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Vertical Optokinetic Stimulation Induces Diagonal Eye Movements in Patients with Idiopathic Infantile Nystagmus

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Purpose. In patients with early ocular misalignment and nystagmus, vertical optokinetic stimulation reportedly increases the horizontal component of the nystagmus present during fixation, resulting in diagonal eye movements. We tested patients with infantile nystagmus syndrome but normal ocular alignment to determine if this crosstalk depends on strabismus.

Methods. Eye movements were recorded in seven patients with infantile nystagmus. All but one patient had normal ocular alignment with high-grade stereopsis. Nystagmus during interleaved trials of right, left, up, and down optokinetic stimulation was compared with waveforms recorded during fixation. Six patients with strabismus but no nystagmus were also tested.

Results. In infantile nystagmus syndrome, horizontal motion evoked a mostly jerk nystagmus with virtually no vertical component. A vertical optokinetic pattern produced nystagmus with a diagonal trajectory. It was not simply a combination of a vertical component from optokinetic stimulation and a horizontal component from the subject’s congenital nystagmus, rather in six of seven patients, the slow-phase velocity of the horizontal component during vertical optokinetic stimulation differed from that recorded during fixation. In the six strabismus patients without nystagmus, responses to vertical optokinetic stimulation were normal.

Conclusions. In patients with congenital motor nystagmus, a vertical noise pattern drives a diagonal nystagmus. This appears to arise because of crosstalk between the vertical and horizontal components of the optokinetic system. This abnormal response to vertical stimulation is not caused by strabismus because it occurs in patients with infantile nystagmus without strabismus. Moreover, it is absent in patients with strabismus and no spontaneous nystagmus.

Keywords: congenital motor nystagmus, strabismus, exotropia, accommodative esotropia, optokinetic nystagmus, reversed optokinetic nystagmus, slow-phase velocity, fusional maldevelopment, crosstalk
This finding led us to examine a larger cohort of patients with congenital motor nystagmus. We selected patients with normal binocular alignment to determine whether the occurrence of such crosstalk depends on the presence of strabismus. We also tested a cohort of patients with strabismus, but no nystagmus, for evidence of crosstalk.

METHODS

This study was approved by the University of California San Francisco Committee on Human Research and it adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from adult participants; minors granted their assent with a parent providing informed consent.

Patient Selection

The first patient in this study, with congenital motor nystagmus and strabismus, was encountered during a routine neuro-ophthalmology clinic visit. His findings prompted further inquiry, focusing on patients with congenital motor nystagmus without strabismus. To locate such patients, the electronic patient records of a single neuro-ophthalmologist (J.C.H.) from 2008–2018 were searched using the keyword “motor nystagmus.” This yielded 20 potential subjects. Eight out of 20 had been recorded as able to identify the butterfly image hidden in a Randot test (Stereo Optical Company, Inc., Chicago, IL, USA), suggesting orthotropic ocular alignment. The families of these eight patients were contacted and six agreed to bring their child back to the clinic for further testing.

Each patient underwent an ophthalmodiologic examination that included assessment of the best-corrected visual acuity in each eye, pupils, eye movements, ocular alignment, and stereopsis. The latter was tested by confirming the ability to identify a hidden Randot butterfly (Stereo Optical Company, Inc.), signifying at least 2000 seconds of arc of stereopsis. The finest level of depth discrimination was determined by presenting a series of nine circle tests, ranging from 800 to 40 seconds of arc. Slit lamp and fundus examination were also performed.

All seven patients were in excellent health and took no medications on a regular basis. Most had a history of horizontal nystagmus starting soon after birth, although it was noticed at a later age in two patients. Ocular disease was otherwise absent. Specifically, no patient had iris transillumination defects or foveal hypoplasia to indicate albinism. None had a media opacity, optic nerve hypoplasia, history of prematurity, or neurologic disease. Dilated fundus examination showed no evidence of a tapetoretinal degeneration. No patient had previously undergone ocular or eye muscle surgery. Several patients had received negative magnetic resonance imaging and full-field electroretinography. The cohort fit the profile of “infantile nystagmus syndrome,” as defined by the Committee for the Classification of Eye Movement Abnormalities and Strabismus. Before the advent of this classification scheme, the patients would have been assigned the diagnosis of “congenital motor nystagmus.” They showed typical properties such as absence of oscillopdia, damping of nystagmus with a null head position, accelerating velocity of slow phases, and a predominately jerk waveform with occasional pendular oscillations. The did not exhibit features associated with fusional maldevelopment nystagmus syndrome, such as an increase in nystagmus velocity or change of direction induced by monocular occlusion. During monocular testing of smooth pursuit, gain for nasal tracking was not higher than for temporal tracking.

In addition, six patients with onset of strabismus between ages 1 and 4 years were tested. None had nystagmus. The goal was to determine whether strabismus alone results in diagonal eye movements in response to vertical optokinetic stimulation. These six patients had normal visual acuity in each eye and no history of eye muscle surgery. Three had a decompensated exotropia, and three had accommodative esotropia. None were able to fuse. They did not exhibit nasal versus temporal asymmetry in horizontal gain to a monocular stimulus.

Eye Movement Recordings

Subjects were seated in a dim room, with their head in a conventional chin/forehead rest. Stimuli were rear-projected onto a tangent screen 57 cm from the subjects using a Hewlett-Packard (Palo Alto, CA) xb31 digital light projector. The position of each eye was monitored independently with an infrared video camera (ViewX; SensoMotoric Instruments, Teltow, Germany). The cameras were mounted overhead, and a hot mirror was oriented at 45° to image the eyes without obstruction of the subject’s view. Eye position was sampled at 120 Hz for offline analysis.

Each eye tracker was calibrated by setting the offset and gain independently while the subject fixated on a grid of nine static points 20° apart. The other eye was occluded by a shutter controlled by a pneumatic piston. The shutter was an infrared filter that blocked visible light but passed infrared wavelengths, so that eye position could be recorded without interruption. For each eye, the calibration was checked by having the subject monocularly track a spot 0.5° in diameter that moved sinusoidally, first in the horizontal (±30°) and then in the vertical plane (±20°). Adjustments were made in offset and/or gain as needed to insure accurate calibration. Eye movement recordings were carried out with no refractive correction.

Optokinetic Stimulation

All optokinetic data reported in this study were acquired with both eyes viewing. A fixation spot 0.5° in diameter was presented at the center of the screen. After fixation by the subject, it was displayed for 2 seconds. The spot was then extinguished. Simultaneously an optokinetic stimulus appeared. It consisted of a noise pattern of 80% contrast random black and white 2° x 2° squares moving at 40°/s. After 10 seconds, the stimulus was replaced by an isoluminant blank screen. The blank screen was displayed for 8 seconds. The fixation spot then reappeared, signaling the advent of the next stimulus trial. The direction of the optokinetic stimulus (up, down, left, right) was interleaved randomly. Subjects generally kept their gaze near the center of the screen during optokinetic stimulation, but occasionally needed a reminder to look at the center. The stimulus subtended ±52° horizontally and ±39°. A minimum of four trials was conducted for each condition.

Data Analyses

Each trial lasted 12 seconds, consisting of 2 seconds of fixation and 10 seconds of optokinetic stimulation. The data were comprised of horizontal and vertical position traces for...
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therighteyeandlefteye.Blinkswereexcised.Thedatawere then digitally filtered (infinite impulse response, 10 Hz) and saccades were removed manually, leaving a series of individual slow-phase events. A linear fit of each slow-phase event provided a measurement of the mean velocity. If the waveform had a pendular shape, the slow-phase event was divided at points of direction reversal, and each fragment was fit separately. Because the traces for both eyes were nearly identical, right eye and left eye mean velocities were averaged to obtain final horizontal and vertical mean velocities for each slow-phase event.

Median values, quartiles, and 95% confidence intervals (CI) were calculated. Significance was assessed using the Wilcoxon-Mann-Whitney test.17

RESULTS

Crosstalk in Idiopathic Infantile Nystagmus Syndrome

Our interest in this project was sparked by a 39-year-old patient who was observed in the clinic to have unusual eye movements evoked by stimulation with an optokinetic drum. stripes drifting downward produced a nystagmus that looked more horizontal than vertical. The patient reported that soon after birth he was observed to have horizontal nystagmus. His medical records documented that by age 13 months he demonstrated a frequent left head turn, with damping of his nystagmus. His ocular examination was otherwise negative. Full-field electroretinography was normal. The diagnosis of congenital motor nystagmus was made.

The patient’s visual acuity was 20/30 in the right eye, and 20/40 in the left eye with corrective lenses. He denied oscillopsia. In primary gaze there was an approximate 2 Hz left-beating jerk nystagmus measuring a few degrees in amplitude. He was unable to detect a hidden Randot butterfly (Stereo Optical Company, Inc.) image. Testing of ocular alignment by the cover-uncover test was difficult, owing to the presence of the horizontal nystagmus. However, eye movement recordings confirmed the presence of strabismus. There was a variable esotropia averaging approximately 2° in primary gaze (Fig. 1A). The nystagmus increased on left gaze (Fig. 1B) and decreased on right gaze (Fig. 1C), with a null point at 15° to 20° right gaze. In far right gaze, the nystagmus became right-beating (data not shown).

Eye movement recordings showed that occlusion of the left eye (Fig. 1D) or the right eye (Fig. 1E) did not increase the amplitude of the nystagmus or cause it to switch direction. The absence of these features excluded a diagnosis of fusional maldevelopment nystagmus syndrome. Interestingly, occlusion of the right eye converted his esotropia to an exodeviation measuring approximately 8° (Fig. 1E).

Binocular stimulation with a leftward drifting optokinetic pattern evoked a right-beating jerk nystagmus (Fig. 2A). When the stimulus drifted rightward, the jerk nystagmus was also right-beating, rather than left-beating (Fig. 2B). The slow phases often exhibited an exponentially increasing velocity (Fig. 2B, inset). Both acceleration of slow phases and “reversed” optokinetic responses are observed frequently in patients with congenital motor nystagmus.11,15,16,18–21

Binocular stimulation with an upward drifting optokinetic pattern evoked a diagonal nystagmus, comprised of both down-beating and right-beating components (Fig. 2C). The median slow-phase velocity of the horizontal compo-

nent (−3.8°/s, 95% CI, −5.1°/s to −2.7°/s) was faster (P < 0.001) than the median slow-phase velocity present during fixation (1.6°/s, 95% CI, 1.2°/s–2.5°/s), and reversed in direction (Fig. 3A). Remarkably, it was not different (P = 0.27) from the median slow-phase velocity produced by a leftward drifting horizontal optokinetic stimulus (−3.0°/s, 95% CI, −3.5°/s to −2.6°/s) (Fig. 3A).

Binocular stimulation with a downward drifting optokinetic pattern also evoked a diagonal nystagmus, comprised of both up-beating and right-beating components (Fig. 2D). Just as for the upward stimulus, the slow-phase velocity...
FIGURE 2. Patient 1. Eye movement recordings of optokinetic nystagmus. (A) Leftward optokinetic pattern moving at 40°/s (green trace) evokes right-beating nystagmus. (B) Rightward pattern evokes reversed right-beating nystagmus. *Inset* example of accelerating slow phases. (C) Upward pattern produces diagonal nystagmus, comprised of a time-locked down-beating vertical component and right-beating horizontal component (*vertical dashed lines*). (D) Downward pattern also produced a diagonal nystagmus comprised of up-beating and right-beating components. Note that for every stimulus condition, the left-beating nystagmus present during fixation (−2 to 0 seconds) is replaced by a more vigorous, right-beating movement.

FIGURE 3. Patient 1. Nystagmus slow-phase velocities. (A) Box plots show median, quartiles, and 1 SD. Vertical optokinetic stimulation produced nystagmus with strong horizontal (h) and vertical (v) components, resulting in diagonal nystagmus. The upward stimulus produced a right-beating component similar in velocity to that produced by a leftward stimulus. The downward stimulus produced a nystagmus with a greater horizontal than vertical velocity. The red asterisks denote greater horizontal slow-phase velocity than during fixation (*P* < 0.001). (B) Horizontal and vertical velocities for each slow-phase movement evoked by an upward or downward optokinetic pattern. Black arrows indicate median of individual slow phases (gray arrows). Note diagonal orientation of median vector, especially to downward moving pattern. Red arrow depicts median slow-phase velocity during fixation epochs.
of the horizontal component (−9.9°/s, 95% CI, −11.8°/s to −7.9°/s) was greater (P < 0.001) than observed during fixation (Fig. 3A). The horizontal slow phases were faster than the vertical slow phases (median −9.9°/s vs. −6.8°/s), accounting for our clinical impression that a downward optokinetic stimulus caused a predominately horizontal nystagmus (Fig. 3B).

The eye movement recordings in this patient showed that vertical optokinetic stimulation can increase the horizontal component of nystagmus in strabismus associated with infantile nystagmus syndrome, as described previously by Garbutt et al.12 for fusional maldevelopment nystagmus syndrome. This finding prompted us to inquire whether this phenomenon requires the presence of strabismus.

Crosstalk in Nystagmus Patients with Normal Eye Alignment

To probe the role of strabismus, we tested six patients with infantile nystagmus syndrome and normal eye alignment. The absence of strabismus was established by eye movement recordings and by the demonstration of high-grade stereopsis (Table). The lack of strabismus ruled out the possibility that the patients’ nystagmus was caused by fusion maldevelopment nystagmus syndrome. This finding prompted us to inquire whether this phenomenon requires the presence of strabismus.

No Crosstalk in Strabismus Patients without Nystagmus

We tested six patients with strabismus, but no nystagmus, for evidence of crosstalk. The goal was to determine if strabismus by itself causes diagonal nystagmus in response to vertical optokinetic stimulation. Half had accommodative esotropia, the other half had a completely decompensated exotropia. The median vertical slow-phase velocity was...
| Patient Number | Age/Sex | Acuity | Stereo | Refraction OD/OS | Deviation | Comments |
|----------------|---------|--------|--------|------------------|-----------|----------|
| 1              | 39 Male | 20/30 OD | None | +1.50 + 4.00 x 100° | 1°–5° ET | Nystagmus since infancy, + null point |
| 2              | 13 Male | 20/20 OD | 40 arc sec | -0.75 | Ortho | Nystagmus noted age 5 years, typical waveforms |
| 3              | 11 Female | 20/20 OD | 60 arc sec | +1.00 + 0.50 x 90° | Ortho | Nystagmus noted age 18 months, + null point |
| 4              | 10 Male | 20/20 OD | 80 arc sec | +1.50 + 1.00 x 90° | Ortho | Nystagmus since infancy, + null point |
| 5              | 8 Male | 20/40 OD | 80 arc sec | +2.00 + 0.50 x 90° | Ortho | Nystagmus since infancy, + null position with chin down |
| 6              | 6 Male | 20/50 OD | 100 arc sec | -1.00 + 1.25 x 120° | Ortho | Nystagmus since infancy, + null point |
| 7              | 10 Male | 20/40 OD | 60 arc sec | -1.00 + 4.25 x 90° | Ortho | Nystagmus since age 8 weeks, + null point |
| 8              | 7 Female | 20/25 OD | None | +3.75 + 1.75 x 95° | 15°–18° R ET | Accommodative ET since age 4 years |
| 9              | 9 Female | 20/20 OD | None | +3.25 w/+3.00 add | 18°–20° R ET | Accommodative ET since age 2 years. High AC/A ratio |
| 10             | 5 Female | 20/20 OD | None | +2.75 | 30°–34° R ET | Accommodative ET since age 4 years |
| 11             | 7 Female | 20/20 OD | None | -1.00 | 15°–20° XT | Intermittent XT starting age 2 years; now constant |
| 12             | 7 Male | 20/20 OD | None | -3.00 + 1.50 x 90° | 12°–15° XT | Intermittent XT starting age 1 year; now constant |
| 13             | 10 Female | 20/20 OD | None | -0.50 + 4.00 x 105° | 22°–25° XT | Intermittent XT since age 4 years; now constant |

AC/A, accommodative convergence/accommodation; ET, esotropia; R, right; XT, exotropia.
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**FIGURE 5.** Patients 2 through 7. Diagonal nystagmus from optokinetic stimulation in congenital motor nystagmus subjects without strabismus. Box plots show median, quartiles, and 1 SD. (A) Patient 2. (B) Patient 3. (C) Patient 4. (D) Patient 5. (E) Patient 6. (F) Patient 7. During fixation, every patient has horizontal nystagmus, with almost no vertical component. Leftward or rightward stimulation produces a largely horizontal nystagmus, sometimes with reversed pursuit in one direction (B, C, F) or both directions (E). In every patient, except patient 7, upward or downward optokinetic stimulation induces a nystagmus with a horizontal component that differs (*P < 0.001) from the horizontal component of the nystagmus present during fixation.

24.0°/s (gain, 0.60), similar to the value (24.9°/s) in the six subjects with congenital nystagmus without strabismus.

There was no significant difference in the gain of slow-phase velocity for upward compared with downward optokinetic stimulation. This was true even when data from all patients were combined (n = 13). The upward gain was 0.65 ± 0.21, versus a downward gain of 0.52 ± 0.22 (P = 0.08).

The main result in the six patients with strabismus, but no nystagmus, was that vertical optokinetic stimulation evoked a nearly purely vertical nystagmus (Fig. 7). Their slow-phase vectors (n = 12) had a median divergence from vertical of 0.9° (95% CI, 0.5°–2.1°). In comparison, the vectors (n = 12) in the six patients with congenital nystagmus, but no strabismus, had a median absolute divergence from vertical of 25.8° (95% CI, 15.0°–41.1°).

**DISCUSSION**

Despite gratifying progress, summarized by Leigh and Zee22 in their magisterial tome, disorders of nystagmus remain incompletely understood. Further progress depends on accurate description of findings in normal subjects and in patients with abnormal forms of nystagmus. Each new observation, especially when associated with a specific clinical feature, may provide a clue to the mechanisms underlying nystagmus. A major challenge, however, is that...
findings often vary widely depending on test conditions and study cohort. As a result, agreement on even simple facts may seem elusive. For example, data are conflicting regarding whether vertical optokinetic nystagmus gain is higher to upward or downward motion. In a scholarly review, Knapp et al.23 surveyed 18 publications addressing this issue in normal subjects. Higher upward gain was reported in 7 articles, higher downward gain in 5 articles, and no difference in 6 articles. Investigation of nystagmus appears to be exceptionally prone to confounding factors, requiring extra caution, especially when generalizing from results obtained in particular patient populations.

Reversed optokinetic nystagmus provides another example of this problem. It has been linked to the abnormal chiasmal decussation of retinal ganglion cell axons in albinism.24,25 In fact, although found in albinism, it is a general feature of subjects with idiopathic infantile nystagmus without albinism.11,19 It was common among our patients, but often only in response to one direction of motion.

Garbutt et al.12 reported that upward stimulus motion elicited a greater response than downward motion in their normal subjects and in their patients with strabismus. However, they noted exceptions. We found subjects with a higher gain in either direction. Overall, our patients showed no significant asymmetry. This property seems idiosyncratic, and it is not even clear that the same patient tested on a different day would give the same result.

The main finding from the study by Garbutt et al.12 was that in strabismus, a vertical optokinetic stimulus produced nystagmus with an increased horizontal component, resulting in diagonal movement of the eyes. Their cohort was mixed; some patients had a history of eye muscle surgery, and others had amblyopia. All had manifest latent nystagmus during fixation on a stationary target. Every patient but one had esotropia; most had dissociated vertical deviation. Although the group was heterogeneous, most were thought to have fusional maldevelopment nystagmus syndrome. An asymmetry of optokinetic gain, better to nasal than temporal motion, is a cardinal feature of this syndrome. Based on the Garbutt et al.12 findings, diagonal nystagmus in response to vertical motion was proposed as another characteristic property of this condition (see Leigh and Zee, 2015, page 338).22

In the patient group tested by Garbutt et al.,12 vertical motion energy was somehow inappropriately translated by the optokinetic system, resulting in increased horizontal nystagmus or reversal of its direction. They proposed three possible explanations12: (1) vertical–horizontal crosstalk could serve to negate certain effects of optic flow that occur in the absence of binocular vision; (2) strabismus could perturb properties of cells in the nucleus of the optic tract, causing abnormal crosstalk; and (3) strabismus could lead to anatomic changes in the orbits, with improper pulley locations causing inappropriate horizontal eye movements in response to vertical optokinetic stimulation.26

Before investing further effort in testing these potential mechanisms, it seemed important to establish first that ocular misalignment actually plays a direct causative role in the phenomenon of crosstalk. To address this issue, we recruited six subjects with idiopathic infantile nystagmus...
who had normal eye alignment. To our surprise, five of the six subjects showed crosstalk, manifested by an increase or reverse in the horizontal velocity of the eyes when a vertical optokinetic stimulus was displayed (Figs. 5, 6). Interestingly, one patient showed no significant change, a reminder of the idiosyncratic nature of nystagmus findings from one patient to the next.

Our findings suggested that the existence of infantile nystagmus, not strabismus, is responsible for crosstalk in response to vertical optokinetic stimulation. To pursue this issue further, we recruited six patients with strabismus onset at a later age than typical for patients with fusional maldevelopment nystagmus syndrome. We selected three patients with accommodative esotropia, and three patients with decompensated exotropia. These conditions are not usually associated with resting nystagmus, either latent or manifest, and indeed, no patient had any measurable nystagmus during steady fixation. The data showed no significant mean horizontal component to the nystagmus evoked by vertical optokinetic stimulation (Fig. 7). This finding strengthens the evidence that strabismus is irrelevant to the phenomenon of crosstalk, except in the sense that infantile strabismus is associated in some patients with the occurrence of horizontal nystagmus.

CONCLUSIONS

Insight into the neural mechanisms underlying the eye movements induced by optokinetic stimulation is still too rudimentary to provide a well-grounded explanation for the phenomenon of crosstalk. Future inquiries should focus on the features in common among patients with nystagmus who show crosstalk. At this point, we can say with some confidence that it is a property of patients with fusional maldevelopment nystagmus syndrome and patients with idiopathic infantile nystagmus (congenital motor nystagmus). In these two groups, nystagmus properties are quite different, suggesting very different mechanisms. It seems likely that further testing will show that crosstalk is present in other forms of pathological nystagmus. It is not, however, dependent on the presence of ocular misalignment.

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