Neuronal Antibody-Associated Corticobasal Syndrome

Dear Sir,

Recent research has drawn attention to the concept of "atypical atypical parkinsonism," which refers to cases where the clinical characteristics either are mixed or do not clearly match the requirements for a "typical" degenerative atypical parkinsonism, such as when there are major sleep difficulties in an otherwise tau-phenotype.[1] In this context, we describe a pair of cases of "atypical atypical parkinsonism" that tested positive for neuronal antibodies and whose clinical picture closely resembled a degenerative cortico-basal phenotype.

Case 1

A 72-year-old gentleman presented with 2-year history of progressive change in gait and cognition. His first symptoms included excessive day time sleepiness and sudden awakenings at night, with a scream and vacant stare, without associated limb movements. He also had difficulty in buttoning and a few episodes of urinary and bowel incontinence. Over the next 6 months, his gait slowed and he walked with short steps, leaning toward the right. He had difficulty walking in a straight line and sustained multiple forward falls. He developed abnormal posturing of the left hand and had difficulty negotiating the slipper with the left foot. He would bump into objects on multiple occasions. He also became increasingly apathetic and had difficulty performing simple calculations. A year into the illness, the behavior worsened (aimless wandering, gobbling food with speed, lack of self-care). His speech output reduced progressively, and he had to put undue effort while speaking. Later, he developed echolalia, stereotypical movements of the right hand (rubbing the head), head nodding, and truncal rocking.

Examination revealed right gaze preference, posturing of the left hand with intermittent levitation, stereotypies in the right hand [Video 1], anterocollis, asymmetrical limb rigidity (left > right), left striatal toe, and oro-buccal, eyelid, and speech apraxia along with echolalia. Due to severe inattention (forward digit span 3) and perseveration, he performed poorly on cognitive examination (Addenbrooke's cognitive examination III score – 3).

MRI Brain revealed asymmetrical, right predominant frontoparietal atrophy [Figure 1a]. On an auto-immune and paraneoplastic antibody panel, his serum sample (1:10 dilution) tested positive for anti GABA-B receptor antibodies (indirect immunofluorescence assay on transfected cell lines, Euroimmun Germany, Figure 2). ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) revealed relative hypermetabolism in bilateral basal ganglia and mesial temporal cortices with diffuse cortical hypometabolism [Figure 3, panel 1]. There was no evidence of metabolically active disease elsewhere in the body. Cerebrospinal fluid (CSF) analysis revealed 15 cells, lymphocytic, protein of 80 mg/dl, and a normal CSF: serum glucose ratio (0.7). CSF cryptococcal antigen, VDRL, Gram stain, gene Xpert, TB-PCR, and neuronal antibody panel were negative. There was a bilateral theta range slowing on electroencephalogram (EEG). The serum sample tested negative for IgLON5 antibody using tissue-based assay by an indirect immunofluorescence method.

The patient was treated with intravenous methylprednisolone 1 g/day for 5 days, followed by oral prednisolone (60 mg/day). He was also given 130 g intravenous immunoglobulins (IVIG) over 5 days. He improved symptomatically in the form of decreased stereotypical movements, reduced gaze preference, and improvement in spontaneity of speech. After 2 weeks, he was given an induction regimen of rituximab (1 g per infusion, 2 weeks apart). However, a month later, he succumbed to respiratory infection.

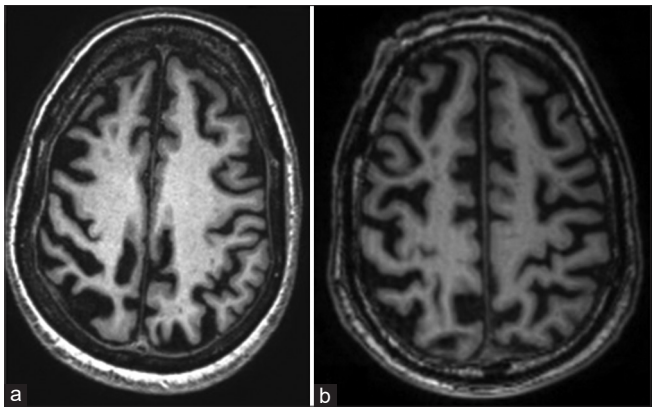

Figure 1: T1-weighted MRI axial sections showing asymmetrical frontoparietal atrophy in (a) case 1 and (b) case 2

Case 2

A 64-year-old-lady presented with 1-year history of cognitive decline (navigational difficulty, followed by recent memory impairment, apathy, food faddism, and emotional incontinence). Three months into the illness, she developed posturing of the left hand and difficulty in using it for daily activities. Later, she became incontinent and developed prominent sleep vocalizations. Two years prior to this presentation, she had two episodes of generalized seizures, for which she was not evaluated. Examination revealed severe inattention, perseveration, and loss of comprehension. There was asymmetric rigidity, bradykinesia, and dystonic posturing in the left upper limb. She was on 300 mg levodopa/carbidopa with no response in parkinsonian symptoms. MRI Brain revealed grossly asymmetric cerebral atrophy, right side predominant [Figure 1b]. Her serum tested positive for anti-Zic-4 antibodies by an immunoblot technique (Euroimmun Germany). ^{18}F-FDG PET showed grossly asymmetrical hypometabolism in the right parietal, frontal, and temporal lobes, along with basal ganglia and thalamus [Figure 3, panel 2], along with an FDG avid enlarged paratracheal lymph node, measuring 1.4 × 1.2 cm. There was no evidence of metabolically active disease in the lungs or elsewhere in the body. She was planned for work-up and treatment with IVIG; however, the caregivers refused further treatment.

Discussion

Auto-immune or paraneoplastic parkinsonism is infrequent in adults and has been linked to antibodies such as NMDAR, CV2/CRMP5, IgLON5, CASPR2, LGl1, DPPX, Ri, and Ma2.[1] Parkinsonism in these conditions is typically subacute in onset, rapidly progressing, with an atypical phenotype, and is found in conjunction with other clinical characteristics, indicating limbic, diencephalic, or brainstem involvement. It may also resemble degenerative conditions such as Parkinson's disease, multiple system atrophy, or progressive supranuclear palsy. The cases listed here exhibited a CBS phenotype but also had warning signs such as rapid advancement, early and noticeable sleep disturbance (rare in tauopathies), stereotypies, and/or seizures.

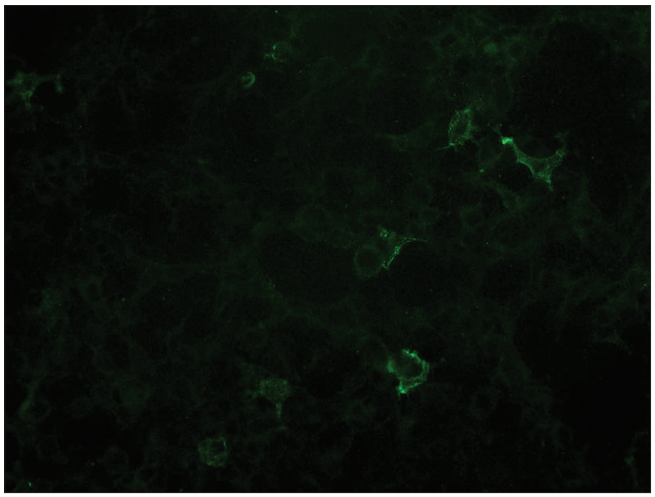

Figure 2: Strong immunofluorescence on transfected cells expressing GABA B. Indirect immunofluyorescencexOng.40

Similar recent instances of rapidly progressing CBS with improvement following immunotherapy are anti-GABABR antibody and anti-GlyR antibody positive.[2,3] This apparent link could be explained by two mechanisms: direct pathogenicity and disease course regulation by antibodies against synaptic proteins and intracellular antigens generated during the early stages of a degenerative disease. The latter hypothesis is backed by the research findings of Endres *et al*.,[4] who identified unique neuronal intrathecal antibodies against axon initial segments (AISs) in tissue-based assays in a patient who had symptoms suggestive of the right temporal variety of FTD.

Certain limitations pertain to our report. The follow-up time frame was brief. In the second case, CSF study was not available. The first patient's CSF contained no anti-GABABR antibodies. Furthermore, the clinical specificity of a cell-based assay and a commercial line blot on their own is not well established.[5,6] Furthermore, since an auto-immune profile may be falsely positive, the decision to administer potent immunosuppression, particularly to elderly patients, should be based on clinical judgement.

To conclude, immune-clinical phenotypes may be under-recognized. Suspecting auto-immune etiology in 'atypical' presentations of 'atypical parkinsonism' could identify potentially treatable etiologies and expand the spectrum of this entity.

Ethical compliance statement

Written informed consent was obtained from all participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Highlights

1. 'Immune-mediated cortico-basal syndrome' could be an entity under the rubric of 'atypical atypical parkinsonism'.
2. Important red flags include a history of rapid progression in the initial disease course, stereotypies, seizures, and prominent early sleep disturbance.

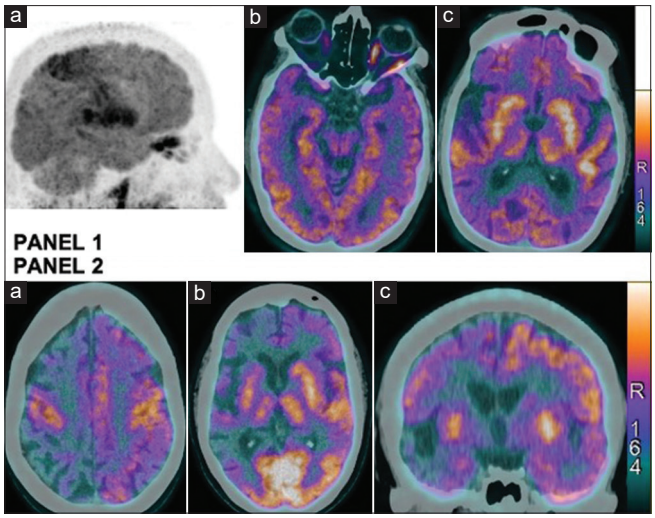

Figure 3: FDG-PET brain imaging. Case 1 (panel 1) - maximum intensity projection (a) and trans-axial fused (b and c) PET/CT images showing relative mesial temporal and basal ganglia hypermetabolism with cortical hypometabolism; Case 2 (panel 2) – trans-axial (a and b) and coronal (c) fused PET/CT images showing hypometabolism in right fronto-parietal (a) and temporal (c) cortices, and right basal ganglia and thalamus (b) > left fronto-parietal cortex (a and b)

3. An auto-immune, paraneoplastic antibody testing (preferably by a two-step approach: brain tissue indirect immunofluorescence, followed by a second appropriate assay), cerebrospinal fluid examination, and a whole body ^{18}F-Fluorodeoxyglucose positron emission tomography scan should be considered in the presence of the above red flags.
4. Early identification of an immune etiology could help initiate appropriate treatment; however, longer follow-up of such cases is required to understand the final disease course and prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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References

1. Gövert F, Leypoldt F, Junker R, Wandinger KP, Deuschl G, Bhatia KP, *et al*. Antibody-related movement disorders-A comprehensive review of phenotype-autoantibody correlations and a guide to testing. Neurol Res Pract 2020;2:6.
2. Abdullah NS, Jan TH, Remli R, Mukari SAM, Ibrahim NM. Anti-GABAB receptor encephalitis presenting with atypical corticobasal syndrome in a patient with Parkinson's disease. J Mov Disord 2020;13:235-7.
3. Muñoz González A, Contreras Chicote A, Vales Montero M, Velázquez Pérez JM, Dela Casa B, Luque Buzo E, *et al*. Antiglycine receptor antibodies and rapidly progressive corticobasal syndrome [abstract]. Mov Disord 2018;33(Suppl 2). Available from: https://www.mdsabstracts.org/abstract/antiglycine-receptor-antibodies-and-rapidly-progressive-corticobasal-syndrome/. [Last accessed on 2022 Sep 26].
4. Endres D, Schlump A, Nickel K, Berger B, Runge K, Lange T, *et al*. Frontotemporal dementia associated with intrathecal antibodies against axon initial segments. Alzheimers Dement 2023;19:736-9.
5. Budhram A, Yang L, Bhayana V, Mills JR, Dubey D. Clinical sensitivity, specificity, and predictive value of neural antibody testing for autoimmune encephalitis. J Appl Lab Med 2022;7:350-6.
6. Ruiz-García R, Martínez-Hernández E, Saiz A, Dalmau J, Graus F. The diagnostic value of onconeural antibodies depends on how they are tested. Front Immunol 2020;11:1482.

Submitted: 25-Jun-2023 **Revised:** 15-Aug-2023 **Accepted:** 16-Aug-2023
Published: 26-Oct-2023

Video available on: https://journals.lww.com/annalsofian

DOI: 10.4103/aian.aian_560_23