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A rare case of anti-IgLON5 disease and its management: A case report and literature review

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Abstract

Anti-Immunoglobulin-Like Cell Adhesion molecule-5 (IgLON5) disease is an enigmatic and rare neurological disorder characterized by diverse and complex clinical presentations. First elucidated in a seminal study by the group at IDIBAPS, Barcelona, this condition presents a unique diagnostic challenge due to its varied symptomatology and the lack of clear pathophysiological understanding. Here, we present a case involving a 66-year-old male patient whose symptoms and clinical course led to the eventual diagnosis of Anti-IgLON5 disease. This case emphasizes the consideration of Anti-IgLON5 disease as a potential suspect behind varied clusters of symptoms. We will also focus on possible treatment options available and corresponding patient outcomes.

Keywords: Anti-IgLON5 disease; Neurological disorder; Respiratory failure; Bulbar dysfunction; Cognitive decline; Anti-IgLON5 antibodies; Intravenous immunoglobulins (IVIG); Rituximab.

Abbreviations: IgLON5: Immunoglobulin-Like Cell Adhesion molecule-5; IVIG: Intravenous Immunoglobulins; CSF: Cerebrospinal Fluid; PSP: Progressive Supranuclear Palsy; OSA: Obstructive Sleep Apnea; AHI: Apnea-Hypopnea Index; RTX: Rituximab; CS: IgLON5 Composite Score.

Key clinical message: Anti-IgLON5 disease presents with symptoms like sleep disturbances, bulbar dysfunction, and cognitive decline. Early diagnosis through antibody detection in CSF/serum is crucial but should be a diagnosis of exclusion. Immunotherapy may improve outcomes, though prognosis remains poor, highlighting the need for awareness and timely intervention, especially in resource-limited settings.

Introduction

Anti-IgLON5 disease is a recently recognized autoimmune disorder characterized by the presence of antibodies against the IgLON5 protein, which is a neural cell adhesion molecule. This condition presents a complex clinical picture, often overlapping with other neurological disorders, and is associated with both neurodegenerative and autoimmune mechanisms [1]. The clinical manifestations of Anti-IgLON5 disease are heterogeneous, with sleep disorders being a prominent feature. Patients frequently experience non-REM sleep parasomnia, REM behavior disorder, and obstructive sleep apnea. In addition to sleep disturbances, neurological symptoms such as gait abnormalities, bulbar dysfunction, cognitive impairment, and various movement disorders—including oculomotor abnormalities and myoclonus—are commonly reported [2]. Notably, parkinsonism may manifest in up to 87% of cases, complicating the clinical picture further. The presence of these diverse symptoms can lead to misdiagnosis, as they may mimic conditions like Progressive Supranuclear Palsy (PSP) or other forms of encephalitis [2,3]. The pathophysiological mechanisms underlying Anti-IgLON5 disease involve the internalization of the IgLON5 protein from neuronal surfaces, leading to neurodegeneration and the accumulation of hyperphosphorylated tau proteins. This suggests that the disease may have a dual nature, incorporating both autoimmune and neurodegenerative processes, which complicates treatment approaches [4].

The diagnosis of Anti-IgLON5 disease is primarily reliant on the identification of Anti-IgLON5 antibodies in serum or Cerebrospinal Fluid (CSF), although standardized diagnostic criteria have not yet been established. The disease typically follows a slow and progressive course, with symptoms emerging gradually over several months, in contrast to the more rapid onset seen in other autoimmune encephalitis. This gradual progression can delay diagnosis and treatment, emphasizing the need for clinicians to remain vigilant about this condition [1,5]. Immunotherapy has been used as a treatment option, which includes corticosteroids, IVIG, plasmapheresis, rituximab, and cyclophosphamide [1]. Patient responses vary significantly. Research shows that only a small percentage of individuals experience lasting improvement with immunosuppressive treatments, highlighting the challenging and resistant nature of the disease. The condition frequently causes progressive sleep disturbances and movement difficulties, necessitating symptomatic treatments including CPAP for sleep apnea and medication for movement abnormalities [4,5]. Here, we present the case of a 66-year-old male patient whose symptoms and clinical course ultimately led to the diagnosis of Anti-IgLON5 disease.

Case presentation

A 66-year-old male with a medical history of type 2 diabetes mellitus, hypertension, and autoimmune hypothyroidism presented with a 2-year history of right upper extremity tremors, initially diagnosed as Parkinson's disease and managed with levodopa. At the initial evaluation, the patient had an IgLON5 Composite Score (ICS) of 18/25, reflecting significant involvement across multiple domains, including bulbar symptoms (dysphagia and dysarthria), sleep disturbances (excessive daytime sleepiness and episodes of gasping), parkinsonism (rigidity and bradykinesia in the right upper extremity, and postural instability), cognitive impairments (mild confusion and memory issues), and autonomic symptoms (significant sweating). In September 2022, the patient experienced a rapid decline, marked by decreased sensorium and gasping respiration, leading to emergency admission and intubation due to respiratory failure. Imaging studies, including a brain MRI, were normal, while chest imaging revealed bilateral lower lobe consolidation. He underwent a tracheostomy on Day 21 and was discharged after 43 days.

In January 2023, four months post-discharge, the patient returned to the emergency room with sudden respiratory failure, decreased sensorium, and significant sweating. He was ventilated, regained sensorium within four hours, and was extubated on Day 3, ultimately being discharged after 11 days. During this visit, the ICS was reassessed and recorded at 15/25, indicating improvement in cognitive functioning but persistent bulbar symptoms and sleep disturbances. By March 2024, he experienced another episode of rapid respiratory failure with similar symptoms, requiring ventilation. He was extubated on Day 3 and discharged after 8 days with CPAP therapy. The ICS for this visit showed slight improvement to 17/25, suggesting some stabilization in symptoms, although the patient continued to experience episodes of respiratory failure and sleep-related issues. Polysomnography (PSG) revealed severe obstructive sleep apnea (AHI>30).

Diagnostic evaluation

A comprehensive neurological evaluation suggested a sleep-related disorder with additional neurological features. Given the recurrent episodes and complexity of symptoms, further diagnostic testing was pursued. Anti-IgLON5 antibodies were tested in both serum and Cerebrospinal Fluid (CSF), revealing serum titres of 1:320 and CSF titres of 1:256, using the ELISA method. GFAP levels were elevated at 12 ng/mL, indicating astroglial activation, while IgG1 Anti-IgLON5 titres were found to be 1:128, relevant for the internalization of IgLON5. In addition to testing for Anti-IgLON5 antibodies, we assessed for other relevant autoantibodies, including Anti-NMDA receptor antibodies, Anti-GAD65 antibodies, and Anti-Aquaporin-4 antibodies. All results were negative, ruling out other autoimmune encephalitis and parkinsonism. We conducted several other blood tests, including thyroid hormones, hemoglobin A1c (HgbA1c), vitamin B12, folate, Antinuclear Antibodies (ANA), and C-Reactive Protein (CRP). The results indicated normal thyroid function, elevated HgbA1c suggesting poorly controlled diabetes, and no deficiencies in vitamins. ANA testing was negative, ruling out systemic autoimmune diseases, while the CRP level was normal, indicating no systemic inflammation. A thorough infectious and autoimmune panel ruled out common causes, with negative results for viral serologies, bacterial cultures, and autoantibodies

Results and management

The diagnosis of Anti-IgLON5 disease was confirmed through the presence of these antibodies, indicating a composite score involving bulbar symptoms, sleep disturbances, parkinsonism, and cognitive impairments. Treatment was initiated with Intravenous Immunoglobulin (IVIg) at a dose of 2 g/kg over 5 days, along with Rituximab (RTX) administered at 375 mg/m² weekly for four weeks. The patient responded well to treatment given and currently in follow-up.

Discussion

Anti-IgLON5 disease is a rare neurological disorder that mainly affects elderly patients, with disease onset occurring between the ages of 45 to 70. The disease shows no sex predominance. The overall prevalence of Anti-IgLON5 disease is 12 out of 150,000 patients per year, although it is believed to be higher due to misdiagnosis of many cases and incorrect reporting [6].

The pathogenesis of Anti-IgLON5 disease is complex and not yet fully understood. It is believed to involve an interplay between autoimmune and neurodegenerative mechanisms. The presence of Anti-IgLON5 antibodies in the Cerebrospinal Fluid (CSF) and serum of nearly all patients strongly suggests an autoimmune component to the disease. These antibodies are primarily of the IgG4 and IgG1 types, with IgG4 predominating over IgG1 [3]. The IgLON family comprises five genes—Lsamp, Ntm, Opcml, Negr1, and Iglon5—that encode cell adhesion molecules (IgLON1 to IgLON5). These proteins interact with each other and are known to be involved in neuronal cell adhesion, neurogenesis, neuroplasticity, and maintaining the blood-brain barrier [5]. The IgG1 isotype of Anti-IgLON5 antibodies is thought to be responsible for the internalization of the IgLON5 protein, while the IgG4 subtype appears to interfere with the interaction of IgLON5 with other family members, disrupting its function [7]. Genetic predisposition has been shown in some patients with this disease. A strong association with the HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles has been observed [8]. Autopsies frequently reveal Tau protein deposits, indicating a concurrent neurodegenerative process alongside autoimmunity. This tauopathy is predominantly composed of 3R and 4R tau deposits, mainly in the hypothalamus and the tegmentum of the brainstem [9]. While both autoimmunity and neurodegeneration have been identified as components of the pathogenesis, their cause-effect relationship remains unclear. Some cases, however, have reported an absence of tauopathy, suggesting that the autoimmune process may precede and possibly drive neurodegeneration [10].

Anti-IgLON5 disease can present with a wide array of clinical manifestations, which primarily include sleep disorders such as parasomnias and Obstructive Sleep Apnea (OSA), bulbar dysfunctions like dysarthria, dysphagia, sialorrhea, stridor, and acute respiratory insufficiency, movement disorders resembling PSP, cognitive deficits or decline, and less common symptoms such as motor neuron disease or acute encephalitis [8]. Otolaryngological symptoms related to bulbar dysfunction are present in up to 91% of patients, and in some cases, these symptoms may be the initial presenting features, as observed in our case. Our patient exhibited decreased sensorium and acute respiratory failure with gasping respirations, which can be attributed to cognitive decline and bulbar dysfunction, respectively. The patient's pneumonia likely acted as a trigger for the disease or could be due to aspiration pneumonia, a known complication of bulbar dysfunction [5]. The broad overlap of the clinical picture of Anti-IgLON5 disease with other common neurological disorders complicates diagnosis. Currently, diagnosis primarily relies on clinical manifestations and the detection of Anti-IgLON5 antibodies in Cerebrospinal Fluid (CSF) and/or serum, with most patients testing positive for these antibodies, aiding in confirmation [1]. Our patient tested positive for these antibodies, confirming the diagnosis. Polysomnography was used to assess Obstructive Sleep Apnea (OSA), revealing an Apnea-Hypopnea Index (AHI) greater than 30, indicative of severe OSA. Additional tests, such as detecting signs of inflammation in the CSF and using imaging tools like MRI, have been employed in some patients.

Management of Anti-IgLON5 disease primarily involves immunotherapy and symptomatic treatment. First-line immunotherapy drugs include steroids, Intravenous Immunoglobulins (IVIG), and plasmapheresis, while second-line treatments include rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil [1]. Our patient was treated with IVIG and rituximab, showing a positive response to therapy, and was followed up accordingly. The response to immunotherapy reflects the underlying pathogenesis and highlights autoimmunity as a key factor in this disease [6]. Symptomatic treatment may include CPAP for Obstructive Sleep Apnea (OSA), as administered in our case, and medications for parkinsonism. The prognosis of Anti-IgLON5 disease is generally poor despite treatment, with a higher mortality rate compared to other autoimmune encephalitides, particularly in patients with respiratory involvement. Important causes of death include respiratory failure, hypoventilation, aspiration pneumonia, and cardiac complications [1]. The IgLON5 Composite Score (ICS) has been developed to assess the severity of various symptoms in patients with IgLON5 antibodies. This score, ranging from 0 to 69, helps evaluate the extent and severity of clinical manifestations, track changes over time, and monitor the effects of immunotherapy [11].

As a relatively novel and potentially fatal disease, further research is needed. Early diagnosis and treatment are crucial for improving outcomes and prognosis. Given the common presence of otolaryngological symptoms, a detailed description of their presentation by ENT specialists is essential [12]. Physicians should maintain a low threshold for diagnostic suspicion in the presence of complex neurological disturbances. A deeper understanding of the pathophysiology of Anti-IgLON5 disease may lead to the development of more targeted treatments and improved patient outcomes.

In comparing our case with existing literature on Anti-IgLON5 disease, several distinctions emerge. Most literature cases describe an onset age between 45 to 70 years, which aligns with our patient's age of 66 years. However, a notable difference lies in the initial symptoms; while bulbar symptoms often precede respiratory issues in reported cases, our patient experienced acute respiratory failure linked to pneumonia, which may have triggered the autoimmune response or resulted from aspiration, a known complication of bulbar dysfunction. Regarding treatment response, literature indicates variable outcomes, but our patient demonstrated a positive response to Intravenous Immunoglobulin (IVIG) and rituximab. The prognosis remains generally poor across cases, particularly with respiratory involvement, which is consistent with our findings highlighting the risks of respiratory failure. Autopsy studies commonly report the presence of tau deposits, which were not performed in our case, but our findings align with literature in terms of symptomology. Lastly, otolaryngological symptoms, frequently present in many cases, were significant in our patient, leading to an acute presentation. These comparisons underscore the variability in clinical presentations and emphasize the importance of early diagnosis and tailored treatment approaches in managing this complex disorder.

Conclusion

Anti-IgLON5 disease presents a diagnostic challenge due to its varied clinical manifestations and poorly understood pathophysiology. This case illustrates the necessity for a com-

prehensive evaluation in patients with recurrent and atypical neurological symptoms, leading to a successful diagnosis and management plan. The use of advanced diagnostic tools and interdisciplinary collaboration is crucial in managing such rare and complex conditions.

Declarations

Acknowledgments: All authors have seen and approved the case report submitted.

Ethics approval and consent to participate: Signed consent for a case report was obtained from the patient's legally authorized representative.

This case report was conducted with adherence to the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patient, and all identifiable information was anonymized to protect confidentiality and privacy.

Patient consent for publication: A Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Conflicts of interest: The authors declare no competing interests

Data availability: Data supporting this manuscript are available upon request from the corresponding author, subject to patient privacy considerations.

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