Case Report

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A Case of Anti-IgLON5 Disease with Aplastic Anemia and Review of the Literature

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Running Title Case report and literature review of Anti-Iglon 5 and anaplastic anemia

ABSTRACT

Anti-IgLON5 is a neurological condition with neurodegenerative and autoimmune etiology. A 64-year-old man with a 2-year history of aplastic anemia presented with symmetrical parkinsonism, fluctuating consciousness, supranuclear gaze palsy, mild fasciculation, and muscular atrophy. He had disturbances in his sleep cycle and brain MRI. CSF analysis was positive for the IgLON5 antibody. We initiated immunotherapy with high-dose methylprednisolone, intravenous immunoglobulin, and rituximab. The patient showed a mild to moderate response to treatment. We reviewed 29 published case reports regarding anti-Iglon-5 and examined the clinical manifestation. None of the cases showed aplastic anemia, which was the main presentation in our case. All of the patients experienced sleep disturbances, while other symptoms were heterogeneous. Anti-Iglon-5 is usually diagnosed late, leading to a weak prognosis. This study helped us establish a better understanding of the correlation between anti-Iglon5 disease and other autoimmune disorders like anemia.

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Introduction

IgLON5 is a neuronal cell adhesion protein. IgLONs are a family of immunoglobulin-like adhesion proteins that were recently discovered. Anti-IgLON5 disease was first described in 2014 as an abnormal neurological condition explained by a dual etiology hypothesis of neurodegeneration and autoimmunity. Although the clinical picture is almost heterogeneous, it predominantly features sleep disturbances in addition to other neurological features, including gait abnormalities, bulbar symptoms, and cognitive dysfunction [1].

Neuropathological findings have revealed abnormal deposition of tau proteins, mainly in the tegmentum of the brainstem and hypothalamus [2,3]. The currently

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available treatment options are immunosuppressive agents with different responses to treatment depending on various factors [4].

Case Presentation

A 64-year-old man with a 2-year history of diagnosed aplastic anemia presented with complaints of recently evolved symptoms, including rapidly progressive sleep and cognitive disturbances, symmetrical parkinsonism, and fluctuation in consciousness over the past six months. He was admitted to the neurology ward. He also had a thirty-year history of type 2 diabetes managed with insulin injections and coronary disease treated with stent placement.

Neurological examinations revealed supranuclear gaze palsy in all directions, symmetrical rigidity and tremor on both sides, muscular atrophy in the temporal area and left hand (Figure_1A), and mild fasciculations on both upper and lower extremities. The patient's low state of consciousness made it impossible to examine gait and cognitive status.

Two years earlier, he was diagnosed with aplastic anemia. He experienced several events of pancytopenia, was admitted, and underwent treatment with high-dose methylprednisolone and danazol. A year after the diagnosis, following a positive test for CoViD-19, cyclosporine, which was prescribed as maintenance therapy for aplastic anemia, was discontinued. Shortly after, progressive cognitive and behavioral symptoms and signs started to form, including forgetfulness, isolation, thought and judgment disturbances, and disorientation. Sleep disturbances began to develop in eight months. Two months before admission, he was referred to the sleep clinic following several episodes of sleep apnea, somnolence, and fluctuation in consciousness, where the Epworth Sleepiness Scale was calculated to be 11.

A polysomnography (PSG) study was performed that resulted in a sleep efficiency of 63.6%, increased sleep stages 1 and 2, and a decrease in slow-wave sleep. Neither sleep stage 3 nor REM sleep was present. Finally, the patient was diagnosed with severe obstructive sleep apnea (OSA), having 214 episodes of apnea during 780 minutes of bedtime. CPAP was prescribed.

Compared to the previous one, the brain MRI at admission shows extensive cortical atrophy with significant enlargement of perivascular spaces (Virchow-Robin spaces) (Figure_1B), which could be a remarkable finding for anti-IgLON5 disease. A brain 18-FDG PET CT scan (Figure_1C) revealed a relative hypermetabolism in the primary sensorimotor cortices and basal ganglia compared to other cortical regions. Electromyography – nerve conduction velocity (EMG-NCV) showed a motor-neuron disorder pattern. Resting EEG, cerebrospinal fluid (CSF) analysis, and autoimmune antibody panel findings were unremarkable. Further investigation for finding any traces of paraneoplastic syndromes was inconclusive.

The correlation of dementia-like symptoms with sleep disturbances and other neurological features raised suspicion of the novel anti-IgLON5 disease. Subsequently, a strongly positive test result was obtained for the antibody against IgLON5 (Figure_2).

Immunotherapy was initiated with intravenous immunoglobulin (IVIG), and high-dose methylprednisolone was prescribed for inpatient treatment. A significant clinical improvement was observed within a few days; the patient opened his eyes, was able to communicate verbally, and his orientation to person and location improved considerably. During the second admission, second-line treatment with a high dose of rituximab was added to the IVIG. Mild to moderate improvements in

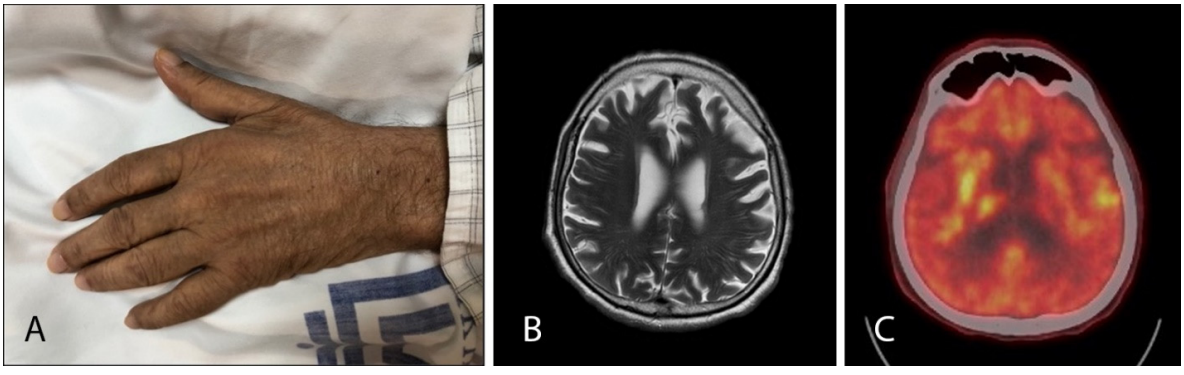

Fig. 1. A diagnostic figureLeft-hand muscular atrophy is visible here, showing motor neuron abnormalities due to anti-IgLON5 disease. **B** Axial MRI reveals generalized cortical atrophy with prominent enlarged Virchow-Robin spaces. **C** FDG-PET CT scan shows relative hypermetabolism in the primary sensorimotor cortices; and basal ganglia compared to other cortical regions.

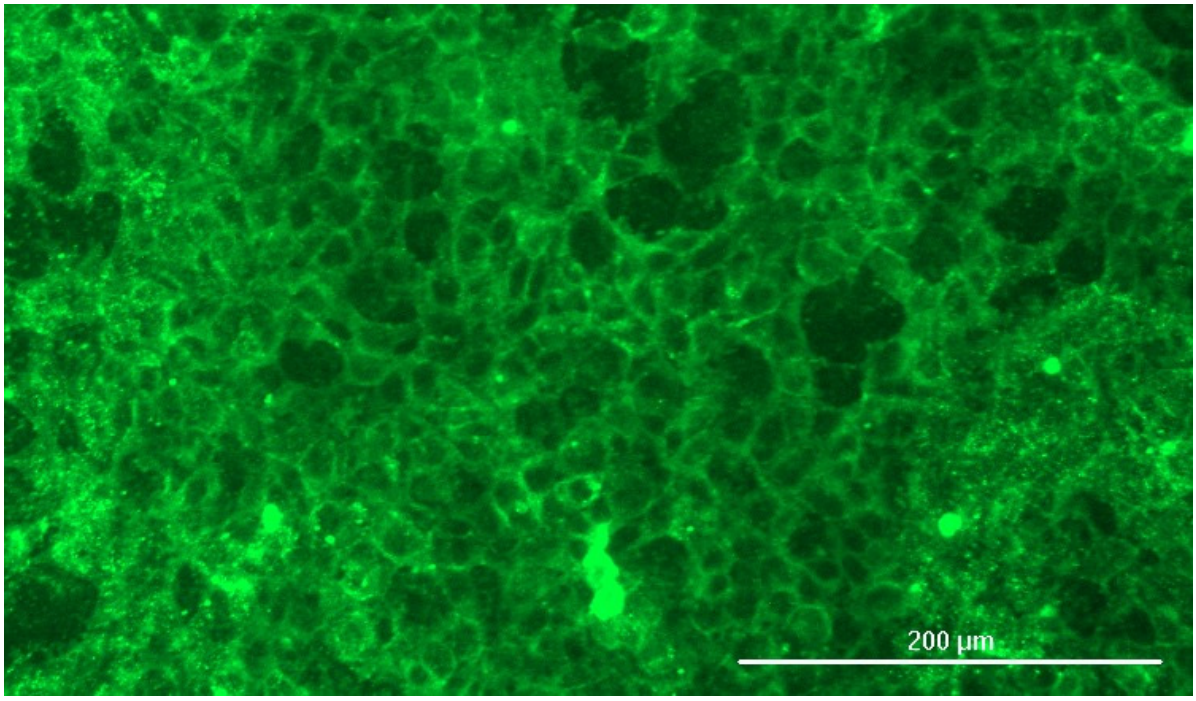

Fig. 2. A positive test result for the anti-IgLON5 antibody

consciousness and cognition were observed.

Review Of The Literature

Methods

We conducted a search of the PubMed database on March 28th, 2023, for case series and case reports related to anti-Iglon 5 disease. After eliminating duplicate cases and two irrelevant cases, we included 29 cases in our review.

We meticulously examined all the cases, focusing on demographic parameters (age and sex) and clinical manifestations in each patient. Table 1 provides a detailed descriptive analysis of the prevalence of each clinical presentation. An additional table presents the demographic and clinical features of each case in greater detail, with references to each study [see Data Set 1 file].

Results

In this study, we found that anti-Iglon5 disease affected men (62.07%) more than women (37.93%). The mean age at referral was 61.72 years, with an age range from two to 76 years. None of the cases exhibited or had a history of aplastic anemia. This could suggest that this presentation was independent of the anti-Iglon5 disease or that it was a very rare complication.

All of the cases experienced sleep disorders, either as an initial symptom or as a developing one. The most frequent sleep disorders were abnormal muscle movements during sleep (44.83%), obstructive sleep apnea (37.39%), daytime sleepiness (37.39%), sleep cycle disturbances such as REM and non-REM disturbances (27.58%), snoring (17.24%), and insomnia (17.24%). Other sleep disorders were rare, such as central sleep apnea (10.34%) or parasomnia (3.44%).

Other clinical presentations were diverse. Patients experienced involuntary muscle contractions (58.62%], speech difficulties (62.07%), disequilibrium and gait impairment (55.17%), psychiatric disorders (41.38%), brain damage (44.83%], memory loss (31.03%), respiratory disorders (37.93%), cognitive impairment (44.83%), dysphagia (44.83%), and cardiovascular disorders (27.59%). Other presentations were less common, such as fever (10.34%), ocular symptoms (13.79%), and weight loss (6.9%).

Discussion

In this case report, the preceding course of aplastic anemia in the context of anti-IgLON5 disease is a noteworthy feature. The clinical presentation of an anti-IgLON5 patient, which began with isolated cognitive abnormalities following the discontinuation of the immunosuppressant-oral cyclosporin

Table 1. Demographic characteristics and Incidence of different clinical presentations

Variable	Number (or mean)	Percent (or range)
Demographics		
Gender (F)	11	37.93%
Age	61.72 (mean)	2 – 76 (range)
Clinical manifestations		
Aplastic anemia	0	0%
Disequilibrium and gait impairment	16	55.17%
Talking problems	18	62.07%
Involuntary muscle contractions	17	58.62%
Face of facial organs	8	27.58%
Cervical	2	6.90%
Upper limb	6	20.69%
Lower limb	3	10.34%
Trunk	1	3.44%
Global (seizures or chorea)	5	17.24%
Unspecified	1	3.44%
Psychiatric disorders	12	41.38%
Depression	3	10.34%
Apathy	2	6.90%
Anxiety	1	3.45%
Obsessive compulsive disorder	1	3.45%
Hallucination and Delusions	5	17.24%
Dementia	1	3.45%
Borderline disorder	1	3.45%
Acute confusion	1	3.45%
Akathisia	1	3.45%
Mood changes and irritability	1	3.45%
Behavioral changes and disinhibition	2	6.90%
Sleep disorder	29	100%
Obstructive sleep apnea	11	37.39%
Central sleep apnea	3	10.34%
Insomnia	5	17.24%
Parasomnia	1	3.44%
Abnormal movements during sleep	13	44.83%
Daytime sleepiness	11	37.93%
Snoring	5	17.24%
Sleep cycle disturbances	8	27.58%
Sleep talking	5	17.24%
Brain damage	13	44.83%
Calcification	1	3.45%
Atrophy	2	6.90%
Encephalitis	6	20.69%
Blood brain barrier damage	1	3.45%
Mild cranial atherosclerosis	1	3.45%
Hemorrhage	1	3.45%
Infection	2	6.90%
Enhanced lesion	1	3.45%
Severe white matter destruction	1	3.45%
Bulbar dysfunction (symptoms, syndrome)	3	10.34%
Multiple scattered diffusion restrictions in MRI	1	3.45%
Memory loss	9	31.03%
Respiratory disorder	11	37.93%
Respiratory failure	4	13.79%
Deep bradycardia	1	3.45%
Hypoxemia	1	3.45%
Severe central apnea	1	3.45%
Stridor	3	10.34%
Central hypoventilation	1	3.45%
Bilateral vocal cord palsy	2	6.90%
Aspiration pneumonia	2	6.90%
Hoarseness	1	3.45%
Voice change	1	3.45%

Table 1. Demographic characteristics and Incidence of different clinical presentations

Variable	Number (or mean)	Percent (or range)
Vocal cord paresis	1	3.45%
Dyspnea	1	3.45%
Cognitive impairment	13	44.83%
Cardiovascular disorders	8	27.59%
Recurrent syncope	1	3.45%
Hypertension	6	20.69%
Carotid stenosis	1	3.45%
Diabetes mellitus type2	4	13.79%
Atrial fibrillation history	1	3.45%
Weight loss	2	6.90%
Dysphagia	13	44.83%
Ocular symptoms	4	13.79%
Gaze limitations	3	10.34%
Horizontal nystagmus of the eye	2	6.9%
Ptosis	2	6.9%
Diplopia	1	3.45%
Blepharospasm	1	3.45%
Abnormal saccade and pursuit	1	3.45%
Fever	3	10.34%

prescribed for aplastic anemia, might be another significant finding.

To our knowledge, this is the first case of anti-IgLON5 disease with preceding aplastic anemia. However, Gaig et al. [5] conducted a study in which a patient was diagnosed with an autoimmune disorder-factor VIII deficiency, before being diagnosed with anti-IgLON5 disease. This is the only reported case of anti-IgLON5 disease with a concomitant autoimmune disorder in the literature.

In this case, the primary presentation with isolated cognitive disorders, including memory dysfunction and behavioral abnormalities in the absence of sleep disorder or PSP-like syndrome, raised suspicion for dementia spectrum disorders, especially Lewy body dementia. Negative findings on initial brain MRI, in addition to unremarkable results of the routine antibody panel for autoimmune encephalitis and no trace of inflammation in CSF, led to a late diagnosis of the recently defined anti-IgLON5 disease

The occurrence of bulbar symptoms, especially sleep disorders with a pattern of obstructive sleep apnea (OSA), redirects the suspicion to this rarely reported disease. Based on the diagnostic criteria previously suggested by Gelpi et al. [2], a positive test result for the IgLON5 antibody in CSF, in addition to the clinical history appropriate for anti-IgLON5 disease, must be accompanied by appropriate neuropathological findings to confirm the diagnosis. However, we were unable to perform a tau-PET/CT scan to learn more about the neuropathology [2]. The study of HLA alleles to identify both subtypes (HLA-DRB1*10:01, HLA-DBQ1*05:01) associated with the disease is also recommended in previously published literature [1, 3].

We implemented therapy based on previously used immunotherapies for anti-IgLON5 disease [6]. Intravenous immunoglobulin (IVIG) and rituximab, in addition to high-dose methylprednisolone, were the treatments of choice. We achieved a fair response considering the progression of the disease and the patient's condition.

Based on our review of the literature, we found that all of the patients experienced sleep disorders, and many of them experienced musculoskeletal, psychiatric, neurological symptoms, involuntary muscle contractions, disequilibrium, gait impairment, and other symptoms.

This case report strengthens the hypothesis of a correlation between anti-IgLON5 disease and other autoimmune diseases. It also provides a substantial reason for adding IgLON5 antibody testing to the routine autoimmune antibody panel, regardless of whether there is clinical suspicion of anti-IgLON5 disease.

List Of Abbreviations

PSG: Polysomnography, REM: Rapid Eye Movement, CSF: Cerebrospinal Fluid, COVID-19: Coronavirus Disease 2019, MRI: Magnetic Resonance Imaging, A FDG: Fluorodeoxyglucose, PET/CT: Positron Emission Tomography/ Computed Tomography OSA:

Obstructive Sleep Apnea, CPAP: Continuous Positive Airway Pressure, IVIG: Intravenous Immunoglobulin, PSP: Progressive Supranuclear Palsy, HLA: Human Leukocyte Antigen

Declaration Section

Ethics Statement And Consent For Publication

As the patient himself was unable to cooperate, informed consent was obtained from a first-degree family member (his daughter and guardian) to share his medical documents and the course of his disease with the researchers of this study.

Consent For Publication

The publication of any images or other personal or clinical details of the patient was also included in the written informed consent mentioned above. Informed consent was obtained from the patient's daughter, who is his guardian.

Availability Of Data And Materials

In this case report, no dataset was available. However, the patient's clinical and laboratory data related to this case report can be made accessible upon reasonable request to the corresponding author.

Competing Interest

There are no financial or non-financial competing interests among the authors and contributors of this article.

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Authors' Contributions

Abbas Tafakhori: drafting/revising the manuscript, planning of clinical diagnostics/diagnostic plan, interpretation of results, making diagnosis, starting treatment. Seyyed Reza Ebadi: drafting/revising the manuscript. Hamed Amirifard: planning and execution of polysomnography, interpretation of results. Saeed Karima: performing the analysis for Anti-IgLON5 and the relevant analysis. Kiana Amani: drafting/revising the manuscript. Arian Hasani: drafting/revising the manuscript and writing the review of the literature and publishing the study. Nazanin Esmaieli: drafting/revising the manuscript and writing the review of the literature.

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Not applicable

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