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Anti-IgLON5 disease exacerbated by asymptomatic SARS-CoV-2 infection

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ABSTRACT

Objective: To report a case of anti-IgLON5 disease unmasked by asymptomatic SARS-CoV-2 infection.
Background: Anti-IgLON5 disease is a clinically heterogeneous disease that shares features of both neurodegeneration and neuroinflammation. The onset can be insidious, posing diagnostic challenges and often resulting in treatment delay. Infectious trigger was rarely reported in this disease.
Case report: A 64-year-old male initially presented with 1-year history of progressive parasomnia and mild cognitive decline that precipitously worsened over the course of 1 month following asymptomatic SARS-CoV-2 infection, resulting in dysphagia, parkinsonism, weight loss and dependence on all activities of daily living. He was found to have high titer (1:3840) of anti-IgLON5 antibody in the serum, confirming the diagnosis of anti-IgLON5 disease.
Conclusion: Anti-IgLON5 disease as a potentially reversible cause of neurodegenerative syndrome in patients with atypical features. Timely diagnosis and treatment may improve clinical outcomes. It is also worth noting that symptoms precipitously worsened following SARS-CoV-2 infection. We suspect that a COVID-19-mediated immune activation response exacerbated the underlying autoimmune encephalitis process, unmasking his symptoms.

Introduction

Anti-IgLON5 disease is a clinically heterogeneous disease that shares features of both neurodegeneration and neuroinflammation. The insidious onset and slowly progressive course pose great diagnostic challenges and oftentimes result in delays in treatment. (Gaig et al. 2017) Infectious trigger was rarely reported in this disease. (Wang et al. 2021). We report a unique case of anti-IgLON5 disease unmasked by an episode of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection after which clinical course precipitously worsened, leading to the final diagnosis. While cases of autoimmune encephalitis following coronavirus disease 2019 (COVID-19) were rarely observed in clinical practice, the rapid exacerbation of the previous indolent course of anti-IgLON5 disease has not been reported. (Valencia Sanchez et al.2021; Nabizadeh et al. 2022; Monti et al. 2020; Patterson et al. 2020)

Case report

A 64-year-old Caucasian male presented with 7 months of mild memory difficulties, fatigue, falls, and sleep disturbance. His-medical history was notable for untreated mild-moderate obstructive sleep apnea (OSA) diagnosed in 2014 by polysomnography, diabetes, hypertension, coronary artery disease, atrial fibrillation, and hypothyroidism. He was noted to have daytime somnolence, vocalization during sleep, and involuntary movements upon awakening. His legs gave out leading to falls. There was no family history of similar symptoms or neurologic disorders. The patient denied drug, alcohol, or tobacco use. The initial exam was notable for a Montreal Cognitive Assessment (MOCA) raw score of 19/30 with mild to moderate impairment of memory, attention, and executive function. He had proximal bilateral lower extremity weakness (bilateral hip flexion MRC 4+/5, knee extension MRC 4+/5, knee flexion MRC 4+/5), fasciculations in biceps, quadriceps, and gastrocnemius muscles without tongue fasciculations, atrophy of the quadriceps, diminished reflexes with down-going toes and a waddling gait.

The patient had an asymptomatic SARS-CoV-2 infection diagnosed with home rapid antigen test, due to exposure to family members with symptomatic COVID-19, 1 year after the symptom onset. The patient did not present to the hospital or a clinic given he was asymptomatic. After the SARS-CoV-2 infection, his cognitive status declined precipitously over 1 month to the point where he became dependent on a caregiver for all activities of daily living, and he developed frequent falls. Three months after COVID-19 illness, he developed prominent formed daytime visual hallucinations and paranoia as well as dysphagia and dysarthria. Upon re-evaluation 1.5 years after initial symptom onset, he had a 45-kilogram weight loss. (Fig. 1) Follow-up neurological exam revealed additional signs including masked facies, limited upward gaze, oculomotor

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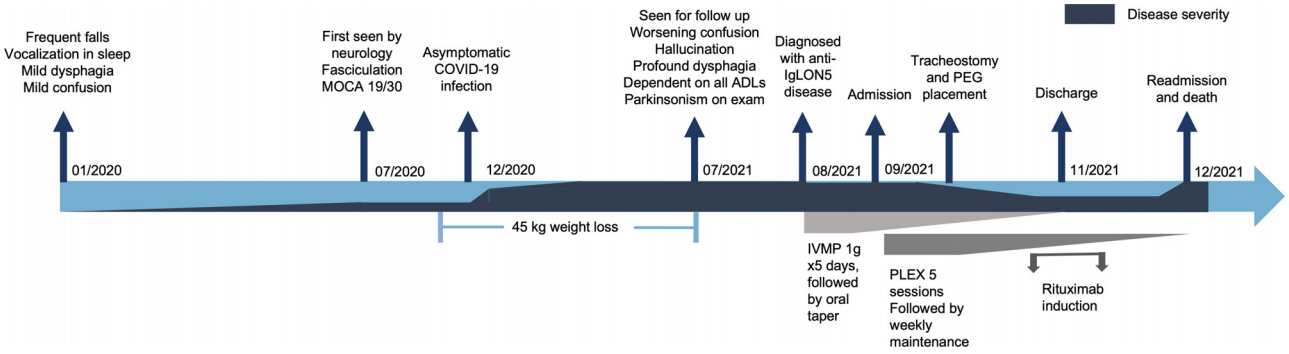

Fig. 1. Evolution of the disease course and treatment timeline. Clinical symptoms rapidly progressed after the symptomatic COVID-19 infection, which led to the diagnosis. The patient partially responded to immunotherapy before rapid deterioration from aspiration pneumonia. PEG: percutaneous gastrostomy tube; IVMP: intravenous methylprednisolone; PLEX: plasma exchange.

apraxia, shuffling gait, bradykinesia, reduced arm swing and hunched over posture, concerning for parkinsonism.

In this elderly man with 18 months of progressive cognitive deficit, gait difficulties and sleep disturbance followed by rapid development of bulbar weakness, weight loss, and visual hallucination after asymptomatic COVID-19 infection, several differential diagnoses were considered, which include: (1) Dementia with Lewy bodies (DLB): visual hallucinations, fluctuating cognition, and parkinsonism; (2) Progressive Supranuclear Palsy (PSP): parkinsonism, limited upward gaze and early falls; (3) Frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) variant: prominent bulbar symptoms and fasciculations; (4) Rapid progressive dementia of paraneoplastic, infectious or autoimmune etiologies. (5) Vascular dementia due to multiple cardiovascular risk factors; (6) Reversible causes of dementia such as hypothyroidism, nonconvulsive seizures, and untreated OSA.

MRI brain with and without contrast showed no abnormal contrast enhancement and only mild diffuse parenchymal volume loss, mild periventricular small vessel changes and a few scattered chronic microhemorrhages in the bilateral basal ganglia (likely due to patient's known history of cardiovascular disease), but otherwise unremarkable, which did not explain the extent of his clinical symptoms. Electromyography and nerve conduction study was notable for right median neuropathy at the wrist and a mild sensorimotor polyneuropathy, likely attributable to know history of diabetes. Right tibialis anterior, gastrocnemius, vastus lateralis, iliopsoas, lumbar paraspinal, first dorsal interosseous, abductor pollicis brevis, flexor carpi radialis, biceps brachii and cervical paraspinal muscles were sampled, with no abnormal spontaneous activity, normal recruitment pattern. Although motor neuron disease phenotype can be seen in IgLON5 disease and there was concern for fasciculation observed on this patient's physical exam, there was no electrodiagnostic evidence to support the diagnosis of motor neuron disease. An overnight polysomnography was performed which showed mild OSA, frequent periodic limb movements and frequent vocalizations in Rapid Eye Movement (REM) sleep, suggesting REM sleep behavior disorder, without clear evidence of non-REM sleep disturbance or poorly structure stage 2 sleep. 48 h ambulatory electroencephalogram revealed mild encephalopathy but no seizure or epileptiform discharges. His-thyroid function and vitamin B12 level were within normal limits.

While his clinical symptoms may partially be consistent with degenerative processes such as DLB or PSP, the mixed features as well as the precipitous decline over a course of a month post infection raised concerns for a secondary autoimmune process. Lyme, RPR, HIV testing in blood were negative. A serum autoimmune encephalopathy panel was sent which revealed high titer positive (1:3840, indirect tissue immunofluorescence with reflex confirmatory fixed CBA via commercially available testing) anti-IgLON 5 antibody. No lumbar puncture was performed given the high serum titer and typical clinical presentation of anti-IgLON5 disease. Computed tomography of the chest, abdomen and pelvis showed no evidence of malignancy. In retrospect, his clinical manifestations were consistent with anti-lgLON5 disease.

The patient was treated with intravenous methylprednisolone 1000 mg daily for 5 days followed by 7 sessions of serial therapeutic plasma exchange. He was maintained on a slow prednisone taper and weekly therapeutic plasma exchange prior to starting rituximab (1 g for 2 doses, 14 days apart). His-cognition markedly improved and visual hallucinations were completely resolved. However, he continued to have significant bulbar weakness requiring tracheostomy and percutaneous gastrostomy tube placement. Positive pressure ventilatory support was required during sleep due to apnea events. He was discharged home in stable condition. One month after discharge, the patient had a precipitous decline in his mental status over a week. He was readmitted and found to be hyponatremic and septic with a positive lower respiratory culture for pseudomonas aeruginosa, raising concerns for an aspiration event. He unfortunately went into pulseless electric activity (PEA) arrest twice and passed away after the decision was made to transition to comfort-based measures.

Discussion

Anti-IgLON5 disease is a clinically heterogeneous disorder associated with antibodies against a neuronal cell adhesion molecule protein of unknown function. It was first described in patients with prominent sleep disturbances including non-REM and REM parasomnia, OSA and stridor. While the patient in this case report may not have had all the sleep features typical of anti-IgLON5 disease, he had REM parasomnias which are frequently found in patients with IgLON5 disease. (Sabater et al. 2014; Gaig, et al. 2017) The clinical phenotypes have expanded over the past few years, which now include: (1) sleep disorders; (2) bulbar symptoms: dysphagia, dysarthria; (3) movement disorders: PSP-like syndrome, craniofacial dyskinesias, chorea, and parkinsonism; (4) cognitive impairment; (5) neuromuscular manifestations: weakness and fasciculations mimicking motor neuron disease. (Gaig et al. 2017; Gaig et al. 2021; Werner et al. 2021) Respiratory failure and sudden death may occur in patients with central hypoventilation and bulbar weakness. (Werner et al. 2021) The diagnosis of anti-IgLON5 disease is often delayed due to the significant overlap with neurodegenerative conditions. Brain MRIs are usually unremarkable. Cerebrospinal fluid (CSF) analysis may have mild protein elevation but can also be unremarkable. A strong association with human leukocyte antigen (HLA)-DRB1×10:01 and HLA-DQB1×05:01 alleles has been reported, suggesting an immune predisposition. (Gaig et al. 2017; Gaig et al. 2021) It is suspected that an antibody-mediated disruption of IgLON5 function may result in neuronal cytoskeletal alteration and tau protein accumulation. (Landa et al. 2020) A trial of immunotherapy is usually warranted. While earlier reports suggested poor treatment response, more recent studies showed that at least partial response can be observed.

(Honorat et al. 2017; Cabezudo-García et al. 2020) Classical phenotypes such as sleep disorder, bulbar symptoms and PSP-like syndrome tend to be less reversible. Combination therapies with second-line agents are more likely to be effective in achieving a sustained response. (Cabezudo-García et al. 2020)

It is worth noting that symptoms precipitously worsened following the asymptomatic SARS-CoV-2 infection. In retrospect, the patient's insidious symptoms had prior to SARS-CoV-2 infection were within the spectrum of IgLON5 disease but it was quite nonspecific and provided a diagnostic challenge early on in the disease course. It was not until the patient had rapid exacerbation and developed the full spectrum of pathognomonic symptoms after SARS-CoV-2 infection that the final diagnosis was made highlighting that clinical worsening was quite specific to IgLON5 disease. Since the COVID-19 pandemic, there have been reports of autoimmune encephalitis associated with SARS-CoV-2 infection, although the overall incidence is quite low. (Valencia Sanchez et al. 2021) Among these reported cases, limbic encephalitis, seronegative autoimmune encephalitis, and anti-NMDA receptor encephalitis are the most common. (Valencia Sanchez et al.2021; Nabizadeh et al. 2022) It was speculated that cytokine-mediated inflammatory response to the SARS-CoV-2 virus may facilitate antibody production and increase the permeability of the blood-brain barrier. (Mehta et al. 2020) However, with limited number of cases reported so far, coincidental development of autoimmune encephalitis independent of COVID-19 cannot be ruled out. The association between the SARS-CoV-2 infection and the onset of autoimmune encephalitis is not definite. In this case, it was clear that the patient developed initial symptoms 1 year preceding the SARS-CoV-2 infection. However, he rapidly deteriorated and developed a full spectrum of symptoms typical of anti-IgLON5 disease 2 weeks after being tested positive for SARS-CoV-2 virus. This clinical observation is supportive of the fact that COVID-19-mediated immune activation response may have exacerbated the underlying autoimmune encephalitis process, unmasking the symptoms. Further studies on the dynamic changes in the antibody titers and related cytokine signatures pre- and post-infection may help elucidate the role of SARS-CoV-2 infection in the genesis of autoimmune encephalitis.

Conclusion

Anti-IgLON5 disease can be a potentially reversible cause of neurodegenerative syndrome in patients with atypical features. Timely treatment and appropriate management of disease-associated complications may improve clinical outcomes. We present a unique case where the initial slow and insidious course was accelerated by asymptomatic SARS-CoV-2 infection, revealing the clues to the final diagnosis. We suspect that a COVID-19-mediated immune activation response exacerbated the underlying autoimmune encephalitis process, unmasking his symptoms.

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Declaration of Competing Interests

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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