Journal of Ophthalmology & Visual Sciences

Open Access

Austin Publishing Group

Case Report

# Downbeat Nystagmus (DBN)? Could the Anti-GAD Antibodies be the Culprit? A Case Report

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**Received:** August 16, 2021; **Accepted:** October 07, 2021; **Published:** October 14, 2021

**Abstract**

Downbeat Nystagmus (DBN) is a vertical nystagmus characterized by fast phase in the downgaze, usually caused by diseases of vestibulocerebellum. We describe a 67-year-old woman with hypothyroidism and diabetes mellitus, who presented with imbalance and hearing loss and was thought to have Meniere's disease. She was referred for evaluation of nystagmus that was noted during vestibular rehabilitation. Exam revealed DBN but was otherwise unremarkable. MRI head revealed ischemic white matter changes. A serum paraneoplastic antibody panel revealed elevated Glutamate Decarboxylase (GAD) 65 antibodies. This is a unique case of DBN which we believe was caused by anti-GAD 65 antibodies besides also being linked to her diabetes but interestingly she did not show cerebellar degeneration clinically or radiologically when monitored over time.

**Keywords:** Downbeat nystagmus; Cerebellar degeneration; Anti-glutamic acid decarboxylase (GAD) antibodies; Case report

## Introduction

Downbeat Nystagmus (DBN) is a vertical nystagmus characterized by fast phase in the downgaze with velocity increasing on lateral and downward gaze and on convergence. The causes of DBN are diverse. The most common cause is a structural lesion of the cervicomedullary junction, such as a Chiari Malformation or a meningioma. Other etiologies include cerebellar degeneration (idiopathic or induced by alcohol), spinocerebellar degeneration such as in spinocerebellar ataxia type 6, an acquired autoimmune disorder, multiple sclerosis and brainstem infarction (accounting for about 10%) [1], toxicity from lithium and anticonvulsants and nutritional causes such as hypomagnesemia and thiamine deficiency. The cause remains unknown in about 40% [2]. Anti-Glutamic Acid Decarboxylase (GAD) antibodies have been associated with down beat nystagmus and cerebellar ataxia [3]. Glutamic Acid Decarboxylase (GAD) is the enzyme that catalyzes the conversion of glutamic acid to the neurotransmitter Gamma-Amino Butyric Acid (GABA). GAD is synthesized mainly in presynaptic GABAergic neurons in the Central Nervous System (CNS) and in the βcells in the islets of Langerhans in the pancreas. There are two GAD isoforms - one with 67kDa and other with 65kDa. Although both are expressed in the CNS, autoimmunity is usually directed against the 65kDa isoform in neurological diseases. Antibodies Against GAD (anti-GAD-Ab) are associated with an array of autoimmune-related neurological conditions, such as stiff-person syndrome, cerebellar ataxia, epilepsy and limbic encephalitis [4,5] We hereby report a unique case of down beat nystagmus without any cerebellar dysfunction in a patient who was found to have anti GAD 65 antibodies.

## Case Presentation

This is a 67-year-old female with a history of hypothyroidism and diabetes mellitus type 2 who developed symptoms of dizziness, imbalance, vertigo, nausea and vomiting about 4 years ago. Patient reported a 15-20 lb. weight loss from vomiting. There was no history of headache, motor weakness or sensory symptoms. Upon further evaluation, bilateral hearing loss was noted, and the patient was diagnosed with Meniere's disease by otolaryngologist. She was started on diazepam and hydrochlorothiazide and noted symptomatic relief of both vertigo and nausea. She was noted to have nystagmus during her vestibular rehabilitation that initiated a referral to neuro-ophthalmology. She was also experiencing oscillopsia. On her neuro-ophthalmology exam best corrected visual acuity was 20/30 OU, with normal color vision OU, reduced contrast sensitivity OU and poor stereopsis. She had high frequency low amplitude downbeat nystagmus more pronounced in end gaze and down gaze that interestingly showed dampening with convergence. She was orthophoric for distance and near. Anterior segment exam showed age related cataract and fundus exam was unremarkable except for incidental choroidal nevi in the right eye. Neurology exam was otherwise unremarkable with no evidence of cerebellar dysfunction. Contrast enhanced Magnetic Resonance Imaging (MRI) of the brain showed multiple periventricular white matter lesions consistent with chronic ischemic changes, but without brainstem or cerebellar lesions. MRI of the whole spine did not show any cord lesions. A serum paraneoplastic antibody panel revealed significantly high levels of anti-GAD65 antibody (46 nmol/lt). CT chest with contrast showed 2-3 mm benign appearing nodules in the lung that was previously known to her. No abnormalities were noted on CT abdomen and pelvis with contrast. Anti- Neuromyelitis Optica (NMO) and anti-Myelin Oligodendrocyte Glycoprotein antibodies (MOG) were negative. She declined lumbar puncture. Patient was placed on baclofen and reported symptomatic improvement of her oscillopsia. She declined further treatment with immune suppressive agents. The pattern of her nystagmus remained unchanged during her follow-up over 3 years with no other abnormal findings noted on ophthalmology and neurology exam.




**Citation:** Sudhakar P and Hyder S. Downbeat Nystagmus (DBN)? Could the Anti-GAD Antibodies be the Culprit? A Case Report. J Ophthalmol & Vis Sci. 2021; 6(3): 1056.

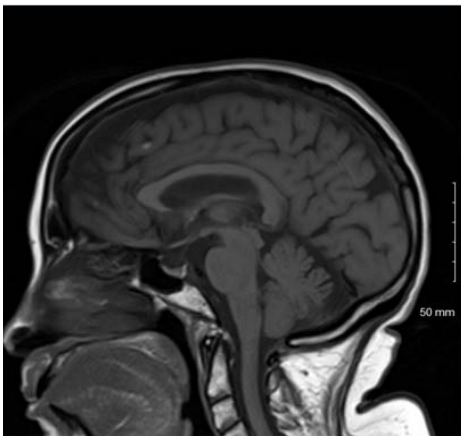


**Figure 1:** MRI head Sagittal T1 sequence showing no cerebellar atrophy.

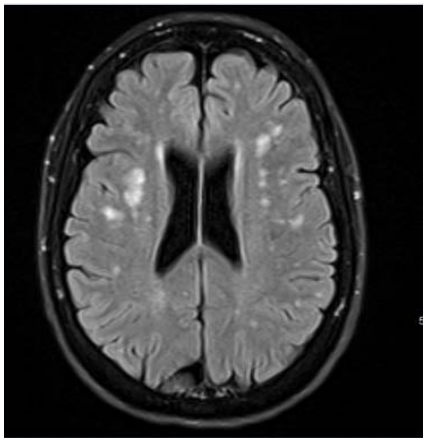

**Figure 2:** MRI head Axial Flair sequence showing numerous hyper intense lesions scattered in the cerebral white matter that was suggestive of ischemic white matter disease.

## Discussion

The heterogeneity of neurological syndromes associated with anti-GAD-Ab is most likely related to the widespread distribution of GABAergic neurons in the CNS as these cells have a large amount of GAD [6]. Thus, antibodies to GAD could cause dysfunction of GABAergic cerebellar Purkinje Cells (PCs), which are part of the vertical gaze-velocity system located in the flocculus and inhibit the Superior Vestibular Nucleus (SVN). The dysfunction of these GABAergic cells leads to hyperactivity of SVN neurons which project to the third cranial nerve nucleus, leading to upward gaze deviation followed by a corrective downward quick phase [7]. The most common cause of secondary DBN is cerebellar degeneration. Other secondary causes include anti-epileptic medications and underlying malignancies [8,9]. The most common presenting symptom of DBN is persistent rather than episodic unsteadiness of gait. Oscillopsia was seen with 38% of secondary and 44% of idiopathic cases [10]. The exact role of anti-GAD-Ab and GABAergic neurotransmission in the pathogenesis of the neurological manifestations is not well understood, however a number of neurological disorders have been described in patients with autoimmunity related to anti-GAD antibodies [6]. Downbeat nystagmus and periodic alternating nystagmus have been

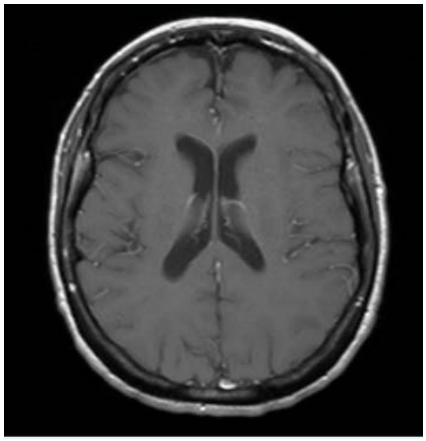

**Figure 3:** MRI head axial post contrast T1 sequence shows no enhancement of the white matter lesions.

reported as an isolated manifestation of anti-GAD autoimmunity. While our patient's diabetes and hypothyroidism could be associated with the presence of anti-GAD antibodies [11], we strongly suspect that her downbeat nystagmus was immunologically mediated by her anti-GAD positivity. Interestingly her MRI head that has now been repeated more than once has not shown cerebellar degeneration yet, but still needs periodic monitoring. Also, there is no definite evidence for a demyelinating or autoimmune disease like MS, NMO or MOG. Unfortunately, she declined further evaluation with lumbar puncture and treatment with immune modulating therapy.

## Conclusion

This is a rare case of downbeat nystagmus that seems central in origin and related to anti GAD antibodies suggesting possible autoimmune etiology.

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