Potential Role of Anti-GAD Antibodies in Abnormal Eye Movements

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ABSTRACT: Glutamic acid decarboxylase (GAD) catalyzes the conversion of glutamic acid to γ-aminobutyric acid (GABA). Autoantibodies directed against GAD (antiGAD-Ab) have been described in patients with insulin-dependent diabetes mellitus, stiff-man syndrome, and in a few patients with progressive cerebellar ataxia. The presence of these autoantibodies suggests an autoimmune pathophysiological mechanism for the neurological manifestations in these disorders. However, the exact role of antiGAD-Ab and GABAergic neurotransmission in the pathogenesis of the neurological manifestations, particularly in progressive cerebellar ataxia, is not fully understood. The cases of two patients with subacute cerebellar ataxia associated with antiGAD-Ab presenting with abnormal eye movements are reported. One patient presented a periodic alternating nystagmus (PAN), whereas the other presented a downbeat nystagmus (DBN) and slow vertical saccades. The potential role of antiGAD-Ab and the resultant GABAergic neurotransmission deficit in oculomotor manifestations is discussed.

KEYWORDS: glutamic acid decarboxylase (GAD); antiGAD-Ab; nystagmus; γ-aminobutyric acid (GABA); progressive cerebellar ataxia; saccades

INTRODUCTION

Glutamic acid decarboxylase (GAD) is a major enzyme in the nervous system that catalyzes the conversion of glutamic acid to γ-aminobutyric acid (GABA). GABA is a major inhibitory neurotransmitter in the nervous system, but also is present within the β cells of the pancreas. GAD has long been identified as an essential autoantigen in the development of stiff-person syndrome and insulin-dependent diabetes mellitus.
Anti-GAD antibody (antiGAD-Ab) has more recently been identified in association with late-onset cerebellar ataxia.\textsuperscript{5–8}

The specific and pathogenic role of antiGAD-Ab in neurological disorders such as cerebellar ataxia is not fully understood.\textsuperscript{9,10} These autoantibodies could be an epiphenomenon caused by destruction of the nervous system. However, the increased association with other autoimmune manifestations, as well as evidence for intrathecal inflammation, suggest an autoimmune-mediated cerebellar impairment. In the case of a direct role of antiGAD-Ab in this disease, can we provide evidence that neurological manifestations are related to a functional deficit in GABAergic neurons?

We report on two patients presenting with late-onset cerebellar ataxia and abnormal eye movements associated with the presence of anti-GAD antibodies. We suggest that precise knowledge of the pathophysiology of abnormal eye movements in these cases may help to better understand the pathophysiology of neurological symptoms associated with antiGAD-Ab. Moreover, the occurrence of abnormal eye movements with antiGAD-Ab antibodies may also help to better understand the neurochemistry of the eye-movement neural network. One of the two cases has been reported previously.\textsuperscript{11}

\textbf{CASE REPORTS}

\textbf{Case 1}

This 76-year-old female was admitted to hospital with a three-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.

On examination, she presented with axial and appendicular cerebellar ataxia. Neuropsychological examination disclosed memory and executive dysfunction. There were no signs of stiff-person syndrome. Oculomotor examination disclosed a horizontal jerk–form nystagmus in primary gaze, changing direction every two minutes, which was diagnosed as a periodic alternating nystagmus (PAN). Gaze-evoked nystagmus, impaired smooth pursuit, and absent suppression of the vestibulo-ocular reflex by fixation were also observed. Ophthalmological examination disclosed retinal signs of macular degeneration. Brain MRI showed marked cerebellar atrophy with moderate cortical and subcortical atrophy of both cerebral hemispheres. Her cerebrospinal fluid (CSF) showed oligoclonal IgG bands. Blood cell count and biological tests performed for cerebellar ataxia were normal except for antiGAD-Abs, which were found at high levels in both serum and CSF.

She was treated with baclofen (30 mg/day). PAN was abolished within three weeks of progressive treatment. Ataxia did not improve, cognitive functions were not modified, and higher doses were not tolerated by the patient.

\textbf{Case 2}

This 60-year-old female was admitted to hospital with a six-month history of slowly progressive cerebellar ataxia and oscillopsia. She had no history of insulin-dependent diabetes mellitus.
On examination, she presented with marked ataxia of stance and gait with diffuse hypotonia. Oculomotor examination disclosed a downbeat nystagmus in primary gaze, increasing in lateral gaze. Oculomotor examination did not reveal gaze-evoked nystagmus in lateral gaze. Vertical smooth pursuit was broken and suppression of the vestibulo-ocular reflex by fixation was weak. She had interestingly very slow upward saccades. Horizontal, downward saccades as well as torsional saccades during VOR were clinically normal. Ophthalmological examination was normal. Brain MRI was unremarkable. CSF showed oligoclonal IgG bands. Blood cell count and biological tests performed for cerebellar ataxia were normal except for antiGAD-Abs, which were found at high levels in both serum and CSF.

She was treated with baclofen (30 mg/d) without any change in the nystagmus or in saccade velocity. She was subsequently placed on 3,4-diaminopyridine for three months, but has not been examined since then.

**EYE-MOVEMENT RECORDING**

The two patients gave informed consent for eye-movement recording in accordance with the requirements of the ethical committee and the Declaration of Helsinki. Normative data (mean ± 2 SD) were obtained from 20 normal subjects (8 males, 12 females; mean age = 41 years, range 34 to 47).

**Slow Eye-Movement Recording**

Low-frequency (50-Hz sampling) two-dimensional (2D) infrared video-oculography was used (VNG Ulmer, Synapsys, Marseille, France). Each patient wore a mask, with a camera fixed in front of the right eye. Using contrast image detection of the eye and iris, the horizontal and vertical positions of the eye were calculated on-line. After calibration, spontaneous nystagmus was recorded in the central eye position. Thereafter, horizontal (0.1 Hz, 3-deg amplitude) and vertical (0.1 Hz, 28-deg amplitude) smooth pursuit, sinusoidal vestibulo-ocular reflex (VOR) (0.25 Hz, 60-deg/s peak velocity), visuovestibular interaction (VVOR) (0.25 Hz, 60-deg/s peak velocity), and postrotatory VOR (60-deg/s constant velocity for 1 min, 100-deg/s/s deceleration) were elicited in the horizontal plane. The measurements made were of the horizontal and vertical slow-phase velocity of spontaneous nystagmus, and gain (peak slow-phase velocity/peak stimulus velocity) for horizontal and vertical smooth pursuit, VOR, and VVOR.

**Saccade Recording**

High-frequency (200-Hz sampling) 2D binocular infrared video-oculography was used (Visuo200, Synapsys, Marseille, France). Each patient wore a helmet on which a camera was fixed 10 cm from the nose and oriented to record both eyes at the same time. Saccades were elicited by LEDs, presented on a ramp located 1.5 m in front of the patient. LEDs evoked 30-deg horizontal saccades (right or left) and 12.5-deg vertical saccades (up or down). The parameters used were the latency, peak velocity, and gain (amplitude of initial eye movement/amplitude of target movement) of horizontal and vertical saccades.
RESULTS

Results of eye-movement recording in the control group and the two patients are summarized in Table 1.

Case 1

Eye-movement recording in Case 1 showed periodic alternating nystagmus, with a peak slow-phase velocity of 30 deg/s in darkness and an oscillatory period of 4 min (Fig. 1). It also showed gaze-evoked nystagmus in eccentric eye position. A few downward beats were observed when the horizontal nystagmus paused before reversing. This horizontal nystagmus was taken into account for the following gain measurements. Horizontal smooth-pursuit gain was found to be increased as compared with controls, whereas vertical smooth pursuit was absent. Sinusoidal VOR gain was within the normal range. However, VOR showed insufficient gain decrease during VOR suppression. The time constant of postrotatory VOR (the step was applied when the nystagmus paused before reversing) was abnormally long for both directions. Finally, both horizontal and vertical saccades showed velocity, latency, and accuracy within the normal range.

Case 2

Eye-movement recording in Case 2 showed downbeat nystagmus, with a peak slow-phase velocity of 8 deg/s in primary gaze, increasing to 15 deg/s in lateral gaze. There was decreased gain of horizontal smooth pursuit as compared with controls, whereas only downward smooth pursuit was absent. Sinusoidal VOR gain was with-
## TABLE 1. Normative range for oculomotor and vestibular testing (20 normal subjects) and patient data

<table>
<thead>
<tr>
<th></th>
<th>Normative range</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous nystagmus</strong></td>
<td>None</td>
<td>Periodic alternating nystagmus</td>
<td>Downbeat nystagmus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15°/s</td>
<td>8°/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gaze-evoked nystagmus</td>
<td></td>
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<tr>
<td><strong>Ocular motor testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Saccades</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal (±30°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td>210 to 490°/s</td>
<td>To the left</td>
<td>To the right</td>
</tr>
<tr>
<td>Latency</td>
<td>155 to 295 ms</td>
<td>220°/s</td>
<td>225°/s</td>
</tr>
<tr>
<td>Accuracy</td>
<td>82 to 100%</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td>Vertical (±12.5°)</td>
<td></td>
<td>Upward</td>
<td>Downward</td>
</tr>
<tr>
<td>Velocity</td>
<td>170 to 450°/s</td>
<td>325°/s</td>
<td>178°/s</td>
</tr>
<tr>
<td>Latency</td>
<td>125 to 325 ms</td>
<td>302 ms</td>
<td>310 ms</td>
</tr>
<tr>
<td>Accuracy</td>
<td>85 to 105%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Pursuit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal (0.1 Hz, 35°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.55 to 0.95</td>
<td>To the left</td>
<td>To the right</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.17°/s</td>
<td>1.17°/s</td>
</tr>
<tr>
<td>Vertical (0.1 Hz, 28°)</td>
<td></td>
<td>Upward</td>
<td>Downward</td>
</tr>
<tr>
<td>Gain</td>
<td>0.45 to 1.05</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Pendular VOR (0.25 Hz, 60°/s peak velocity)</td>
<td>0.30 to 0.70</td>
<td>Left rotation</td>
<td>Right rotation</td>
</tr>
<tr>
<td>Gain</td>
<td></td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>VVOR (0.25 Hz, 60°/s peck velocity)</td>
<td>0 to 0.13</td>
<td>Left rotation</td>
<td>Right rotation</td>
</tr>
<tr>
<td>Gain of VOR fixation</td>
<td></td>
<td>0.46°/s</td>
<td>0.46°/s</td>
</tr>
<tr>
<td>Post rotatory VOR (at 100°/s²)</td>
<td>7 to 19 s</td>
<td>Left deceleration</td>
<td>Right deceleration</td>
</tr>
<tr>
<td>Time constant</td>
<td></td>
<td>25°/s</td>
<td>25°/s</td>
</tr>
</tbody>
</table>

*For abnormal data. **ABBREVIATIONS:** VOR: vestibulo-ocular reflex; VVOR: visuo-vestibular interaction.
in the normal range. However, VOR showed insufficient gain decrease during VOR suppression. The time constant of postrotatory VOR was found to be normal for both directions. Horizontal and vertical saccades showed hypometria in all directions. However, vertical saccades were almost absent or were hypometric with very slow velocities less than 100 deg/s (Fig. 2). Main sequence analysis was uninterpretable, because of the low number of upward saccades made by the patient. The upward

**FIGURE 2.** Recording of (a) horizontal and (b) vertical saccades in Case 2. In both plots, eye position (in deg) is represented by the *thick line* and left-sided scale, and eye velocity (in deg/s) is represented by the *thin solid line* and right-sided scale. Target positions are also represented by *dotted lines*. For both horizontal position and velocity, positive values are assigned to rightward movements, negative values to leftward movements. For both vertical position and velocity, positive values are assigned to upward movements and negative to downward ones. Vertical saccades were almost absent or with very slow velocities, less than 100 deg/s.
slow phase may partly explain the hypometric upward vertical saccades. However, the major observation was absent upward saccades, suggesting a specific involvement of vertical rapid eye movements.

**DISCUSSION**

We report the cases of two patients showing different oculomotor manifestations in association with cerebellar ataxia and anti-GAD antibodies. The main oculomotor manifestation in Case 1 was a periodic alternating nystagmus, whereas Case 2 presented with downbeat nystagmus (DBN) and slowed or absent vertical saccades. In the following, we discuss the potential involvement of antiGAD-Ab and the resultant GABAergic neurotransmission deficit in these oculomotor manifestations.

As previously discussed, PAN in Case 1 provides the opportunity to invoke the direct implication of antiGAD-Ab in cerebellar dysfunction. In man 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 the postrotational vestibulo-ocular response (VOR), leading to prolonged VOR, as found in our patient. Normal vestibular repair mechanisms act to reverse the direction of the nystagmus, causing periodic oscillations of the nystagmus. Such oscillations would normally be suppressed by visual fixation. In our patient, poor visual acuity due to age-related macular degeneration, as well as floccular involvement, known to control smooth pursuit and fixation, might explain the occurrence of the nystagmus. Pharmacological evidence suggests that the maintenance of nodular and uvular inhibitory control on the duration of vestibular rotational responses is mediated by GABA. Indeed, in our patient, as in most patients with acquired PAN, the GABAergic drug, baclofen, abolishes nystagmus. Therefore, in Case 1, we suggest that acquired PAN is linked to a functional GABAergic deficit of cerebellar pathways that can be alleviated by the GABAergic drug baclofen.

DBN is the most frequent oculomotor manifestation associated with progressive cerebellar ataxia. It has been attributed to lesions involving the posterior cerebellum, especially the flocculus and paraflocculus. The exact pathophysiological mechanism of DBN is not yet known. The more widely accepted explanation currently is an asymmetry in the activity of vertical slow-phase pathways (see Ref. 20 for review). Whether this asymmetry involves a vertical vestibulo-ocular, smooth pursuit, or velocity-to-position integrator has not been determined yet. However, it is widely assumed that this tonic asymmetry is nearly perfectly suppressed by a posterior cerebellar central mechanism, but is released from inhibition when these cerebellar structures are lesioned. In our patient, the presence of abnormal horizontal and vertical smooth pursuit and VOR suppression support the hypothesis of floccular involvement. A case of isolated downbeat nystagmus associated with antiGAD-Ab has been reported recently. Both these cases suggest GABAergic neurotransmission involvement at the floccular level. Absence of drug response (baclofen) might be due to the more complex neural circuitry for the control of vertical slow-phase eye movements.

Both PAN and DBN could be explained by GABAergic neurotransmission impairment at the Purkinje cell level. Case 2 presented with abnormal vertical saccades, suggesting a specific involvement of upward vertical saccade pathways. Although
much has been learned about the anatomy and physiology of the saccadic system, the pharmacology is still being elucidated. Slow saccades are best explained by lesions involving the excitatory burst neurons or omnipause neurons. In order to explain isolated slowness or absence of upward vertical saccades, involvement of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), where burst neurons for vertical and torsional saccades are located, might be suggested. However, looking for GABAergic neurons in the rostral mesencephalon, Horn et al. could not show direct inhibitory GABAergic neurons from the riMLF to the oculomotor nucleus. On the other hand, these authors found direct GABAergic projections from the interstitial nucleus of Cajal (INC) to the oculomotor neurons that could be involved in the inhibition of premotor down burst tonic neurons during upward eye movements. In Case 2, a GABAergic neurotransmission deficit due to antiGAD-Ab could alter the function of these inhibitory neurons and the execution of upward saccades. A precise analysis of the velocity waveform of upward saccades could help to demonstrate abnormal braking instead of general slowness of vertical saccades. Other unknown GABAergic saccadic inhibitory pathways might also be involved in the upward vertical saccade deficit in Case 2.

In conclusion, we report the cases of two patients in whom nystagmus is probably explained by GABAergic neurotransmission deficits. These observations suggest a direct pathogenic role of antiGAD-Ab in the occurrence of neurological manifestations. Given such a hypothesis, the occurrence of other abnormal eye movements, such as the abnormal upward saccades in Case 2, may help to better understand the neurochemistry of the eye-movement neural network. However, questions remain unsolved, such as the diversity of clinical manifestations and the variable efficiency of GABAergic drugs. This heterogeneity of antiGAD-Ab syndromes may be related to different antigenic targets, an aspect that remains to be resolved.

REFERENCES