Anti-GAD Antibodies and Periodic Alternating Nystagmus

Caroline Tilikete, MD; Alain Vighetto, MD; Paul Trouillas, MD; Jérome Honnorat, MD

**Background:** Autoantibodies directed against glutamic acid decarboxylase (GAD-Ab) have recently been described in a few patients with progressive cerebellar ataxia, suggesting an autoimmune physiopathologic mechanism.

**Objective:** To determine the exact role of GAD-Ab and γ-aminobutyric acid (GABA)-ergic neurotransmission in the pathogenesis of cerebellar ataxia.

**Design:** Case report.

**Setting:** University neurological hospital.

**Patient:** We report the case of a patient with subacute cerebellar ataxia associated with GAD-Ab showing periodic alternating nystagmus (PAN).

**Intervention:** Baclofen, a GABAergic medication, was given to the patient.

**Main Outcome Measures:** Eye movement recording of spontaneous nystagmus and postrotatory vestibular responses.

**Results:** Baclofen was effective in suppressing PAN and improving postrotatory vestibular responses but not for improving cerebellar ataxia.

**Conclusion:** The presence of PAN and the response to baclofen provide a unique opportunity to suggest a direct role of GAD-Ab in cerebellar dysfunction in this patient.

Arch Neurol. 2005;62:1300-1303

---

GluTAMIC ACID DECARBOXylase (GAD) is a major enzyme of the nervous system that catalyzes the conversion of glutamate to γ-aminobutyric acid (GABA). Antibodies against GAD (GAD-Ab) have been identified in association with neurological manifestations such as stiff-person syndrome and more recently late-onset cerebellar ataxia. The frequent association of the latter with other autoimmune diseases as well as cerebrospinal fluid (CSF) inflammation suggests that late-onset cerebellar ataxia could have an autoimmunemediated pathogenesis when associated with GAD-Ab.

The pathogenic role of GAD-Ab is controversial. Whether GAD-Ab can be present as an epiphenomenon caused by destruction of the nervous system or whether neurological manifestations can be related to impaired GABA synthesis due to GAD-Ab is debated. We report the case of a patient presenting with late-onset cerebellar ataxia associated with periodic alternating nystagmus (PAN). Precise knowledge of the physiopathologic mechanism of this nystagmus and its response to treatment may help to better understand that of neurological symptoms associated with GAD-Ab.

A 76-year-old woman was admitted to the hospital for a 3-year history of slowly progressive cerebellar ataxia, blurred vision, and cognitive dysfunction. She had age-related macular degeneration but no history of insulin-dependent diabetes mellitus.

At examination, she presented with marked ataxia of stance and gait, mild ataxia of the right side of the body, and hypotonia. Adiadochokinesis was marked in her right hand. She had a score of 37 of 100 on the International Cooperative Ataxia Rating Scale. A neuropsychological examination disclosed memory and ex-
ective dysfunction. There were no signs of stiff-person syndrome. An oculomotor examination disclosed a horizontal jerk-form nystagmus in the primary position of gaze, changing direction every 2 minutes, which was diagnosed as PAN. Gaze-evoked nystagmus, impaired smooth-pursuit movements, and absent suppression of the vestibulo-ocular reflex (VOR) by fixation were also observed. Visual acuity, measured when the nystagmus stopped before reversing, was 20/50 OD and 20/100 OS at distance and 20/60 OD and 20/200 OS at near. An ophthalmological examination disclosed retinal signs of macular degeneration. Magnetic resonance imaging of the brain showed marked cerebellar atrophy with moderate cortical and subcortical atrophy of both cerebral hemispheres. Although the CSF cell count and protein content were normal, numerous oligoclonal IgG bands were found. The complete blood cell count and standard biological test results were normal. Infections with human immunodeficiency virus and borreliosis were excluded. There was no evidence of any malignancy or paraneoplastic cerebellar degeneration; the patient tested negative for anti-Yo, anti-Hu, anti-Ri, antiamphiphysin, and anti-CV2 antibodies in the serum and CSF. There was no diabetes mellitus; thyroid hormone and thyroid antibody levels were normal. There was no evidence of any other autoimmune disease; results of tests for antinuclear, anticytoplasm of the neutrophile polynuclear, antientomysium, and antigludin antibodies were negative. Vitamin E, B1, B6, B12, and folate deficiencies were excluded. The GAD-Ab were measured by immunohistochemical analysis on frozen sections of paraformaldehyde-fixed rat cerebellum as previously described. GAD-Ab were found at high levels in both the serum sample (1:16000) and the CSF (<1:500).

Our patient was treated with baclofen (30 mg/d), and PAN was abolished within 3 weeks of progressive treatment. Visual acuity slightly improved at near: 20/50 OD and 20/100 OS. The ataxia did not improve, although a slight improvement on the ataxia scale was noted: 30 of 100. Cognitive functions were not modified, and higher doses were not tolerated by the patient.

**EYE MOVEMENT RECORDING**

Low-frequency (50-Hz sampling) 2-dimensional infrared video-oculography was used (VNG Ulmer; Synapsys, Marseille, France). The patient wore a mask, with a camera fixed in front of the right eye. Using contrast image detection of the eye and iris, horizontal and vertical positions of the eye were automatically calculated online. After calibration, spontaneous nystagmus was recorded in the primary eye position. Eye movement recording in our patient showed PAN, with a peak slow-phase velocity of 15% in darkness and an oscillatory period of 4 minutes (Figure 1). The patient gave informed consent for eye movement recording in accordance with the requirements of the hospital’s ethics committee and the Declaration of Helsinki.

Right and left postrotatory VORs (progressive ramp of 60% of constant velocity for 1 minute followed by 100% of deceleration step) were elicited in the horizontal plane. The step was applied when the nystagmus was stopping before reversing. The time constant of postrotatory VOR was about 25 seconds and was abnormally long for both directions (Figure 2A and B). During treatment with baclofen, PAN was abolished and the postrotatory time constant returned to normal (Figure 2C and D).

Periodic alternating nystagmus is the best-understood form of acquired central nystagmus, with an animal model, a mathematical model, and drug treatment (baclofen) that works in both animals and humans. Therefore, PAN in this patient provides a unique opportunity to better understand the mechanisms of cerebellar dysfunction in GAD-Ab disorders.

Acquired PAN is a spontaneous horizontal nystagmus present in primary gaze that reverses its direction about every 2 minutes. In humans and monkeys, PAN has been reported with lesions of the caudal and medial parts of the cerebellum, involving mostly the nodulus and uvula. The nodulus and uvula appear to control the time course of postrotational VOR, leading to prolonged VOR as found in our patient. Normal vestibular repair mechanisms act to reverse the direction of the nystagmus, determining its periodic oscillations. Such oscillations would normally be suppressed by visual fixa-
tion. In our patient, poor visual acuity due to age-related macular degeneration as well as floccular involvement, known to control smooth-pursuit movements and fixation, might explain the occurrence of nystagmus. In most patients with acquired PAN, a GABAergic drug, baclofen, abolishes nystagmus.\textsuperscript{9,10} Pharmacological evidence suggests that the nodulus and uvula maintain inhibitory control of the duration of vestibular rotational responses by using GABA.\textsuperscript{14} In our patient, we suggest that acquired PAN is linked to a functional GABAergic deficit of the cerebellar pathways that can be alleviated by a GABAergic drug, baclofen.

The pathogenic effect of GAD-Ab in neurological manifestations is not yet fully accepted, specifically in progressive late-onset cerebellar ataxia. The frequency of insulin-dependent diabetes mellitus and other organ-specific autoimmune manifestations observed in this group of patients, as well as the high percentage of CSF inflammation, suggests that this cerebellar syndrome could have an autoimmune-mediated pathogenesis.\textsuperscript{15,16} In this case, one could suggest that autoimmunity directed against GAD would disturb GABA synthesis and GABAergic neurotransmission. Experimental data have shown that the serum or CSF of patients with stiff-person syndrome leads to functional impairment of GABAergic synaptic transmission in vitro, suggesting a specific effect of GAD-Ab.\textsuperscript{16} This functional impairment of GABAergic transmission is not found in the serum of patients with stiff-person syndrome without GAD-Ab.\textsuperscript{16} Furthermore, it has been shown that immunoglobulins present in the CSF of a patient with ataxia associated with GAD-Ab selectively suppress presynaptic GABA-mediated transmission from the basket cells to the Purkinje cells in the cerebellum.\textsuperscript{17}

Our study supports the hypothesis of GABAergic neurotransmission impairment by showing that at least some neurological manifestations are the result of a GABAergic neurotransmission deficit, suggesting a pathogenic role of these antibodies. Along these lines, isolated downbeat nystagmus associated with GAD-Ab has recently been reported.\textsuperscript{18} Although no attempt to treat the patient with GABAergic drugs was mentioned in the publication, the authors suggest GABAergic neurotransmission involvement at the floccular level. Our patient also presented with cerebellar ataxia and cognitive impairment that did not respond to baclofen. This absence of a drug response might be due to the more complex GABAergic neural circuitry for the control of ataxia and cognitive functions. It could also be caused by permanent neuronal loss and/or other mechanisms, such as a cellular-mediated autoimmune pathogenesis.

Accepted for Publication: July 12, 2004.

Correspondence: Caroline Tilikete, MD, Neuro-Ophthalmology Unit, Hôpital Neurologique, Hospices Civils de Lyon, 59 Bd Pinel, 69 677 Bron CEDEX, France (tilikete@lyon.inserm.fr).

---

Figure 2. Recording of postrotatory vestibulo-ocular reflex (VOR) before (A and B) and after (C and D) treatment by baclofen in the patient. Postrotatory VOR was elicited in the horizontal plane, either to elicit a leftward response (A and C) or a rightward response (B and D). The cumulative slow-phase eye position is presented (y-axis) as a function of time (x-axis) in postrotatory conditions. Note the longer duration and slope of postrotatory responses before as compared with after treatment for both rotations. The time scale is equivalent on the 4 plots.
Author Contributions: Study concept and design: Tilikete, Vighetto, Trouillas, and Honnorat. Acquisition of data: Tilikete. Analysis and interpretation of data: Tilikete, Vighetto, and Honnorat. Drafting of the manuscript: Tilikete, Vighetto, Trouillas, and Honnorat. Critical revision of the manuscript for important intellectual content: Vighetto, Trouillas, and Honnorat. Study supervision: Honnorat.

REFERENCES