Upbeat Nystagmus in Late Onset Cerebellar Ataxia: Think of Anti-Glutamate Decarboxylase 65 Antibody-Associated Cerebellar Ataxia

The Editor,

Glutamate decarboxylase (GAD) is an intracytoplasmic enzyme involved in the conversion of excitatory neurotransmitter glutamate to inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Antibodies against 65-kDa isoform of GAD (GAD 65) are known to cause immune-mediated cerebellar ataxia.[1] GAD 65 associated cerebellar ataxia (CA) is second common neurologic manifestation of GAD 65 antibodies associated neurological syndromes. It is seen commonly in women in about 80–90% of cases usually in sixth decade. Most of the patients present with chronic ataxia with one-third of the patients having subacute presentation.[2] Patients with GAD 65 associated CA can have other autoimmune diseases such as insulin-dependent diabetes mellitus, Addison's disease, hemolytic anaemia, or thyroiditis.[3] The neuro-ophthalmological manifestation in GAD 65 associated CA is downbeat nystagmus, periodic alternating nystagmus (PAN), ocular flutter, opsoclonus and impaired smooth pursuits.[4,5] The occurrence of upbeat nystagmus in GAD 65 associated CA is uncommon. Hereby, we describe a 52-year-old lady with seropositive GAD65 antibodies who presented with slowly progressive ataxia with dysarthria and gravity independent upbeat nystagmus.

A 52-year-old lady presented with history of gait unsteadiness since 1 year. Gait unsteadiness was insidious in onset and slowly progressive with no diurnal variation. She was able to ambulate on her own with occasional need of support at the time of presentation. She had tremulousness of both upper limbs on target oriented activities like holding glass of water, placement of morsel of food into the mouth, etc., slurring of speech in the form of scanning speech and vertiginous sensation while walking since 6 months. There was no headache, seizures, myoclonus, cognitive, or behavioral disturbance. There was no family history of similar complaints. She did not have any medical comorbidity. Systemic examination was unremarkable. Cognitive assessment was normal. She had scanning dysarthria. Fundus examination was normal. Saccades and pursuit were normal. Upbeat nystagmus was noted on asking her to look up with fast phase up both in supine and upright position [Videos 1 and 2; consent taken]. There

was ill-sustained horizontal gaze-evoked nystagmus. Motor and sensory examination was normal. She had bilateral finger–nose incoordination, dysdiadochokinesia, knee–heel incoordination and gait ataxia. Plantar responses were flexor. Routine blood examination including thyroid function test was within normal limits. Glycosylated hemoglobin was normal. Brain magnetic resonance imaging showed mild cerebellar atrophy [Figure 1]. Serum anti-GAD 65 antibodies were strongly positive (qualitative assay). Cerebrospinal fluid analysis was normal. Computed tomography of thorax and abdomen was normal. She was treated with intravenous methylprednisolone (1 g for 5 days) with no improvement followed by large volume plasmapheresis (5 cycles on alternate days) with mild improvement in gait.

Upbeat nystagmus is seen in patients with brainstem infarctions, hemorrhages, tumors, multiple sclerosis, Wernicke encephalopathy, epilepsy, brainstem encephalitis, Creutzfeldt-Jakob disease, Behcet syndrome, meningitis, Chiari malformation, and cerebellar degeneration. It occurs in pontomesencephalic, pontomedullary, and anterior vermis of cerebellum lesions.[6] The cause of spontaneous nystagmus in GAD65 associated CA is due to deficiency of GABAergic neurotransmission in cerebellum with or without brainstem involvement. Downbeat nystagmus is due to the dysfunction in flocculus/parafloccculus. PAN is due to the dysfunction of nodulus/uvula of cerebellum. The cerebellar flocculus inhibits anterior canal vestibular pathways though not the posterior canal pathways. As a result, GAD65 antibodies mediated reduced GABAergic inhibitory control of floccular Purkinje cells cause downbeat nystagmus.[4]

The occurrence of upbeat nystagmus in GAD 65 associated CA is uncommon but has been reported. Martins *et al.*, reported a 68-year-old lady with seropositive GAD65 antibodies who had paraoxysmal central positioning upbeat nystagmus in supine position. On upright position, there was asymptomatic downbeat nystagmus with alternating skew deviation.[7] Feldman *et al.*, reported a 72-year-old woman with progressive cerebellar ataxia, dysarthria of 1 year duration, and upbeat nystagmus which was gravity independent.[8] The involvement of afferents from the vestibular nuclei projecting to the flocculus through caudal medulla, and involvement of cerebellar feedback loop cause upbeat nystagmus which is gravity dependent.[9] The dysfunction of neural integrator for vertical gaze holding also causes upbeat nystagmus which is gravity independent.[10]

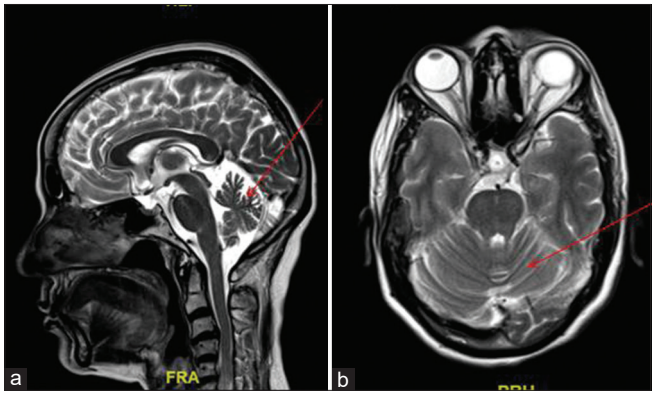

Figure 1: Brain MRI T2 sagittal image (a) and (b) axial image shows cerebellar atrophy (red arrow)

We report a middle-aged lady with progressive pan-cerebellar syndrome with gravity independent upbeat nystagmus and seropositive for GAD65 antibodies. The occurrence of upbeat nystagmus in GAD 65 associated CA widens the aetiology of upbeat nystagmus and provides a clue for the etiological diagnosis in patients presenting with late-onset cerebellar ataxia.

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.

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Conflicts of interest

There are no conflicts of interest.

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