CASE REPORT

A Rare Cause of Respiratory Failure: Anti-immunoglobulin-like Cell Adhesion Molecule 5 Disease

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Abstract

Background: Anti-immunoglobulin-like cell adhesion molecule 5 (anti-IgLON5) disease is a strange disorder with a complex interplay between autoimmunity and neurodegeneration. The first case with severe air-flow disturbance and sleep apnea associated with the presence of anti-IgLON5 in cerebrospinal fluid (CSF) or serum was described in 2014. The initial common presentation among these patients is sleep apnea with respiratory failure.

Case description: A 68-year-old man presented with excessive daytime sleepiness, loud snoring, nocturnal awakening, breathlessness, involuntary movements, and difficulty in swallowing for 1 year. His arterial blood gas (ABG) showed hypercapnic respiratory acidosis. Both CSF analysis and magnetic resonance imaging (MRI) brain were normal. Polysomnography (PSG) showed sleep apnea and rapid eye movement (REM) behavioral disorders. He was tested positive for myasthenia gravis and treated accordingly. Neurological involvements are explained by the presence of serum anti-IgLON5 antibodies.

Case discussion: The IgLON5 proteins are cell adhesion molecules involved in neuroplasticity. Patients with anti-IgLON5 disease present with obstructive sleep apnea (OSA), REM, and nonrapid eye movement (NREM) parasomnia, chorea, cognitive decline, and sleep-disordered breathing with stridor and bulbar symptoms. Respiratory failure is explained by bulbar symptoms, sleep apnea, and respiratory muscle fatigue due to myasthenia gravis. Detection of anti-IgLON5 antibodies is crucial for diagnosis. Patients with anti-IgLON5 disease were treated with steroids and immunosuppressants.

Conclusion: The variable clinical presentation of neurological symptoms makes it difficult to distinguish the anti-IgLON5 disease from other neurological diseases. When a patient presents with heterogeneous neurological symptoms including distinctive sleep disorders with respiratory failure often accompanied by bulbar symptoms, the anti-IgLON5 disease should always be suspected.

Keywords: Anti-immunoglobulin-like cell adhesion molecule 5 disease, Autoimmunity, Case report, Hypercapnic respiratory failure, Noninvasive ventilation, Nonrapid eye movement, Obstructive sleep apnea, Rapid eye movement related, Sleep apnea, Slow-wave sleep.

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Abbreviations used in this Article

ABG = Arterial blood gas; AHI = Apnea–hypopnea index; BIPAP = bilevel positive airway pressure; BMI = Body mass index; CASPR2 = Contactin-associated protein 2; CD19 = Cluster of differentiation 19; CRMP5 = Collapsin response-mediator protein-5; CSA = Central sleep apnea; CSF = cerebrospinal fluid; CT = Computed tomography; EEG = Electroencephalogram; GAD 65 = Glutamic acid decarboxylase 65; HLA = Human leukocyte antigen; IgLON5 = Immunoglobulin-like cell adhesion molecule; IgG = Immunoglobulin G; Intravenous = IV; IVIg = Intravenous immunoglobulin; MRI = Magnetic resonance imaging; NIV = Noninvasive ventilation; NMDAR = N-Methyl-D-aspartate receptor; NREM = Nonrapid eye movement; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnea; PLM = Periodic limb movement; PLMI = Periodic limb movement index; PLMD = Periodic limb movement disorder; PSG = Polysomnography;

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RBD = Rapid-eye-movement behavioral disorder; REM = Rapid eye movement; VGKC LGI1 = Voltage gated pottassium channel complex leucine rich glioma inactivated protein 1.

Case Description

A 68-year-old man who is a never smoker, never alcoholic, an office manager by occupation, and a known case of systemic hypertension for 10 years, had complaints of decreased sleep and nocturnal awakening for 1 year for which he went to a local hospital and he was prescribed with benzodiazepines for sleeplessness. After benzodiazepine intake, he became drowsy and unconscious within a day. He presented to the emergency department in an unconscious state and he was intubated.

His wife revealed that he had observed apneas, involuntary movements during sleep which he was not able to recollect on awakening, tiredness, difficulty in articulation, and excessive daytime sleepiness for 1 year. On examination, the patient was afebrile with body mass index (BMI), 26.7; neck circumference, 17.5 inches; and BP, 120/80 mm Hg. The upper respiratory tract examination was normal. No neck stiffness. No facial asymmetry. On auscultation bilateral decreased breath sounds were present. His ABG revealed respiratory acidosis with pH, 7.21; pCO_2, 90.1 mm Hg; pO_2, 52 mm Hg; and HCO_3, 35.9. Routine investigations and computed tomography (CT) chest were normal. Magnetic resonance imaging (MRI) brain showed mild ischemic changes in periventricular white matter and age-related cerebral and cerebellar atrophy. Cerebrospinal fluid (CSF) analysis done to rule out any infections showed CSF pressure, 143 mm H_2O; protein 60 mg/dL and 10 white blood cells. Electroencephalogram (EEG) has normal sleep and awake records. During the hospital stay patient was observed to have recurrent apneic and hypopnea episodes and involuntary movements both during sleep and awake state. In consistent with the above findings and workup, the patient was subjected to polysomnography (PSG). Polysomnography revealed increased limb movements during rapid eye movement (REM) and nonrapid eye movement (NREM) sleep, periodic limb movement (PLM) index, 8.3; apnea–hypopnea index (AHI), 32.8; and oxygen desaturation index (ODI), 43.5 with poor sleep efficiency (Table 1; Fig. 1). So, the patient was diagnosed with a case of both central and obstructive sleep apnea (OSA) with NREM and REM parasomnia. The patient was started on BIPAP and treated with tetrabenazine for involuntary movements. He was monitored with repeated ABG measurements.

Table 1: The PSG findings

Sleep symptoms	*Comments*
Sleep apnea	CSA and OSA
AHI	32.8
Parasomnia	RBD
Excessive daytime sleepiness	Yes
Sleep latency (minutes)	12.5
Sleep architecture	Disturbed sleep architecture
Arousal index (events/hour)	25.2
PLMI (events/hour)	8.3
ODI (events/hour)	43.5
Nocturnal SpO_2 (%)	94
Hypoventilation	Yes
Summary of sleep abnormalities	Sleep apnea, parasomnia, and PLMD

CSA, central sleep apnea; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; PLMI, periodic limb movement index; PSG, polysomnography; RBD, rapid-eye-movement behavioral disorder

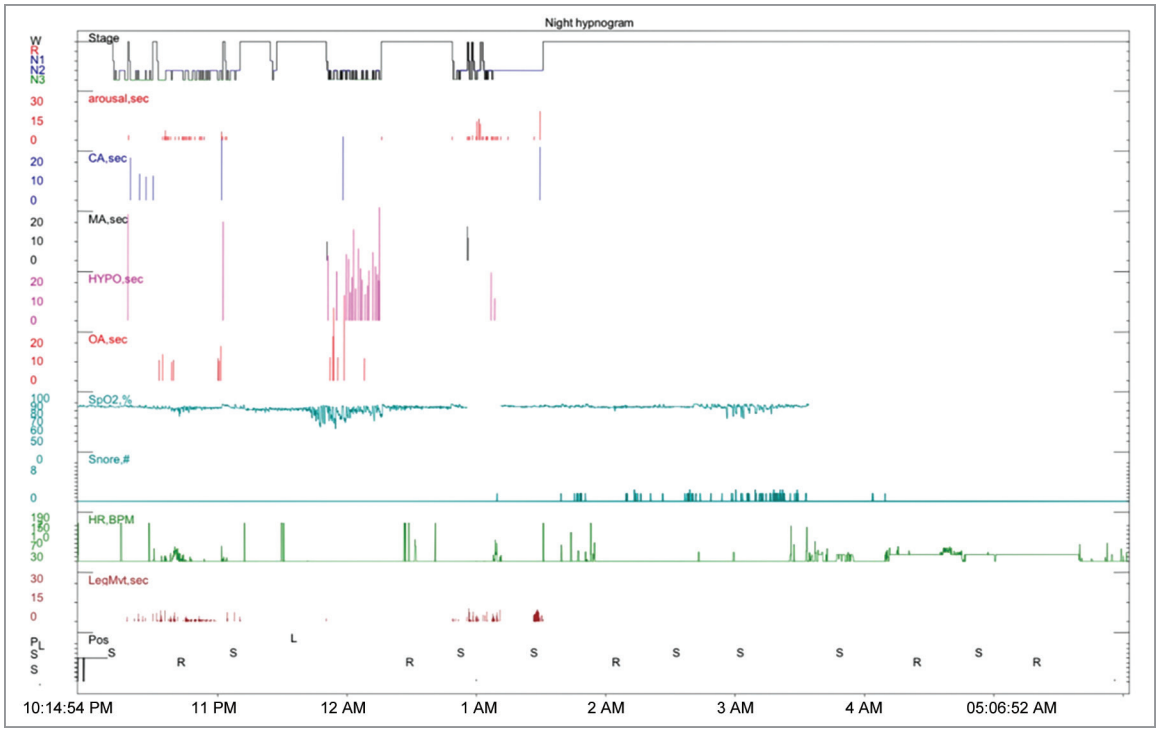
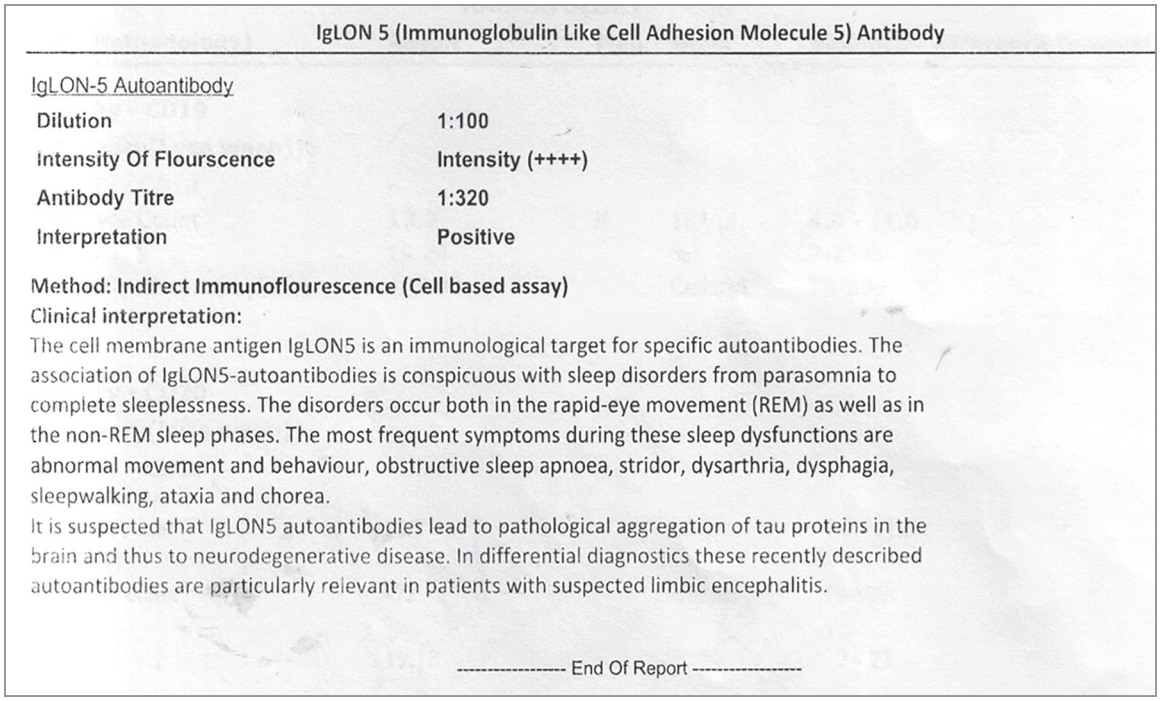


Fig. 1: Sleep hypnogram



IgLON 5 (Immunoglobulin Like Cell Adhesion Molecule 5) Antibody

IgLON-5 Autoantibody

Dilution	1:100
Intensity Of Flourscence	Intensity (++++)
Antibody Titre	1:320
Interpretation	Positive

Method: Indirect Immunoflourescence (Cell based assay)

Clinical interpretation:

The cell membrane antigen IgLON5 is an immunological target for specific autoantibodies. The association of IgLON5-autoantibodies is conspicuous with sleep disorders from parasomnia to complete sleeplessness. The disorders occur both in the rapid-eye movement (REM) as well as in the non-REM sleep phases. The most frequent symptoms during these sleep dysfunctions are abnormal movement and behaviour, obstructive sleep apnoea, stridor, dysarthria, dysphagia, sleepwalking, ataxia and chorea.

It is suspected that IgLON5 autoantibodies lead to pathological aggregation of tau proteins in the brain and thus to neurodegenerative disease. In differential diagnostics these recently described autoantibodies are particularly relevant in patients with suspected limbic encephalitis.

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Fig. 2: Serum IgLON5 antibody test – positive

As the patient's symptoms such as involuntary movements and daytime sleepiness were not improved despite the above treatment, sleep disorders associated with neurological diseases were suspected. An autoimmune encephalitis panel was done. Serum was tested for the following antibodies: N-Methyl-d-aspartate receptor (NMDAR) antibody, Voltage gated pottassium channel complex leucine rich glioma inactivated protein 1 (VGKC LGI1) antibody, contactin-associated protein 2 (CASPR2) antibody, glutamic acid decarboxylase 65 (GAD 65) antibody, anti-Hu antibody, anti-Yo antibody, anticollapsin response-mediator protein-5 (anti-CRMP5) antibody, and immunoglobulin-like cell adhesion molecule 5 (IgLON5) antibody of which IgLON5 antibody came out to be positive (Fig. 2). The final diagnosis was an anti-IgLON5 disease with both central and OSA with REM and NREM parasomnia. The patient was treated with IV immunoglobulins (0.4 mg/kg) and injection. Methylprednisolone 1 gm intravenous (IV) for 5 days. Four doses of injection. Rituximab was given at once-weekly intervals after measuring cluster of differentiation 19 (CD19) and CD20 levels. His abnormal movements in sleep and difficulty in articulation were decreased and daytime drowsiness was improved. As the patient's attenders were not willing for plasmapheresis he was discharged with mycophenolate mofetil 1000-mg twice a day, and home bilevel positive airway pressure (BIPAP). Despite the above treatment and use of home BIPAP, the patient frequently developed respiratory failure and needed mechanical ventilation which denotes a poor prognosis.

Case Discussion

Anti-immunoglobulin-like cell adhesion molecule 5 disease is a rare case with an incidence of 12 in 150,000 cases per year,[1,2] The family of IgLON proteins has cardinal functions in neuronal synaptic formation during brain development.[3] The IgLON5 proteins are neuronal cell adhesion proteins and their molecular nature can induce the production of specific antibodies in some cases and whose presence is pivotal for the diagnosis of anti-IgLON5 disease.[4] These antibodies are identified in both serum and CSF. The onset of anti-IgLON5 disease is insidious and occurs between 45 and 75 years of age with no sex predominance.[1,2] The robust association between human leukocyte antigen (HLA) DRB1*10:01 and HLA DQ1*05:01 with the anti-IgLON5 disease was reported in previous studies.[4,5,11]

The First case of anti-IgLON5 disease presented with severe airflow obstruction and sleep apnea associated with respiratory failure.[1] Sleep disorders are common in all anti-IgLON5 disease patients to an extent forcing them to seek medical help.

Patients with anti-IgLON5 disease present with sleep apnea, sleep-related disorders, movement disorders, tremors, chorea, bulbar symptoms, and neuropsychiatric symptoms.[2,4] The disease is an insidious process and symptoms take years to manifest. Owing to heterogeneity and the infancy of anti-IgLON5 disease, accurate diagnosis is often prolonged. When performed, PSG was found abnormal in 95% of cases and symptoms included insomnia, low sleep efficiency, NREM, and REM parasomnia with finalistic movements.[4–6] About 46% of the patients had normal MRI.[5,7,8] In some cases, MRI findings that were shown were cerebellar atrophy, T2 hypothalamic, thalamic, and brainstem hyperintensities.[4–7,8]

In this case, the predominant symptoms shown were sleep-disordered breathing with involuntary movements.

The underlying pathophysiology of sleep-disordered breathing in anti-IgLON5 disease is multifactorial. The characteristic neuropathological findings are gliosis and accumulation of hyperphosphorylated tau proteins in the brainstem and hypothalamus.[7] The diffuse involvement of the brainstem in anti-IgLON5 patients probably explains the gait instability, sleep-related breathing disorders, and bulbar symptoms.[3,9] The hypothalamus plays a main role in the regulation of sleep and its organization. Hence, abnormalities in the hypothalamus contribute to the

finalistic movements and difficulty in initiating sleep.[3,9] In this case, the bulbar involvement causes oropharyngeal muscle spasm and respiratory muscle weakness which eventually leads to the development of hypercapnia and central hypoventilation which is responsible for respiratory failure. The airway obstruction and OSA probably play a minor role in the development of hypercapnia. Given the high incidence of type-2 respiratory failure in anti-IgLON5 disease, routine screening with PSG is recommended.

Treatment

The frequently used treatment methods are cycles of IV corticosteroids, IV immunoglobulins, plasma exchange, Mycophenolate mofetil, and Rituximab. Previous studies show that patients who received steroids alone or patients not receive treatment other than steroids have higher mortality.[10] Combination therapy which includes steroids, intravenous immunoglobulin (IVIg), plasmapheresis, and Rituximab is recommended. A combination of immunotherapy with IVIg could decrease the IgLON5 immunoglobulin G (IgG) titer and improve REM sleep disorder.[6,9,–11] Noninvasive positive airway pressure ventilation can be used in patients with sleep apnea. Positive airway pressure acts as a pneumatic skeleton in OSA patients which prevents the upper airway from sinking during sleep.[12] Home noninvasive ventilation (NIV) improves respiratory symptoms and hypercapnic state but has no effect on abnormal sleep behavior and movements.[10,13] In this case, involuntary movements were decreased but respiratory symptoms were not improved. Large randomized trials are needed to determine the safety and long-term efficacy of treatment options for sleep apnea.

Conclusion

With some neuronal diseases, it is well known that sleep-disordered breathing impairs the quality of life compromising day-to-day longevity. The majority of the patients with anti-IgLON5 disease have symptoms of sleep apnea and present with hypercapnic respiratory failure. Hence for all nonresponding cases of OSA and in all cases of central apnea, we have to search for neurological involvement. These cases not only need isolated sleep apnea management but also need a multidisciplinary approach as they have high mortality and poor prognosis. Hence, central sleep apnea (CSA) patients who are recurrently landing in type-2 respiratory failure with some neurological involvement should be evaluated for autoimmune diseases.

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