Anti-GAD65 Related Neurological Disorder Presenting as Isolated Hemiataxia: A New Report with Review of Previously Published Patients

To the Editor,

Gamma-aminobutyric acid (GABA) is one of the inhibitory neurotransmitters in the central nervous system. It is synthesized by the action of the enzyme glutamic acid decarboxylase (GAD) on glutamate and GAD65 is mostly confined to the nerve terminals while GAD67 is widely present in various organs and cells.[1] In some individuals, autoantibodies are formed against GAD65 that block the conversion of glutamate to GABA leading to decreased activity of inhibitory neurotransmission and increased motor activity. Anti-GAD antibody syndromes are known for their multiple forms of clinical presentation- classically the stiff person syndrome, ataxic syndrome, limbic encephalitis, and epilepsy.[1,2] Even more complex is the presentation with unilateral symptoms which usually indicate structural diseases of the brain rather than an immune phenomenon. We present one such rare case of anti-GAD antibody-mediated hemiataxia syndrome.

A 40-year-old lady presented with unsteadiness of right upper and lower limbs for the preceding one year. Her initial symptom was overshooting of the right hand past the target while rubbing soap on body. After a month, this difficulty was

noted while washing plates in the kitchen and over the next few months she had to switch to eating with the left hand as her right hand would overshoot and smear food around her mouth. Two months after her hand unsteadiness, she developed a similar overshoot of her right foot while putting on a slipper. Once the slipper was worn, she could grip on to it tightly and walk. Though her right foot was unsteady, she did not have swaying of her body while walking. She had no slurring of speech. There were no twisting movements, abnormal postures, jerks, weakness, or sensory changes in the involved limbs. There was no cognitive decline, seizures, or bulbar symptoms. She followed a non-vegetarian diet, was not diabetic, had never taken alcohol or any chronic medications. There was no exposure to heavy metals or toxins and her family history was non-contributory.

On examination, she had gaze-evoked nystagmus at 30° left gaze, hypotonia of her distal right upper and lower limbs, appendicular ataxia strictly limited to her right upper and lower limbs (past pointing, intention tremor, dysdiadochokinesia, rebound phenomenon, abnormal heel shin test). Truncal ataxia was minimal; evident only on tandem walk, and there was no weakness, extrapyramidal system involvement or features of raised intracranial pressure. The patient thus had a progressive hemiataxic syndrome of 1 year duration; a structural lesion in the right neocerebellum such as a slow-growing mass or inflammatory granuloma was considered.

Investigations revealed normal hemogram, thyroid function tests, liver and renal function tests. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain revealed no structural lesion of the cerebellum or its peduncles. Anti-thyroid peroxidase antibody, anti-TTG-IgA levels, and anti-nuclear antibody were negative. Her serum anti-GAD65 antibody was strongly positive; however, other paraneoplastic antibodies such as anti-yo, Tr, Hu, and CRMP5 were negative. The cerebrospinal spinal fluid examination was normal. A thorough search for occult malignancy revealed none. A diagnosis of anti-GAD65 antibody-mediated cerebellar ataxia was made. She had partial improvement after methylprednisolone pulse treatment and monthly intravenous immunoglobulin infusions. Her post-treatment Scale for the Assessment and Rating of Ataxia (SARA) score[3] was eight (pre-treatment was 11). At 10 months follow up she continued to have unilateral limb ataxia (SARA score-6).

Antibodies against GAD65 result in multi-faceted neurological presentations and are all characterized by a fundamental loss of inhibitory transmission. Cerebellar ataxia is the second most common form of anti-GAD65 disease.[4] Female gender, subacute onset cerebellar dysfunction, preceding episodes of vertigo, brainstem dysfunction, coexisting features of stiff person syndrome, or systemic autoimmunity are clinical pointers towards this entity.[4,5] Anti-GAD65-associated cerebellar ataxia is typically generalized and patients predominantly present with gait disturbance and eye movement abnormalities. Asymmetric involvement of the two sides is a described feature (seen in 20 out of 34 cases in a study[5]) but anti-GAD65 disease presenting as hemiataxia is extremely rare and only a few cases have been described in the literature.

A systematic English literature review was performed to identify previously reported cases of anti-GAD65 disease who presented with hemiataxia in the databases of Scopus, PubMed, and Google Scholar using the keywords "Anti-GAD65-associated cerebellar ataxia" and "Hemiataxia" and "Autoimmune cerebellar ataxia" and "immune-mediated cerebellar ataxia" combined with study filters for original research, case reports and case series. We reviewed the reference list of published articles to increase the sensitivity and to select more studies, which we could not retrieve from databases. Our search found four reports[6-9] describing five cases of anti-GAD65-associated hemiataxia in the literature. Including our case, there was a total of six cases for analysis [Table 1].

All of the cases were above 40 years of age and the majority of them were female (except one). The duration of ataxia symptoms was highly variable (3 weeks to 8 years) and there was no right-left predominance. Four patients had underlying diabetes mellitus (two had insulin-dependent diabetes mellitus), three had thyroiditis and one patient each had pernicious anemia, hepatitis C infection, and primary generalized epilepsy. No associated comorbid condition was noted in one patient (index case). MRI of the brain was normal in two individuals, two patients had generalized cerebellar atrophy, one patient had asymmetric atrophy of the left cerebellar hemisphere, peduncle, and vermis and one patient showed MRI features of chronic small vessel disease. Functional neuroimaging (positron emission tomography [PET] scan) was performed in three out five previously published patients (two had abnormal and one had normal MRI) and all of them had normal PET findings. We could not perform functional neuroimaging in our patient due to nonavailability of these investigations in our institute. Solnes *et al*.[10] performed a retrospective analysis in 23 patients of proven antibody positive autoimmune encephalitis assessing the positivity rate of ^{18}F-FDG PET and MRI. Their results have shown that around 96% patients had at least one region of interest with metabolic changes and the most predominant finding was lobar hypometabolism (commonly in parietal lobe followed by occipital lobe). Overall, the PET scan was more often abnormal during the diagnostic period than MRI (in 96% versus 43% patients, respectively). They concluded that the PET scan may play an important role in the initial diagnostic evaluation of suspected autoimmune encephalitis.

All of the patients received immunotherapy predominantly with pulse methylprednisolone and monthly intravenous immunoglobulins. Two patients showed excellent response to immunomodulation, three had partial recovery, and no

Table 1: Brief details of the patients with anti-GAD65 mediated hemiataxia

Author/ year	Age/ sex	Duration of ataxia	Side of ataxia	Other associated conditions	MRI brain	PET scan (brain/ whole body)	Treatment received	Response to treatment/ comments
Schreck *et al*.,[6] 2016	70/F	3 weeks	Right arm and leg	IDDM, Pernicious anemia, thyroiditis, breast cancer, coronary artery disease, dyslipidemia, progressive encephalopathy	Extensive periventricular and subcortical white matter T2/FLAIR hyperintensities suggestive of chronic small vessel disease	Normal	Plasmapheresis, Rituximab	No improvement, Lost to follow-up after 3 months
Wiels *et al*.,[7] 2017	68/F	2 months	Right leg followed by right arm	DM, Hepatitis C	Normal	Normal	IV MPS, IVIG, Azathioprine	Excellent response to IV MPS
Alchaki *et al*.,[8] 2019	44/M	6 years	Left arm and leg	DM, Primary generalized epilepsy	Asymmetric atrophy of the left cerebellar hemisphere, peduncle, and vermis	Normal	Mycophenolate mofetil	Partial recovery/ stabilization
Hill *et al*.,[9] 2020	75/F	8 years	Left arm and leg	Hashimoto's disease, stiff-person syndrome	Diffuse cerebellar atrophy	Not done	IVIG	Excellent response initially but later had stiff-person syndrome
Hill *et al*.,[9] 2020	62/F	2 months	Left arm, trunk, and leg	IDDM, hypothyroidism	Cavernoma (1.8 cm) in the left putamen and mild diffuse cerebellar atrophy.	Not done	IVIG and Pulse MPS	Partial recovery
Index case	40/F	One year	Right arm, trunk, and leg	None	Normal	Not done	IVIG and Pulse MPS	Partial recovery

response was seen in one patient. Interestingly, one patient who showed an initial excellent response developed other signs of the disease during the illness (stiff-person syndrome and brain-stem dysfunction).[9]

There are interesting examples of autoimmune neurological disorders which present with unilateral signs and symptoms such as Rasmussen's encephalitis, unilateral faciobrachial dystonic seizures of anti-LGI-1 receptor encephalitis, etc.[7] The neurotropism for a particular area of the brain in these autoimmune neurological disorders is intriguing; it may suggest that a particular part or hemisphere of the brain is more susceptible to the destructive effects of the autoantibodies probably due to the variable density of the targets or receptors.

Anti-GAD65-associated cerebellar ataxia is typically generalized and patients predominantly present with gait disturbance and eye movement abnormalities. Anti-GAD65 related hemiataxia is rare and could have been missed if not specifically looked for, as a striking hemiataxia is unusual from non-structural aetiologies.

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.

Aparna Ramachandran, Abdul Gafoor Vazhappully, James Jose, Smita Das, Neetha Balaram

Department of Neurology, Government Medical College, Kozhikode, Kerala, India

Address for correspondence: Dr. Abdul Gafoor Vazhappully, Department of Neurology, Government Medical College, Kozhikode, Kerala - 673 008, India.
E-mail: dragdm@gmail.com

References

1. Tohid H. Anti-glutamic acid decarboxylase antibody positive neurological syndromes. Neurosci Riyadh Saudi Arab 2016;21:215-22.
2. Muñoz-Lopetegi A, de Bruijn MAAM, Boukhrissi S, Bastiaansen AEM, Nagtzaam MMP, Hulsenboom ESP, *et al*. Neurologic syndromes related to anti-GAD65: Clinical and serologic response to treatment. Neurol Neuroimmunol Neuroinflamm 2020;7:e696.
3. Barker RA, Revesz T, Thom M, Marsden CD, Brown P. Review of 23 patients affected by the stiff man syndrome: Clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 1998;65:633-40.
4. Saiz A, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R, *et al*. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: Diagnostic clues for this association. Brain J Neurol 2008;131:2553-63.
5. Ariño H, Gresa-Arribas N, Blanco Y, Martínez-Hernández E, Sabater L,

Petit-Pedrol M, *et al*. Cerebellar ataxia and glutamic acid decarboxylase antibodies: Immunologic profile and long-term effect of immunotherapy. JAMA Neurol 2014;71:1009-16.
6. Schreck KC, Orthmann-Murphy JL, Newsome SD. Clinical reasoning: A 70-year-old woman with acute-onset weakness and progressive hemiataxia. Neurology 2016;87:e264-8.
7. Wiels W, Guisset F, Vandervorst F, Peeters I, Seynaeve L, Costa O, *et al*. Rapidly progressive cerebellar hemiataxia with high levels of GAD65 reactive antibodies. Mov Disord Clin Pract 2017;4:632-4.
8. Alchaki AR, Anadani N, Morrison P, Samkoff L. Anti-GAD 65 antibody mediated cerebellar hemiataxia. Neurology 2019;92:P2.2-043.
9. Hill EJ, Jankovic J. Antiglutamic acid decarboxylase 65 antibody-associated hemiataxia. Neurol Clin Pract 2021;11:e564-6.
10. Solnes LB, Jones KM, Rowe SP, Pattanayak P, Nalluri A, Venkatesan A, *et al*. Diagnostic value of 18F-FDG PET/CT versus MRI in the setting of antibody-specific autoimmune encephalitis. J Nucl Med 2017;58:1307-13.

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