Vestibular and optokinetic responses were recorded in three albino subjects with congenital nystagmus. Although an ice-water caloric stimulus did not elicit nystagmus, all patients showed a response to rotational stimuli containing high frequency components. Vestibular responses to a constant velocity rotation decremented with abnormally short time constants of 1–2 sec (normal 15–20 sec). For sinusoidal oscillation, in one subject, the cut-off frequency (where the amplitude of the response was 70% of maximum) was increased to 0.8 Hz (normal about 0.01 Hz). Full-field optokinetic stimulation generated no nystagmus response. These abnormalities may be due to defects in networks that act as mathematical integrators: either the final common neural gaze-holding network that converts velocity into position information for the ocular motor neurons or the "velocity-storage" mechanism that normally combines sensory inputs from both the labyrinths and visual system to generate appropriate (per-rotatory) nystagmus during rotation and to suppress inappropriate (post-rotatory) nystagmus after rotation. Invest Ophthalmol Vis Sci 25:739–745, 1984

Congenital nystagmus (CN) is a common ocular motor disorder in which fixation is impaired by the presence of spontaneous, predominantly horizontal oscillations. The waveform of CN may be pendular, with nearly sinusoidal motion; jerk, in which slow phases alternate with quick phases; or complex, with a variety of waveforms.¹⁻³

CN is associated with other ocular motor abnormalities including impaired vestibular and optokinetic responses. Forssman reported that 39 of 79 patients with CN did not show a response to caloric stimulation.⁴ Yamazaki noted unilaterally hypoactive caloric responses in three of five patients with CN.⁵ Yee and co-workers quantified the vestibular response to rotational stimuli in a group of patients with CN.⁶ These investigators measured the gain (ratio of slow-phase eye velocity to head velocity) of the vestibulo-ocular reflex (VOR) for sinusoidal head rotation at a frequency of 0.05 Hz. (A VOR gain of 1.0 represents perfect compensation. The eye and head movements are of equal amplitude (but in opposite direction). In this way, eye position in space or gaze does not change and images of stationary objects remain stable on the retina during head rotation.) Yee et al⁶ found that the mean VOR gain of their patients, measured in darkness, was within the normal range (0.47–0.69) but some individual patients had values that were low. The apparent discrepancy between the results of Yee, et al and those of other authors may reflect not only different patient populations but also the different types of stimuli used. No prior study, however, has investigated the vestibular responses of CN to a broad spectrum of frequencies of head oscillation.

Optokinetic nystagmus (OKN) is a physiologic form of jerk nystagmus evoked by movement of the entire visual field. It is associated with a sense of self-rotation (circularvection) even though the head is actually stationary. In OKN, slow-phases track the visual field and alternate with resetting quick phases. If the lights are extinguished abruptly following full-field optokinetic stimulation, the nystagmus continues in the original direction with a slowly decaying velocity of slow phases—a phenomenon called optokinetic afternystagmus (OKAN).

Yee and co-workers measured responses to a full-field optokinetic stimulus in a group of 46 patients with CN.⁷ They quantified OKN by measuring its gain—the ratio of slow-phase eye velocity to stimulus velocity. Some of their patients exhibited absent or reversed (slow-phases directed opposite to the stimulus) OKN. Those that displayed normally directed OKN had an abnormally low gain (0.22–0.38, normal being about 0.8). None of the patients of Yee et al displayed OKAN. Similar findings were observed by LeLiever and Barber in 12 CN patients.⁸
Modern views of the neural control of vestibular and optokinetic nystagmus suggest that these two reflexes share much neural circuitry. In particular, there appears to be a "velocity-storage mechanism" by which a per-rotatory nystagmus can be sustained during a constant velocity head rotation in the light and post-rotatory nystagmus can be prevented when the head suddenly comes to rest. Therefore, we thought it useful to study both OKN and VOR responses in a group of patients with CN to seek evidence of deficits arising from a possible common anatomic anomaly.

We studied three albino patients with CN. All forms of ocular and oculocutaneous albinism are associated with CN. Albinos have abnormally decussated retinofugal projections and it has been suggested that their CN may be related to aberrant visuomotor connections. Some nonalbinos with CN also show evidence of abnormally decussated visual projections. In our patients, we recorded eye movements and quantified vestibulo-ocular response to both a broad spectrum of frequencies of head rotation as well as to caloric stimuli. OKN also was measured. The pattern of VOR and OKN deficits was considered in terms of neural processing common to both reflexes.

Materials and Methods

Report of Cases

Patient 1: A 23-year-old, fair-skinned, light yellow-haired woman of black percentage was noted to have "dancing and crossed eyes" since early in life. She appeared to have complete oculocutaneous albinism.

Physical examination revealed white skin and light yellow hair. Her pupils were equal, round, and reactive to light. The irides were brown but transilluminated in a cartwheel pattern. The ocular fundi were hypopigmented and the choroidal vessels were prominent. Corrected visual acuity was 20/40 in the right eye and 20/40 in the left. Color vision was normal.

An alternating exotropia of 90 prism D was present and she had difficulty completely adducting the eyes. The range of vertical eye movements were normal. In the horizontal plane, there appeared to be a mixed pendular and jerk nystagmus. Vestibulo-ocular response (doll's head maneuver) appeared intact but only at high frequencies of head oscillation.

Patient 2: A 35-year-old black man with ocular albinism was known to have had "dancing eyes" since infancy.

Physical examination revealed a well-developed, dark-skinned man with marked exotropia and pendular-appearing nystagmus. The ocular fundi were albinotic. Corrected visual acuity was 20/60 in the right eye and 20/100 in the left.

After disclosure of the purposes and risks of this study, the patients' written informed consent was obtained according to a protocol approved by the Institutional Human Subjects Review Committee. Each patient's eye movements were recorded in one session by DC-coupled electro-oculography, with separate sets of electrodes for recording the horizontal and vertical movements of each eye. During the other sessions, we recorded movements of each eye with better vision using an annulus with the magnetic field search coil technique.

Eye movement and stimulus records were displayed on a pen recorder and were recorded on magnetic tape. The bandwidth of the entire recording system was 0–70 Hz. Slow-phase eye velocity was obtained by electronic differentiation of the eye position signal (bandwidth 0 to 4 Hz). The patient was seated in a chair that could be rotated in the horizontal plane continuously or sinusoidally by a servo-controlled DC motor: the chair was manually oscillated to achieve high accelerations.

Optokinetic responses were elicited by rotating around the patient a plaid, cloth drum, 1.2 meter in diameter. This technique of optokinetic stimulation will be called the optokinetic drum method. Alternatively, the patient was rotated at constant velocity in darkness until cessation of vestibularly-evoked eye movements; the room was then illuminated as body rotation continued to provide the optokinetic stimulus. This technique of optokinetic stimulation will be referred to as the sustained rotation method; it tests the optokinetic system alone because the visual stimulus is not presented until all vestibular effects have ceased.

The patient's head was fixed to the chair, using a chinrest, so that the signal for chair velocity also would represent head velocity. Head position also was transduced by an electromagnetic search coil attached to a snug headband. This enabled correction of any possible errors in measurement of head velocity due to slippage of the head in the chinrest. Caloric responses were elicited by irrigating the patients' external auditory canals with 5–10 ml of ice water.

VOR gain for constant velocity head rotation was taken as the ratio of maximum slow-phase eye velocity divided by head velocity. VOR gain for sinusoidal head rotation was computed as the ratio of peak-to-peak slow-phase eye velocity divided by peak-to-peak head velocity. The sinusoidal character of the velocity profile was approximated by eye. VOR phase advance for
Fig. 1. Record of vestibuloocular response of an ocoulocutaneous albino, patient 1, during head rotation in darkness. Note decreased response at frequencies of head rotation below 1 Hz. The amplitude of the response on the eye position trace at 0.45 Hz oscillation is about the same as that at 1.0 Hz which, since stimulus velocity is constant, corresponds to a lower eye velocity and correspondingly lower gain at the lower frequency.

Patients exhibited a predominantly pendular nystagmus. This nearly sinusoidal horizontal movement typically had a frequency of 0.6 Hz and a peak-to-peak amplitude ranging from 2–6 deg. Vertical oscillations were absent. In darkness, and at times during other visual tasks, the patients exhibited a jerk nystagmus whose direction alternated with a period of 100–200 msec. The direction of nystagmus was not determined solely by the position of the eye in the orbit. At times the slow-phases of this nystagmus were exponentially increasing, while at other times, they were of the type described by Dell’Osso and Daroff as pseudocycloid.3

Vestibular stimulation with 10 ml of ice water, in darkness, in either ear, elicited no change in the patient’s spontaneous CN. Likewise stimulation with constant velocity head rotations (10 or 60 deg/sec) elicited no superimposed vestibular nystagmus—either during (per-rotatory) or after (post-rotatory) rotation.

The vestibulo-ocular response to sinusoidal head rotation is illustrated in Figure 1. While the patient exhibited a normal VOR gain (eye velocity/head velocity) of about 1.0 at 1 Hz, her gain declined rapidly as the stimulus frequency was decreased. The way that VOR gain depended on frequency is illustrated in Figure 2, which is a plot of VOR gain and phase as functions of the frequency of head rotation. (Note that the amplitude of the stimulus was held constant over the range of frequencies tested.) Figure 2 shows that phase advance and reduction of gain occur at a much higher frequency in this patient than in a normal subject. The low cutoff frequency—that frequency at which gain decreases to 0.7 and phase advance increases to 45 deg—is increased from the normal value of about 0.01 to about 0.8 Hz.

The patient showed no superimposed nystagmus response to optokinetic stimulation either with the sustained rotation method (10 and 60 deg/sec) or with the optokinetic drum method (using a slowly accelerating stimulus) to a final velocity of 20 deg/sec. The patient did, however, report circularvection.

Patient 2: In the light and the dark, the patient exhibited a horizontal nystagmus at a frequency of 3–4 beats/sec, with a complex and variable waveform. The nystagmus was pendular at times, jerk at others, and the direction of the jerk nystagmus was variable. Stimulation with 5-ml ice-water irrigation of either ear canal in darkness elicited no vestibular nystagmus response.

Attempts were made to measure VOR gain for sinusoidal head rotation (0.05–0.9 Hz) in darkness with
Fig. 2. Upper. Plot of VOR gain (eye velocity/head velocity) in darkness as a function of frequency of head rotation for patient 1. Plotted values are means ± SD of 6-10 measurements at each frequency. Lower. As in upper but displaying phase advance.

the head velocity held constant at 60 deg/sec peak. In some traces, there was a suggestion of sinusoidal modulation of slow phase eye velocity (Fig. 3A), but the superimposed CN made it impossible to obtain reliable phase or gain measurements.

The patient's VOR response in darkness to steps of head velocity (10-150 deg/sec) also was difficult to discern on some trials. On others, though, one could see a definite response and at times the velocity of the evoked slow-phases exceeded that of the rotatory stimulus. For one trial of 60 deg/sec rotation to the left, a peak slow-phase eye velocity of 145 deg/sec was reached. On this trial, the nystagmus response decayed over 6-9 sec, which corresponds to a time constant of 2-3 sec (Fig. 3B). Vestibular nystagmus was evoked on four other trials, with a total duration of slightly less than 3 sec in each. VOR gain, averaged over both directions, was 1.76 ± 1.32 (mean ± standard deviation, n = 7) for trials in which nystagmus was clearly evoked. Such high values for the VOR gain may reflect the superposition of the vestibular response and the underlying CN. The patient experienced a brief sense of rotation during the constant velocity stimuli.

No OKN or OKAN could be elicited by either the sustained rotation or optokinetic drum methods, although the amplitude of pendular nystagmus usually was increased during optokinetic stimulation.

Patient 3: This patient exhibited spontaneous horizontal pendular appearing nystagmus although there were periods of jerk nystagmus (amplitude, 3 deg) alternating in direction every 110-130 sec. The nystagmus was pendular during the time of direction reversal and had a frequency of 2-6 beats/sec. Vertical fixation was normal. There was no vestibular nystagmus response to irrigation of either external auditory canal with 10-ml of ice-water, but the patient did experience a sense of rotation.

The patient exhibited no VOR response in darkness to 10 and 60 deg/sec steps of chair rotation. With the head free, brief accelerations of the head with speeds of 170 to 280 deg/sec evoked transient eye velocities with a gain of 0.50 ± 0.08 (mean ± SD, n = 7). During sinusoidal head rotation, the mean position of the eye in the orbit moved toward the direction of head motion (anticompenatory) but gain and phase measurements were uninterpretable. There was no OKN or OKAN response to sustained rotation in either direction.

All three patients had the findings of ocular or oculocutaneous albinism and horizontal CN. OKN and OKAN were absent in all. Although objective nystagmic responses to caloric irrigation were absent, all exhibited at least some VOR response to head rotations containing high-frequency components, such as high-frequency sinusoids or rapidly accelerating velocity steps.

Discussion

Our patients exhibited no OKN or OKAN, and in this respect are more severely affected than many CN patients. In the series of Yee et al, however, OKN gain could not be measured in 18% of the CN patients with
"motor-defect" nystagmus and 44% of the patients with "sensory-defect" nystagmus.7

The absence of caloric responses observed here is consistent with the vestibulo-ocular areflexia noted by Forssman in 44% of the CN patients in his series4 and the 60% incidence of unilateral hyporesponsiveness to caloric irrigation observed by Yamazaki.5 Our patients, though, did exhibit some vestibular responses to head velocity sinusoids or steps.

Patient 1 in the present series exhibited a normal VOR gain but only when gain was measured at or above a frequency of 1.0 Hz. Patient 2 had some response in the initial period of constant velocity rotation (which contains the high frequency components of the movement). Patient 3 had a response to sudden, rapid head rotations. None of our patients had responses to ice-water caloric irrigation. These results imply that our CN patients did not have a total absence of vestibular response but only an absent response to the low-frequency components of the head velocity waveform. Although the duration of the VOR response to brief acceleration of the head or of head velocity steps was reduced, it appears that these patients might obtain some physiologic benefit from their VOR because most natural head movements are brief and consist predominantly of frequency components in the range of 2 to 7 Hz.21 The preservation of useful high-frequency responses to vestibular stimulation might be missed by relatively brief caloric irrigations. These findings suggest that it is important to attempt to measure VOR gain at a variety of frequencies of sinusoidal oscillations and with constant velocity rotations before concluding that vestibular function is absent.

The persistence of a VOR response to steps of head velocity observed in patients 2 and 3 and the elevated low-cut-off frequency for VOR sinusoids measured in patient 1, suggest a deficiency in generating a sustained response to vestibular stimuli. The vestibular time constant implied by patient 1's low-cut-off frequency of 0.8 Hz is only 0.2 sec. The markedly shortened time constant is the likely reason she exhibited no response to velocity steps. In patient 2, the VOR response to head velocity steps did not persist much beyond three seconds. This finding implies that his vestibular time constant were also shortened to about 1 sec. Sinusoidal responses in patients 2 and 3 were too difficult to discern from the spontaneous nystagmus.

It is surprising that the presumed VOR time constants in our patients are shorter than that of the normal vestibular sensory organ (4–7 sec). Normally, the central velocity-storage mechanism has to act to prolong the cupula time constant by a factor of about 3,10,11 so that the normal human being has a VOR time constant, as measured by the nystagmus response, of about 20 sec. It would thus appear that our patients either have a peripheral sensory defect causing a greatly reduced cupula time constant, or a central defect causing an active shortening of vestibular responses, or both.

A peripheral origin of this phenomenon seems unlikely in our patients for several reasons, although a recent study has demonstrated markedly shortened time constants in patients with peripheral vestibular lesions.22 First, none of the patients in the present study had any history or clinical evidence of hearing loss to suggest eighth nerve damage. Second, blind patients show similar vestibular responses to those of our albino patients. Forssman noted that blind patients
have diminished or absent caloric responses, similar to the defect in patients with CN. A degree of shortening of the VOR time constant similar to that observed in our subjects has been reported in patients with both congenital and acquired blindness, suggesting that eighth nerve lesions are not required to produce this effect. Third, since the cupula time constant is determined by mechanical properties of the labyrinth, one would expect its dynamic characteristics not to vary greatly, particularly throughout life. Groen has shown that the VOR time constant in both infant dogs and infant humans is comparable to the adult value even during the first two weeks of life. While these arguments do not rule out a peripheral lesion, they do suggest that alternative hypotheses be considered.

A possible explanation for the shortened VOR time constant is that the responsible process is central, possibly in the velocity-storage mechanism itself. Such a central process would have to reverse the normal prolonging action of the velocity-storage mechanism so that the time constant of the VOR would be actively shortened below the cupula value. It is tempting to speculate that a congenital lesion in the velocity storage mechanism, involving a reversal of usual function, might result from the same sort of abnormal neural decussation in the vestibular system as has been documented for albinos in the visual and auditory systems.

One also must consider the possibility that our findings could be accounted for by a more fundamental defect: an abnormality in the so-called ocular motor integrator. This hypothetical neural network integrates, in the mathematical sense, velocity into position coded information for the ocular motor neurons and is responsible for holding positions of gaze after all types of conjugate eye movements. If such an integrator were to become defective or "leaky" it would faithfully transduce only the high frequency components of an input stimulus and lead to a loss of gain and change in phase for lower frequency components. Such a defect could probably account for the observed abnormalities in patients 1 and 3 since they had no sustained per-rotatory response at all. For patient 2, however, a defective ocular motor integrator alone could not account for the shortened per-rotatory vestibular response. Since each quick phase of vestibular nystagmus resets the ocular motor integrator, if there had been a normally sustained vestibular response, it should have appeared as a slowly decaying eye velocity superimposed upon the slow-phase velocity after each resetting quick phase. This was not observed. Unfortunately, the presence of CN itself makes it difficult to evaluate the state of the ocular motor integrator and, in fact, one hypothetical explanation for the CN waveform is based upon an abnormality in the ocular motor integrator itself.

Finally, as suggested by Forssman, the lesion causing the defective vestibular response in CN may represent functional atrophy of the VOR in a situation in which the VOR is not useful. There would be little advantage to stabilize the images against retinal slip due to low frequency head movements when retinal blur is constantly being generated by CN. Perhaps the brain learns to ignore retinal slip that might otherwise be used to bring the metrics of the VOR into calibration. This idea would explain the abnormal VOR responses of blind patients who do not necessarily have CN. Optokinetic responses also might be lost as a result of the effect of functional VOR atrophy on neural circuitry shared by the two reflexes. Experimentally, bilateral labyrinthine destruction does, in fact, reduce or eliminate optokinetic responses.

While explanations of the cause of these defects await confirmation and our findings should be extended to a larger group of CN patients, the concept of cooperative action and shared velocity storage of the VOR and optokinetic system provides a unifying hypothesis to explain distinct ocular motor abnormalities in some patients with CN.

Key words: vestibulo-ocular reflex, optokinetic nystagmus, congenital nystagmus, velocity-storage mechanism, albino, ocular motor integrator

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