Anti-GAD Antibodies and Periodic Alternating Nystagmus

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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 y-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.

Report of a Case

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 borrellosis 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, antiendomysium, and antiglaidin 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°/s 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°/s of constant velocity for 1 minute followed by 100°/s² of deceleration step) were elicited in the horizontal plane. The step was applied when the nystagmus was stop-

*Figure 1. Recording of periodic alternating nystagmus in the patient. Positive values of horizontal eye position are assigned to rightward (R) movements, negative values to leftward (L) movements. A, Nystagmus is right beating. B, Nystagmus is changing direction. C, Nystagmus is left beating. Absent data are due to blinking.*
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.9,10 Pharmacological evidence suggests that the nodulus and uvula maintain inhibitory control of the duration of vestibular rotational responses by using GABA.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.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.16 This functional impairment of GABAergic transmission is not found in the serum of patients with stiff-person syndrome without GAD-Ab.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.17

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.
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REFERENCES


Trial Registration Required

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For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archneurol.com.