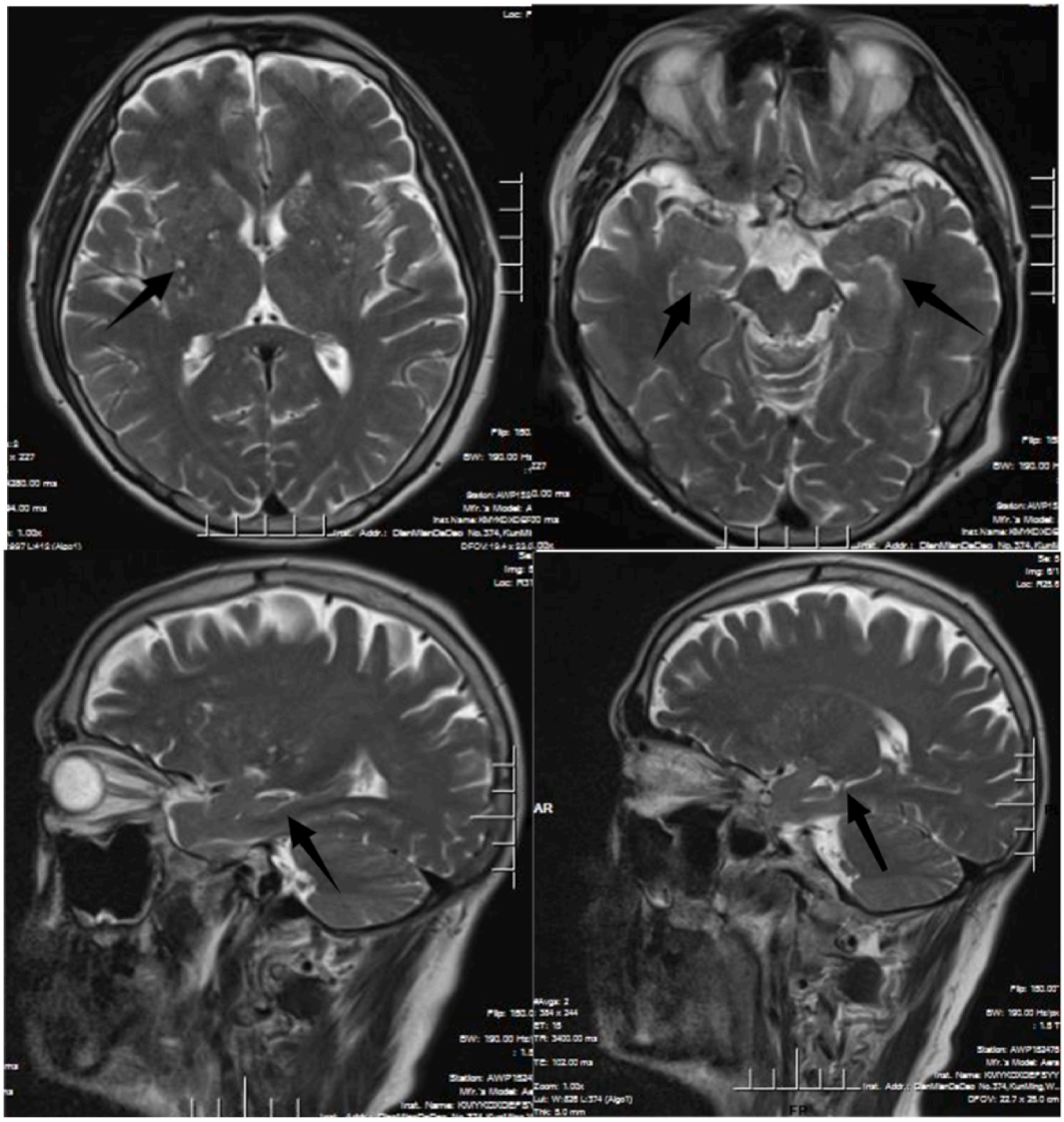

Fig. 2. Magnetic resonance imaging findings.
Cranial MRI shows multiple punctate hyperintensities in the deep white matter of the basal ganglia on T2-weighted images, as well as multiple dilated perivascular spaces; the signal intensity in the bilateral hippocampi is slightly elevated on T2WI.

intravenous immunoglobulin PH4 therapy at a dosage of 0.4 g/kg body weight daily for five days, alongside methylprednisolone pulse therapy for its anti-inflammatory effects. The methylprednisolone dosage was systematically reduced by half every three days. Remarkable improvement was observed following five days of immunotherapy; he was successfully extubated and transitioned to the general ward. Since being transferred to the general ward, he has frequently exhibited symptoms of agitation and incoherent speech, which are particularly pronounced at night. Occasionally, he experiences visual hallucinations and even demonstrates aggressive behavior. These manifestations led to the diagnosis of a cerebral organic mental disorder and pulmonary encephalopathy. Administration of olanzapine at a dosage of 5mg nightly resulted in significant amelioration of the psychiatric symptoms.

Following a five-day regimen of immunotherapy, combined with CPAP treatment, he demonstrated clinical improvement. There was a decrease in the frequency and intensity of his facial and limb twitching episodes compared to the baseline observations prior to treatment initiation. Additionally, there was a significant reduction in his excessive daytime sleepiness.

3. Discussion

Anti-IgLON5 disease is a progressive central nervous system disorder with insidious onset. It is more commonly observed in middle-aged and elderly patients, typically presenting as a subacute course, with considerable individual variation in clinical manifestations [4]. Currently, there are no definitive diagnostic criteria for this disease. Serum and CSF testing for anti-IgLON5 antibodies are crucial

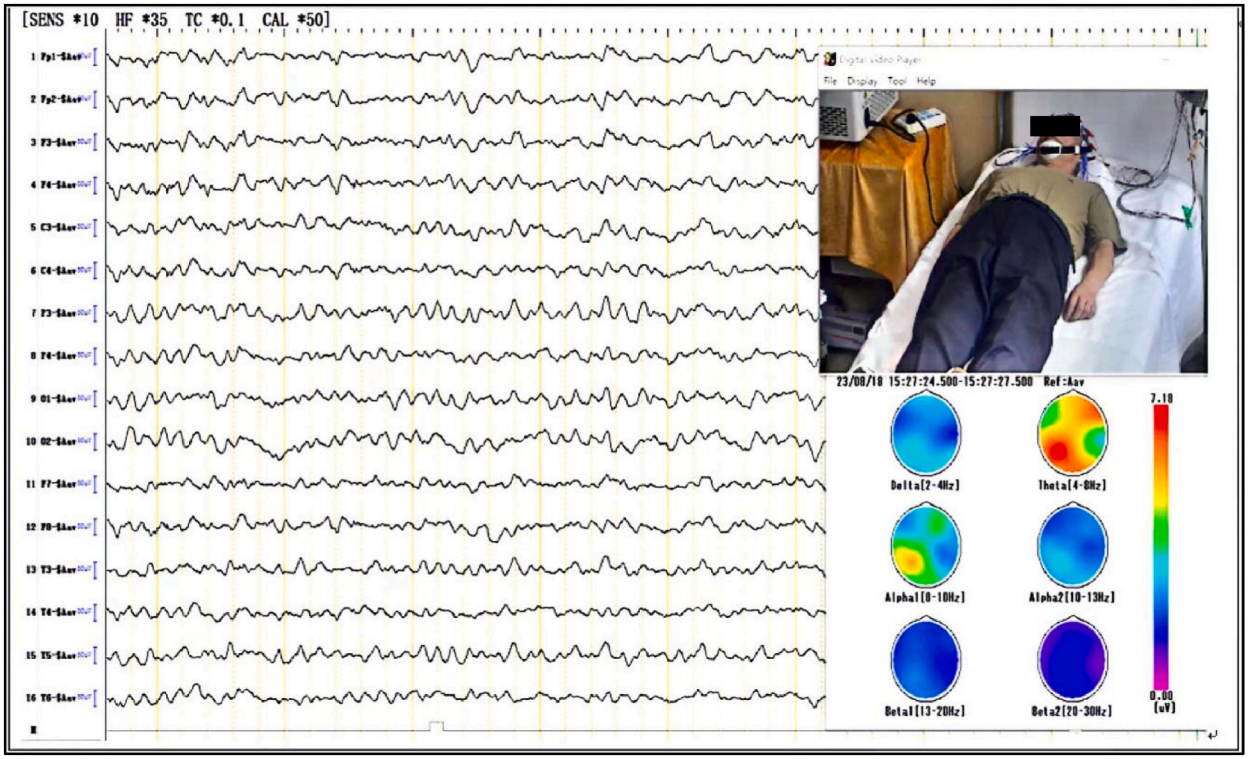

Fig. 3. Electroencephalogram. The EEG shows mild abnormalities, with no typical interictal epileptiform discharges. The alpha wave frequency is slowed, with poor amplitude and rate modulation. The amplitudes of the waves in the right occipital, parietal, central, and temporal regions are lower than those on the opposite side. The low to medium amplitude theta slow waves are slightly increased, with the focus on the frontal region, and are generally symmetrical on both sides.

for confirming the diagnosis of this condition. Sleep disorders are characteristic features of IgLON5 disease, including REM sleep behavior disorder, daily sleep attacks, non-REM parasomnia, and sleep disorder breathing [5]. Most of the reported cases of sleep disorder breathing are obstructive sleep apnea. The current case report details a patient who exhibited severe central sleep apnea, escalating to respiratory failure and pulmonary encephalopathy, alongside psychiatric manifestations. It has been noted in the literature that central hypoventilation may lead to mortality in anti-IgLON5 disease patients [6], underlining the critical nature of recognizing and managing these complex clinical scenarios. The symptomatic manifestations observed in the patient may be intricately linked to the deposition of hyperphosphorylated tau protein within the medulla oblongata. Some researchers deem that IgLON5 dysfunction induced by anti-IgLON5 antibodies may disrupt the interaction of this protein with the internal cytoskeletal network, destabilize the neuronal microtubular system, and induce hyperphosphorylation and accumulation of the microtubule-associated protein tau, leading to neuronal dysfunction [7]. The pathological aggregation of hyperphosphorylated tau protein, notably within the hypothalamus and the midbrain tectum—including key nuclei governing sleep regulation—has been implicated in the pronounced sleep disturbances characteristic of patients with anti-IgLON5 disease [8]. Most patients with anti-IgLON5 disease have normal or mildly abnormal cranial MRI, with some showing high signals in the hypothalamus, brainstem, or hippocampus [4]. The patient we are reporting had abnormal high signals in the basal ganglia and hippocampus.

Immunotherapy is commonly utilized in patients with anti-IgLON5 disease; however, the effectiveness of immunotherapy in treating this condition remains a topic of debate. Previous studies reported very low patient response to immunotherapy [2]; However, recent research has described patients responding well to this treatment [9]. In the case under discussion, notable symptomatic alleviation was observed within five days post-initiation of a combination therapy regimen incorporating both immunoglobulins and corticosteroids. This observation aligns with a recent perspective. Some researchers have suggested that combination therapy appears more effective. Additionally, patients with cognitive impairment, non-classical phenotypes, and the presence of HLA-DQB1*05:01 but not HLA-DRB1*10:01 exhibit a better response to immunotherapy [9]. The timing of intervention plays a critical role, with early treatment initiation yielding more beneficial outcomes. Nonetheless, the intrinsic challenges associated with the early detection of anti-IgLON5 disease—attributable to its rarity, insidious onset, and clinical heterogeneity—necessitate further research to optimize diagnostic and therapeutic approaches.

4. Conclusion

Anti-IgLON5 disease is a rare condition that is prone to misdiagnosis and is characterized by significant variability in clinical

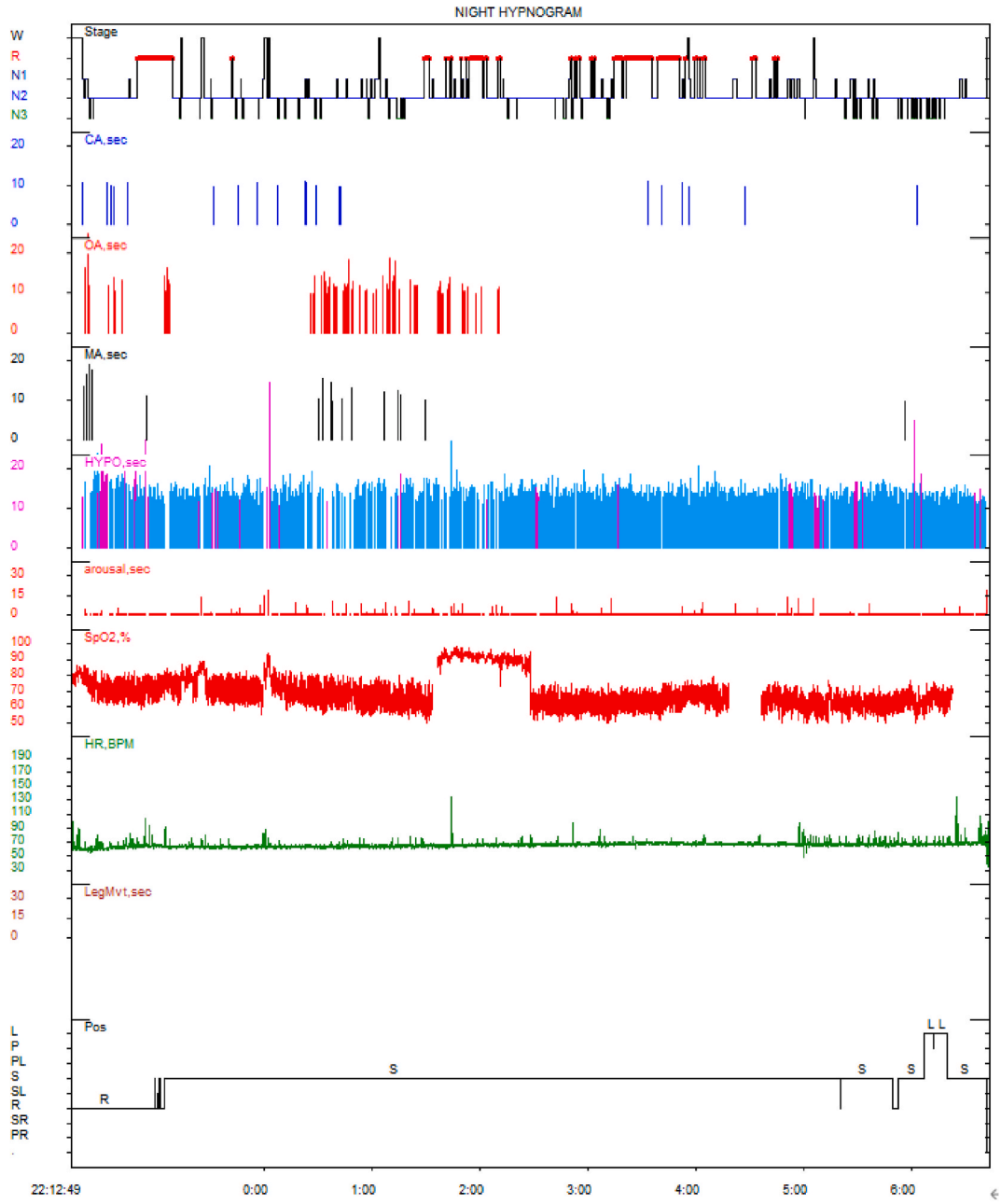

Fig. 4. Polysomnography. [CA (central apnea), OA (obstructive apnea), MA (mixed apnea), HYPO (hypopnea), arousal (awakening event), SpO2% (oxygen saturation), LegMvt (motor event), Pos (posture)]
As shown in the figure, the patient exhibits a reduction in the proportion of REM and N3 sleep stages. Sleep stages are fragmented, with frequent transitions between N1, N2, and N3. Central, obstructive, and mixed apneas are present, and hypopnea is severe during sleep.

presentations. Sleep apnea-hypopnea syndrome is one of the common clinical manifestations of anti-IgLON5 disease, with severe cases posing life-threatening risks. Through the presentation of a clinical case, our article further corroborates this relationship. It focuses on describing central sleep apnea-hypopnea syndrome, providing practical insights into its treatment and illustrating the potential severity of anti-IgLON5 disease progression. This contributes to an enhanced understanding of the individual-level manifestations of this condition. Currently, there are no definitive diagnostic criteria for this disease. When suspicion arises, it is imperative to conduct comprehensive CSF and PSG analyses along with anti-IgLON5 antibody testing to facilitate early diagnosis and treatment, thereby reducing mortality rates and improving prognosis. Furthermore, there is a need for multicenter, large cohort follow-up studies to summarize the clinical manifestations, disease progression, treatment methods, and outcomes of this condition. Such studies will enhance our understanding of the disease's evolution and lead to the development of standardized multidisciplinary treatment and

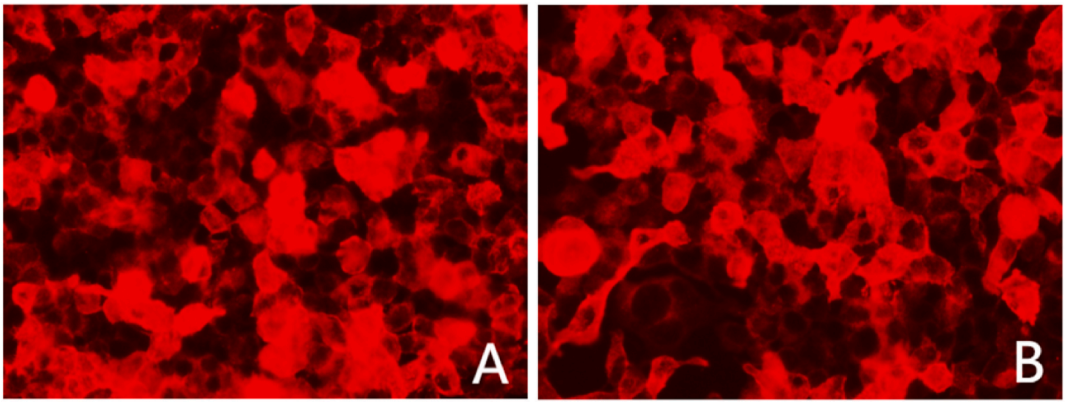

Fig. 5. Autoimmune encephalitis antibody detection
Figures A and B shows strong positivity for anti-IgLON5 antibodies in the CSF and serum on cell-based assays.**Cell based assays (CBA)**: CBA involves transfecting target antigen genes into mammalian cells, resulting in the specific expression of corresponding antigens in mammalian cells. Additionally, green fluorescent protein is co-expressed during transfection as an internal control for detection. Subsequently, the transfected cells are fixed onto wells of a microplate to create antigen slides. The principle of indirect immunofluorescence assay is then used for semi-quantitative detection of specific antibodies in patient serum and cerebrospinal fluid samples. The presence of distinct red fluorescence on the cell membrane of successfully transfected cells in the sample wells indicates antibody positivity.

management protocols.

Ethical compliance statement

We have obtained all required consent from the patient. In the consent form, the patient consented to his images and other clinical information being reported in the journal.

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Data availability statement

All relevant data for this case report has been included in the main article.

CRediT authorship contribution statement

Shiyuan Qin: Writing – original draft, Investigation. **Ying Wang:** Writing – review & editing, Supervision.

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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