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Opsoclonus in a patient with increased titers of anti-GAD antibody provides proof for the conductance-based model of saccadic oscillations

Aasef G. Shaikh [a,b,*], George Wilmot [c]

[a] Department of Neurology, Case Western Reserve University, Cleveland, OH, United States
[b] Daroff-DelOsso Ocular Motility Laboratory and Neurology Service, Cleveland VA Medical Center, Cleveland, OH, United States
[c] Department of Neurology, Emory University, Atlanta, GA, United States

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ABSTRACT

Paucity in gamma-amino butyric acid (GABA) due to blockage in the action of glutamic acid decarboxylase (GAD), as seen in the syndrome of anti-GAD antibody, causes adult onset cerebellar ataxia, muscle rigidity, and episodic spasms. Downbeat nystagmus, saccadic dysmetria, impaired ocular pursuit, and impaired cancelation of vestibular ocular reflex are typical ocular motor deficits in patients with syndrome of anti-GAD antibody. We describe opsoclonus, in addition to downbeat nystagmus, in a patient with increased titers of anti-GAD antibody. Paucity in GABA leading to disinhibition to Purkinje target neurons at deep cerebellar and vestibular nuclei might have caused downbeat nystagmus in our patient. Anti-GAD antibody can also increase levels of glutamate the precursor of GABA and the substrate for the action of GAD. We propose that opsoclonus might be due to increased levels of glutamate and subsequent hyperexcitability of excitatory and inhibitory burst neurons leading to reverberation in their reciprocally innervating circuit.

1. Introduction

Glutamic acid decarboxylase (GAD) is the critical enzyme catalyzing glutamate to gama-aminobutyric acid (GABA). Decreased levels of GABA due to paucity in the action of GAD, as seen in the syndrome of anti-GAD antibody, causes adult onset cerebellar ataxia, muscle rigidity, and episodic spasms [1,6,10,15]. Ocular motor deficits in patients with increased titers of anti-GAD antibody include downbeat nystagmus, saccadic dysmetria, impaired ocular pursuit, and impaired cancelation of vestibular ocular reflex (VOR) [2,8,24,28]. Periodic alternating nystagmus was also reported in one patient with increased titers of antiGAD antibody [23]. There are single case reports of isolated unidirectional saccadic oscillations (ocular flutter) [7], and opsoclonus myoclonus [12] without co-existing other ocular motor deficit.

We saw a combination of opsoclonus and downbeat nystagmus in a patient with increased titer of anti-GAD antibody. We hypothesize that anti-GAD antibody inhibits GAD mediated conversion of glutamate to GABA. As a result there will be paucity in GABA and excess of its precursor, glutamate. We suggest that paucity of GABA causes downbeat nystagmus, while opsoclonus could be due to excessively increased glutamatergic excitability of saccadic burst neurons and subsequent reverberations in their reciprocally innervating circuit [17,18].

2. Material and methods

2.1. Clinical description of the patient

We evaluated a 49 year-old woman with chronic progressive axial stiffness, episodic oscillopsia, vertigo, and falls. Her neurological examination revealed downbeat nystagmus that was prominent in straight-ahead and down-gaze (Video clip). Back-to-back horizontal and vertical saccades causing multi-directional saccadic oscillations or opsoclonus frequently interrupted gaze holding (Video clip). The VOR was normal during head impulses but VOR cancelation was abnormal. Smooth pursuit was impaired in both horizontal and vertical directions. She had bradykinesia but no appendicular ataxia. Her gait was slow and unsteady. Her deep tendon reflexes were brisk. Remaining neurological examination was normal.

She had increased serum and CSF titers of anti-GAD65 antibody [3420 nmol/l (serum); 2536 nmol/l (CSF)] measured using radioimmunoassay. CSF protein was 22 and albumin was 9 mg/dl. Serum albumin was 3400 mg/dl. Intrathecal synthesis rate of anti-GAD65 antibody was 280. Negative laboratory workup included serum thyroid stimulating hormone, vitamin E, vitamin B12, rapid plasma reagin, anti-gliadin, anti-tissue transglutaminase, mutation for spinocerebellar ataxia type 6, anti-ANA antibody, paraneoplastic antibody panel, anti-TPO, anti-Purkinje, anti-PQ calcium channel, anti-potassium channel, anti-ganglioside antibody, and anti-ganglionic neuronal antibody. Radiological workup excluded the possibility of occult malignancy. She did not

* Corresponding author at: Department of Neurology, 11100 Euclid Avenue, Cleveland, OH 44110, United States.
E-mail address: aasefshaikh@gmail.com (A.G. Shaikh).

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experience subjective improvement despite treatment with baclofen, 4-aminopyridine, rituximab, steroids, and several sessions of intravenous immunoglobulin and plasma exchange.

2.2. Experimental design

2.2.1. Eye movement recordings

The Emory University institutional review board approved the experiment protocol. The patient gave written informed consent. We used corneal curvature tracker to non-invasively sample horizontal and vertical conjugate eye positions at 1000 Hz (Jazz-Novo™, Ober Consulting, Poland). The head was supported on a chin-rest, 55 cm away from the LCD monitor. The visual fixation target was projected on the LCD monitor at straight-ahead, at 5° and 15° to the right and left, and 5° and 12° up and down. The target was circular, and its diameter comprised 0.5° visual angle. The patient was instructed to fixate gaze on the target, but when the target shifts, make a saccade to new target location.

2.2.2. Data analysis

Digital output from the Jazz-Novo system was converted to visual angles by using known distance between original and final positions of the visual target and the distance between the LCD screen and the patient's nasion. Further analysis was done on calibrated visual angle vectors. The eye position at the beginning of the drift was used to determine the eye-in-orbit position. Horizontal and vertical positions of each eye were analyzed separately. Quick-phases, saccadic eye movements, and epochs of opsoclonus were interactively identified. Saccades, quick-phases, and opsoclonus were excluded from further analysis of the drifts. Epochs of eye positions that were identified as drifts were differentiated and smoothed with a Savitzky–Golay filter (frame length: 11). The median value of the drift velocity (i.e. the slow-phase eye velocity) determined the severity of nystagmus. We used statistics and curve fitting toolboxes available through Matlab® (Nattick, MA) for further statistical analyses.

Cycle-by-cycle analysis was used to assess the kinematic properties of opsoclonus. Data from each axis and composite vector (square root of the sum of the squared signal from both planes) were processed separately. First we de-trended the data to remove drifts of the eye movement due to superimposed jerk nystagmus. Then we recorded the x-coordinates of the intersection of the trace with the abscissa (moving from the negative value to the positive value). The x-coordinate of the first data point that crossed the abscissa marked the beginning and the subsequent data point marked the end of a cycle. The difference between two crossings measured the cycle width; inverse of the cycle width is cycle frequency, while the difference between the peak and trough is the oscillation amplitude.

3. Results

Fig. 1 depicts an example of gaze holding. The eye movement waveforms had mixture of jerky and sinusoidal oscillations. The jerky oscillations comprised of slow ocular drift (slow-phase, black arrows, Fig. 1) followed by rapid corrective movement (quick-phase) in the opposite direction (red arrows, Fig. 1). The upward drifts are followed by downward quick-phases characterizing the downbeat nystagmus. Back-to-back saccades in both horizontal and vertical direction, consistent with opsoclonus, were mixed with the downbeat nystagmus. In some instances the opsoclonus had larger amplitude and lower frequency (for example, purple arrows), while in others the amplitude was small but the oscillations were high frequency (for example, green arrows). The high-frequency oscillations typically superimposed upon the slow phase of downbeat nystagmus (for example, green arrows depicted in pink box in Fig. 1). Downbeat nystagmus and superimposed opsoclonus are quantified in the section below.

3.1. Downbeat nystagmus

We measured the slow-phase velocity of downbeat nystagmus at various eccentric eye-in-orbit positions. Fig. 2A shows dependence of vertical slow-phase velocity on vertical eye-in-orbit position. The slow-phase eye velocity decreased as the eye-in-orbit position moved from downward to upward (Fig. 2A). The slope of such eye position dependence of vertical eye velocity was 0.4 s and correlation coefficient was 0.6; the correlation was statistically significant ($p < 0.0001$).

3.2. Opsoclonus

We also assessed quantitative features of opsoclonus. The frequency of sinusoidal oscillations comprising opsoclonus ranged between 9.4 Hz and 27.0 Hz (mean ± standard deviation = 12.5 ± 2.1 Hz) (Fig. 2B). The amplitude of saccadic oscillations varied in range of 0.5 and 4.7°, mean amplitude was 2.2 ± 1.0° (Fig. 2C). The trajectory of saccadic oscillation was oblique due to combination of its horizontal and vertical components. The trajectory angle ranged between 22.3 to 85.1°, with a mean of 70.2 ± 12.9° (Fig. 2D).

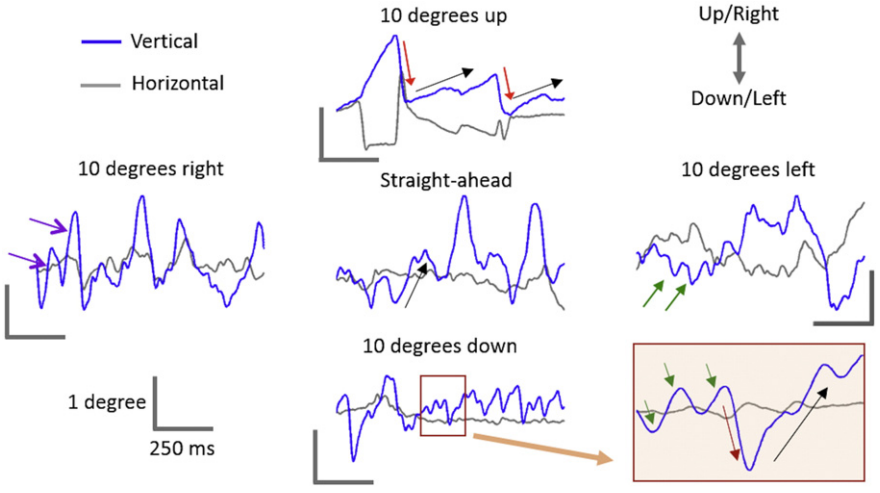

Fig. 1. Example of gaze holding in the patient with syndrome of anti-GAD antibody. Eye positions are plotted along y-axis while x-axis depicts corresponding time. One-second epochs of eye positions are illustrated in this figure. Blue traces depict vertical eye position, while gray traces are horizontal eye positions. Each panel depicts various eye-in-orbit orientations (as labeled). Red box has the trace expanded from the panel showing 10 degrees downward gaze holding. It depicts mixture of back-to-back saccades depicting opsoclonus. In addition there is superimposed upward drifts with downward quick-phase characterizing downbeat nystagmus. Green arrows point to opsoclonus, red arrows show quick phases, while black arrows show upward drifts in eye position.