Atypical Parkinsonism with Positive Anti-amphiphysin Antibodies: Expanding the Phenotypic Spectrum

Dear Editor,

Antibody-mediated parkinsonism is an underdiagnosed entity highly responsive to immunotherapy.[1] Rapidly progressive parkinsonism in the setting of an underlying malignancy is seen in association with anti-Ma2, anti-Ri, or anti-collapsin response mediator protein 5 (CRMP5) antibodies.[1-4] Other antibodies involved in atypical parkinsonism include Leucine-rich glioma-inactivated 1 (LGI1), Contactin-associated protein-like 2 (CASPR2), and Di-peptidyl-peptidase-like protein 6 (DPPX) antibodies in adults and anti-D2 and NMDAR antibodies in children.[1] Non-paraneoplastic parkinsonism mimicking progressive supranuclear palsy (PSP) with sleep abnormalities is observed in anti-IgLON5 disease.[5] We report a 48-year-old gentleman who presented with rapidly progressive parkinsonism with vertical gaze palsy and sleep abnormalities mimicking anti-Immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease, which was related to anti-amphiphysin antibodies.

A 48-year-old gentleman presented with progressive slowness in walking and daily activities for 9 months. He reported stiffness of both lower limbs, with no tremors or postural instability. He also reported that he had been excessively sleepy for the past 3 months, sleeping for over 15 h in a day and snoring. There was no history of cataplexy, hallucinations, hyperphagia, hypersexuality, parasomnia, or rapid eye movement sleep behavioral disorder. His wife had recently observed him to have become more apathetic and emotionally unstable. He had no memory problems, seizures, hallucinations, falls, limb or bulbar weakness, sensory or autonomic dysfunction. His past medical history and family history were unremarkable. He was independent in his activities of daily living and could walk without support at presentation.

Examination revealed mask-like facies, reduced blink rate, and hypophonic speech. Cognitive examination showed decreased verbal fluency, impaired attention, and working memory. Oculomotor examination showed a vertical saccadic (down > up) gaze palsy [Video 1] with preserved vestibulo-ocular reflex. He had axial and appendicular rigidity and body and limb bradykinesia, but no rest tremors. Intention tremors and dysmetria were noticed in hands [Video 1]. He also had impaired tandem walking and a positive pull test. His muscle strength, deep tendon reflexes, and sensory examination were normal. The motor Unified Parkinsons Disease Rating Scale (UPDRS) score was 38 at presentation.

We considered the possibility of an immune-mediated parkinsonism because of the subacute onset and rapid progression of symptoms, along with ocular, cerebellar, and cognitive involvement. In view of the PSP-like phenotype and sleep abnormalities, IgLON5 antibody-mediated disease was kept as a strong possibility. Other potential causes included paraneoplastic syndromes related to anti-Ma2, anti-Ri, and anti-CRMP-5 antibodies, as well as autoimmune encephalitis syndromes related to LGI1, CASPR2, and anti-thyroid peroxidase (anti-TPO) antibodies. We also discussed the possibility of neuroinfections like human immunodeficiency virus (HIV) and central nervous system Whipple's disease, neurosarcoidosis, celiac disease, and late-onset storage disorders like Gaucher's and Niemann Pick disease Type C.

Investigations uncovered normal hemogram, renal, liver, and thyroid functions, non-reactive HIV serology, as well as normal anti-TPO antibody and serum angiotensin converting enzyme levels. Magnetic resonance imaging of the brain revealed mild cerebral and cerebellar atrophy [Figure 1a and b] with no midbrain atrophy. Cerebrospinal fluid (CSF) analysis revealed five white blood cells with 60% lymphocytes, normal glucose, elevated protein (73 mg%), and sterile culture. Tests for infections, including tuberculosis, syphilis, and Whipple's disease, were unrevealing, and CSF malignant cytology was negative. Autoimmune encephalitis panel (N-methyl-D-aspartate receptor [NMDAR], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 [AMPA1], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2 [AMPA2], Contactin-associated-protein-like 2 [CASPR], Leucine-rich-glioma-inactivated 1 [LGI-1], Gamma amino buytric acid-B [GABA-B] antibodies) in serum and CSF and anti-IgLON5 antibodies in serum were negative. Serum paraneoplastic profile (Hu, Ri, Yo, CRMP5, Ma2, SOX1, Tr, GAD65, Zic4, titin, recoverin, and amphiphysin antibodies) revealed 2+ positivity for anti-amphiphysin antibodies (semi-quantitative, immunoblot assay). Positron emission tomography scan uncovered hypometabolism in both prefrontal and left parietal cortices, with no uptake elsewhere

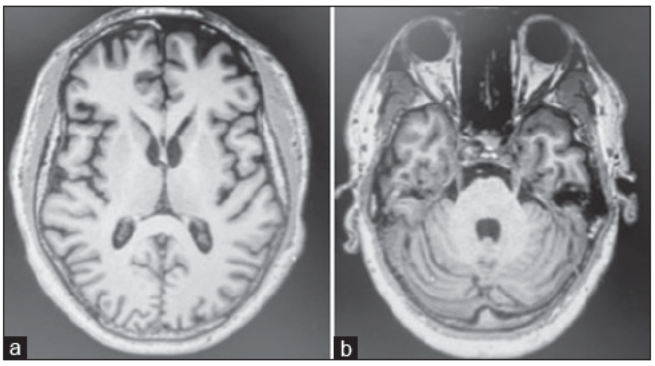

Figure 1: Axial T1W magnetic resonance imaging of the brain shows mild diffuse cerebral atrophy (a) and cerebellar atrophy (b). T1W = T1-weighted

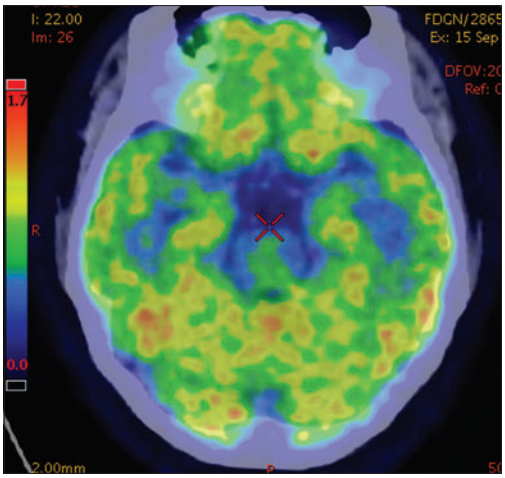

Figure 2: Positron emission tomography scan showing hypometabolism in both prefrontal and left parietal cortices

in the body [Figure 2]. His 99m Technetium labelled TRODAT Single photon emission computed tomography (Tc TRODAT SPECT) was normal. Nerve conduction study was normal. A needle electromyographic examination performed to look for features of stiff person syndrome was normal.

The patient was treated with 1 g of intravenous pulse methylprednisolone over 5 days. However, no significant improvement was observed. Subsequently, he received intravenous immunoglobulins (IVIG; 2 g/kg) over 5 days and was continued on oral steroids (1 mg/kg). In the follow-up teleconsultation after a month, he reported moderate improvements in bradykinesia, hypersomnolence, emotional lability, and apathy. The motor UPDRS scores improved to 20 after treatment. However, gaze abnormalities persisted. He then received two doses (1 g each) of rituximab 2 weeks apart. The improvement in bradykinesia, hypersomnolence, emotional lability, and apathy after treatment with IVIG and steroids remained stable after administration of rituximab. Oral steroid was tapered over the next 2 months. He was stable until 6 months of follow-up, but then developed pneumonia and succumbed to sepsis.

Immune-mediated parkinsonism manifests as an atypical parkinsonian syndrome, with features of brainstem involvement, cognitive dysfunction, and sleep abnormalities.[1] Patients with paraneoplastic parkinsonism often develop limbic encephalitis, diencephalic syndrome, or brainstem syndrome, which progresses rapidly leading to significant disability.[2] Our patient showed PSP-like parkinsonism and sleep abnormalities associated with anti-amphiphysin antibodies.

Anti-amphiphysin antibodies are high-risk antibodies (>70% associated with cancer) directed against intracellular antigens and are encountered commonly in the setting of breast, ovarian, or small cell lung cancers.[6-8] The commonly reported neurologic phenotypes include stiff person syndrome, sensory neuronopathy, encephalomyelitis, polyradiculoneuropathy, limbic encephalitis, sensory cerebellar syndrome, and Lambert–Eaton myasthenic syndrome.[7] The phenotype of our patient was not considered high risk according to the updated diagnostic criteria for paraneoplastic neurologic syndromes.[8] However, the clinical features of rapidly progressive parkinsonism, hypersomnolence (diencephalic involvement), and cognitive dysfunction with high CSF protein suggested an intermediate risk phenotype and a probable paraneoplastic neurologic syndrome (PNS) with a PNS-Care score of 6.[8] The response to immunotherapy further supported the diagnosis. We could not do repeat testing of anti-amphiphysin antibodies in CSF or an immune histochemistry due to financial constraints, and could not perform an autopsy.

We describe an unusual and novel presentation of anti-amphiphysin antibody–associated disorders. It is important to investigate immune causes in rapidly progressing atypical parkinsonism for finding potential treatment options.

Declaration of patient consent

Informed written consent was obtained from patient's wife for writing and publication of the clinical information, video, and images.

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Conflicts of interest

There are no conflicts of interest.

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