Hereditary congenital nystagmus and gaze-holding failure:
The role of the neural integrator

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Article abstract—Congenital nystagmus (CN) may be due to an instability of the neural integrator responsible for gaze holding. This longitudinal study tests that hypothesis, investigates the saccadic instabilities of relatives, and assesses the effects of afferent stimulation on both the CN and the coexisting gaze-holding failure. We recorded four siblings who had CN and gaze-holding failure while fixating in primary position and lateral gaze. In lateral gaze, the CN waveforms were superimposed on the centripetal drift caused by the gaze-holding failure; the drift time constants ranged from 300 to 1,450 msec. CN waveforms lacked extended foveation periods. Saccadic instabilities were present in the father and two clinically unaffected siblings; the mother's eye movements were normal. We conclude that CN in the subjects of this study, and in others with idiopathic CN, is not due to gaze-holding abnormalities, and we speculate that development of the fixation reflexes that produce CN foveation periods requires some minimal foveation interval during which the target image is in the foveal area with low retinal slip velocity and acceleration.

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Congenital nystagmus (CN) is an ocular motor oscillation that usually becomes manifest in early infancy or can appear at birth or, occasionally, in later life.[1] It is easily differentiated from other forms of infantile nystagmus, such as latent/manifest latent nystagmus or the dissociated pendular nystagmus of spasmus nutans, by eye movement recordings.[2]

Congenital nystagmus waveforms. Eleven of the 12 waveforms of CN fall into two major categories, pendular and jerk; the 12th is a combination of the two.[3] Several variations of waveform are found in each type, and most contain a relatively motionless portion called the "foveation period."[3] After this variable period of relative stability, when the image of a target is in the foveal area, the eyes begin to slowly accelerate away from the target. One characteristic separating the jerk forms of CN from acquired horizontal nystagmus or latent/manifest latent nystagmus is that the slow phases in CN exhibit an increasing-velocity curvature. Slow-phase velocities can eventually reach several hundred degrees per second before a "braking" saccade[4] stops the runaway and either refoveates the target (a "foveating" saccade) or initiates a slow movement toward the target. Saccades are thought to reset the output (ie, eye-position signal) of the neural integrator (see "Gaze-holding failure," below). In some CN waveforms, foveating saccades result in an eye position that is on target; in others, braking saccades either leave the eye position relatively unchanged or somewhere between its initial position and that of the target.

Gaze-holding failure. Since the primary ocular motor commands (saccadic, pursuit, and vestibular) are encoded as velocity signals, an integration (in the mathematical sense) is required to achieve the eye-position signal. To hold the eye at an eccentric position in the orbit, against the elastic restoring forces of the orbital tissues, a sustained position command is required. The position of the eyes is maintained by a tonic signal thought to be the output of a neural integrator in the ocular motor system.[5-7] In normal subjects, this integrator is not perfect but somewhat "leaky" (ie, it cannot maintain its output; instead, the output decreases), with a time constant of about 25 seconds in the dark.[8] If the neural integrator becomes more leaky, the output will exponentially decrease more rapidly and the eyes will drift back to primary position; this is referred to as gaze-holding failure. The latter case results in gaze-evoked nystagmus (GEN) when the drifts back toward primary position are interspaced with corrective saccades (fast phases) and has been studied

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using a model with several types of neural integrator deficits.[9] The centripetal drifts are decreasing-velocity exponentials, and the initial post-saccadic velocities are a function of the magnitude of the gaze-angle deviation from primary position.

Hypothetical causes of congenital nystagmus. There have been hypotheses advanced to explain the mechanism responsible for CN. These include a defective saccadic system that results in a high-gain pursuit system,[10] an abnormal pursuit[11,12] or optokinetic[13] system, and chiasmal misrouting as found in albinos.[14] However, the saccadic system is normal in CN,[15] and an early study[16,17] of smooth pursuit and CN concluded that the pursuit subsystem was normal and that the CN waveforms were superimposed on its output (ie, the pursuit signal that matched eye velocity to target velocity). Recent reexaminations[18-22] of smooth pursuit and CN substantiate that conclusion and attribute the observed reversal in the CN waveform direction to a pursuit-induced shift in the null position. In addition, most individuals with CN do not have albinism (neither oculocutaneous nor ocular), and visual evoked potential studies[23,24] in these individuals have shown no evidence of chiasmal fiber misrouting. Since albinos *without CN* also show chiasmal fiber misrouting, a causal connection between CN and misrouting is not supportable.

Another putative cause for CN is an instability of the gaze-holding network. This can be conceptualized as a positive feedback loop around a common neural integrator (needed to compensate for its inherent leakiness). The positive feedback path would have a higher than normal gain, which results in an exponential runaway.[6] We addressed this latter hypothesis in this longitudinal study.

Case histories. The four individuals (three boys and one girl) we studied over a 4-year period were siblings who ranged from 2 months to 9 years old at the times of their recordings. Five additional siblings did not have ocular motor problems. Figure 1 shows their family tree. There was no other family history of ocular motor disorders.

Subject II-1, the oldest child, was born after an uncomplicated pregnancy and delivery. By age 2 months, the parents noticed that he was not focusing and fixating appropriately. An ophthalmologist and two neurologists evaluated the boy and made an initial diagnosis of Leber's congenital amaurosis. A neuro-ophthalmologist examined him at age 8 months and diagnosed him as having CN. The boy had a normal neurologic examination. His visual acuity was 20/200, with a normal fundoscopic examination. He reported a subjective improvement in acuity with monocular vision. In school, he had difficulty with low-contrast print. He noted difficulty in scanning a page of text and in alternating from one page of text to another. Despite problems with vision, he maintained an A average in school and now attends college.

Subjects II-4, II-6, and II-8 are younger siblings of subject II-1. The parents noticed visual problems immediately after birth in all three. In all the children, the eye movements described by the parents were a low-frequency pendular motion. As with subject II-1, all three had visual acuity of 20/200 and normal fundoscopic examination. The three siblings have experienced visual problems similar to those of subject II-1; all are A students. Visual inspection of the eye movements of all affected subjects revealed large oscillatory movements in lateral gaze.

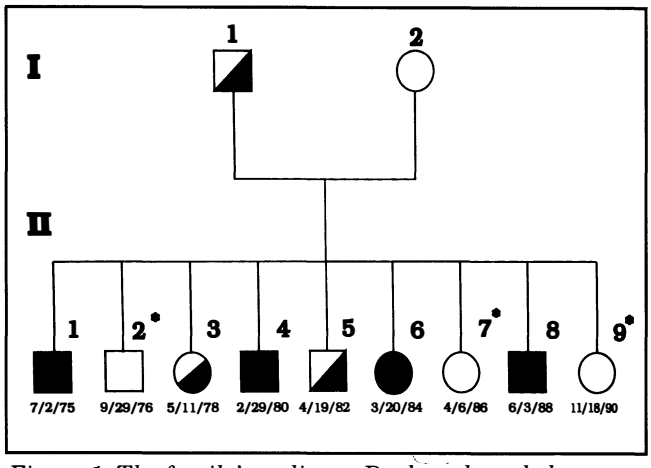

Figure 1. The family's pedigree. Darkened symbols (circles = females, squares = males) indicate which family members were affected. Half-darkened symbols in the clinically unaffected members indicate saccadic instabilities. I = first generation, II = second generation. Each sibling's birth date is shown; asterisks identify those not recorded.

Ophthalmologic examinations of the affected siblings by several ophthalmologists over the past years revealed normal anterior segments and normally colored irises without features of albinism. Tests for color vision were normal, and ocular transillumination tests on the affected siblings were negative; there was no evidence of albinism in other members of the family. Neither parent, nor any of the five other siblings, had visual problems or clinically apparent motility disorders.

Methods. *Recording.* Horizontal eye movement recordings were made using the infrared (IR) reflection method. Eye velocities were obtained by analog differentiation of the position channels. The strip-chart recording system was rectilinear (Beckman Type R612 Dynograph); total system bandwidth (position and velocity) was 0 to 100 Hz. During each recording, the chart-paper speed was adjusted to allow both the CN waveforms and the decreasing-velocity gaze-holding failure to be recognized. Blinks were identified by their triphasic velocity waveforms, marked on the records, and excluded from analysis.

Protocol. Except for the 2- and 5-month-old infants, the following protocol was used. The subject was seated at the center of a 5-foot-radius arc containing light-emitting diode targets. The head was stabilized in primary position and the subject was instructed to move only the eyes to view each target as it was turned on. The IR signal from each eye was calibrated with the other eye behind cover to obtain accurate position information and document small tropias and phorias hidden by the nystagmus. The eye movements of the infants were recorded using a technique we developed to obtain accurate waveform and interocular phase information without absolute amplitude calibration. The IR apparatus (without spectacle frames) are held firmly in front of the infant after proper setting of the interpupillary distance. The experimenter's hands are placed along the temples of the

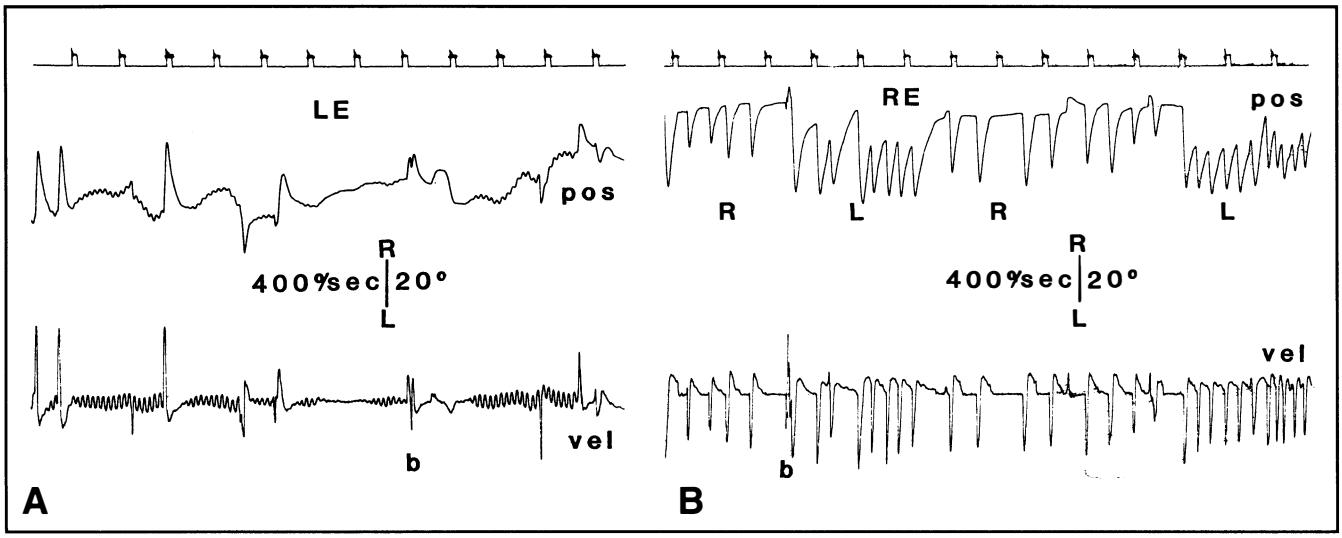

Figure 2. Eye position (pos) and velocity (vel) records of (A) the left eye (LE) and (B) the right eye (RE) of subject II-1. (A) During the neutral phase of his aperiodic alternating CN, the pendular waveform was variable in amplitude and was interspaced with motionless periods (usually implying relaxation of fixation attempt) and double saccadic pulses. Attempts at lateral fixation (eg, the three rightward and one leftward saccades in the first 5 seconds of the record) produced decreasing-velocity drifts back toward primary position. (B) The RE is shown during the jerk-left phase of the nystagmus. The nystagmus frequency was higher with left (L) than with right (R) eye fixation. The CN was superimposed on the drifts, as can be seen in the position (for the slower drifts) and velocity traces of both (A) and (B). In this and subsequent figures, blinks (b), and 1-second intervals (timing ticks at top) are indicated.

infant to stabilize both the head and the IR structure with respect to the head. This method produces binocular records of the waveforms of infants that make possible the diagnosis of the particular type of infantile nystagmus present: CN, latent/manifest latent nystagmus, or spasmus nutans. Attempts at lateral gaze were stimulated by directing the infant's attention laterally. This research, involving human subjects, followed the Declaration of Helsinki, and informed consent was obtained after the nature and possible consequences of the study were explained. The research was approved by an institutional human experimentation committee.

Analysis. The strip-chart recordings of each subject were individually analyzed to establish the CN waveforms and their characteristics under the imposed conditions. The time constants of the centripetal drifts of each subject were also calculated directly using the measurements taken from the recordings. When CN waveforms were superimposed on the drifts, the latter were analyzed by using the same point in each CN cycle to identify only the drift components; the same result would be obtained by using the average value of each CN cycle (ie, by filtering out the CN entirely). Thus, throughout the text and figure legends, references made to decreasing-velocity drifts do not refer to any part of the CN waveforms.

Results. During the course of studying this family, we had the opportunity to record each of the four siblings with CN. The oldest was recorded at 9 years, the youngest was recorded at the ages of 2 months and 3 years, and the two others were recorded several times. Due to their ages at the times of the recordings or (in some cases) the extreme inability to hold eccentric gaze angles, it was not possible to precisely calibrate all of them. However, their eyes moved conjugately and the IR system documented the waveforms and interocular phases of the eye movements accurately despite the lack of amplitude calibration.

Subject II-1. Subject II-1 was recorded at age 9 years (figure 2). His records revealed CN with pendular, asymmetric pendular, and jerk waveforms. The frequency of his pendular CN was as high as 9 to 10 Hz. This subject exhibited the most extreme case of gaze-holding failure of all the siblings; this resulted in a GEN. The fast phases (used to attempt to fixate a target) often contained dynamic overshoots. Complicating this picture was an aperiodic alternating nystagmus (APAN) component of his CN that obscured the gaze-holding failure by varying the gaze angle at which the eyes tended to come to rest. During the neutral phase of the APAN, his pendular CN waxed and waned; double saccadic pulses were also seen during this phase. To avoid the confounding effects of the APAN and dynamic overshoots, time constants of centripetal drifts were measured during the neutral phase of the APAN for saccades with no dynamic overshoots. Time constants were calculated from drifts throughout the record and ranged from 320 to 460 msec. Figure 2A shows the characteristics of his CN. Neither rightward nor leftward saccades resulted in sustained lateral gaze. Instead, they were followed by decreasing-velocity drifts toward primary position; the exponential nature of the drifts is evident from both the position and velocity traces. There were occasional periods of extended foveation in the CN waveforms, but neither a gaze angle nor a convergence null was found. Although no latent component was seen (ie, CN reversal)

with alternate cover, this test resulted in a modulation of the frequency of the nystagmus. As figure 2B shows (during the jerk-left phase of his APAN), the frequency increased with left-eye fixation; this was not due to an increase in slow-phase velocities. The leftward fast phases shown are followed by decreasing-velocity drifts toward primary position.

Subject II-4. Subject II-4 was recorded at ages 4 and 8 years. He exhibited pendular, asymmetric pendular, pendular with foveating saccades, jerk, jerk with extended foveation, pseudocycloid, pseudopendular with foveating saccades, and triangular waveforms during both sessions. Gaze-holding failure was seen at lateral gaze angles. While he was fixating in primary position, the CN waveforms were pendular with foveating saccades and pseudopendular with foveating saccades (see figure 3A). Figure 3B demonstrates the combination of CN and centripetal drift measured while he was attempting to fixate targets at 25° and 30° to the right. As the figure shows, these decreasing-velocity drifts lasted for several seconds and contained the CN waveforms superimposed on them. The time constants of the drifts back to primary position ranged from 920 to 1,450 msec at age 4 and from 300 to 650 msec at age 8. Triangular CN waveforms were also seen in this subject. The only periods of extended foveation that were recorded appeared while he was fixating a target near primary position; they were more common during the second recording session than during the first. No nulls were evident, and there was no latent component.

Subject II-6. Subject II-6 was recorded at ages 5 months, 4 years, and 7 years. As was the case for Subject II-4, her pendular, asymmetric pendular, and dual-jerk CN waveforms remained the same for all sessions over this 7-year interval. However, the later recordings reflected her improved ability to maintain concentration on a target. The second record contained attempts to fixate targets at each gaze angle. Figure 4A demonstrates the improvement with age in her ability to fixate in primary position. Figure 4B, recorded at age 4, demonstrates the gaze-holding failure that produced a coarse GEN overlay on the CN. As with subject II-4, the drifts lasted several seconds and contained the CN waveforms. Gaze-holding failure was evident in all records, with time constants of 750 msec

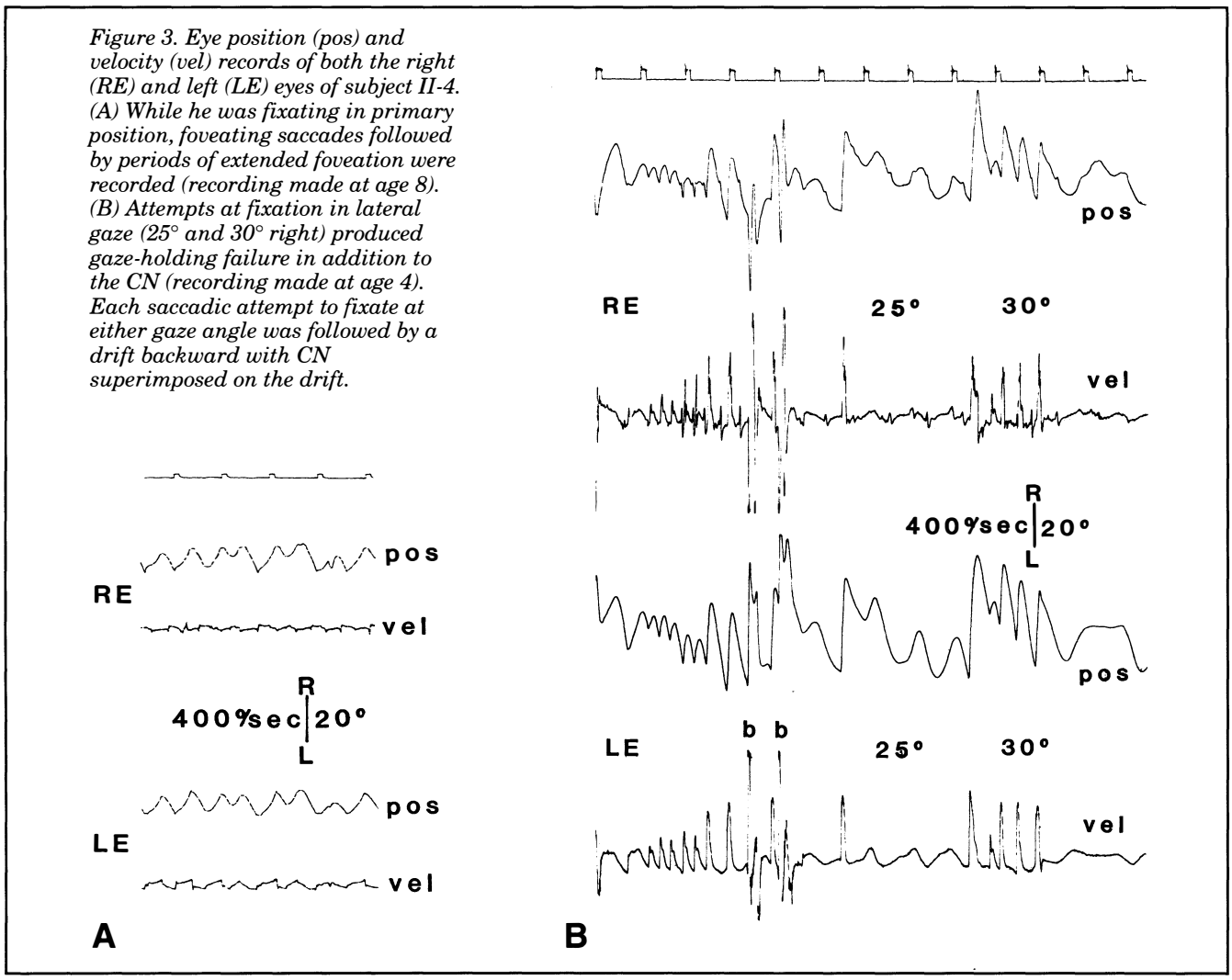

Figure 3. Eye position (pos) and velocity (vel) records of both the right (RE) and left (LE) eyes of subject II-4. (A) While he was fixating in primary position, foveating saccades followed by periods of extended foveation were recorded (recording made at age 8). (B) Attempts at fixation in lateral gaze (25° and 30° right) produced gaze-holding failure in addition to the CN (recording made at age 4). Each saccadic attempt to fixate at either gaze angle was followed by a drift backward with CN superimposed on the drift.

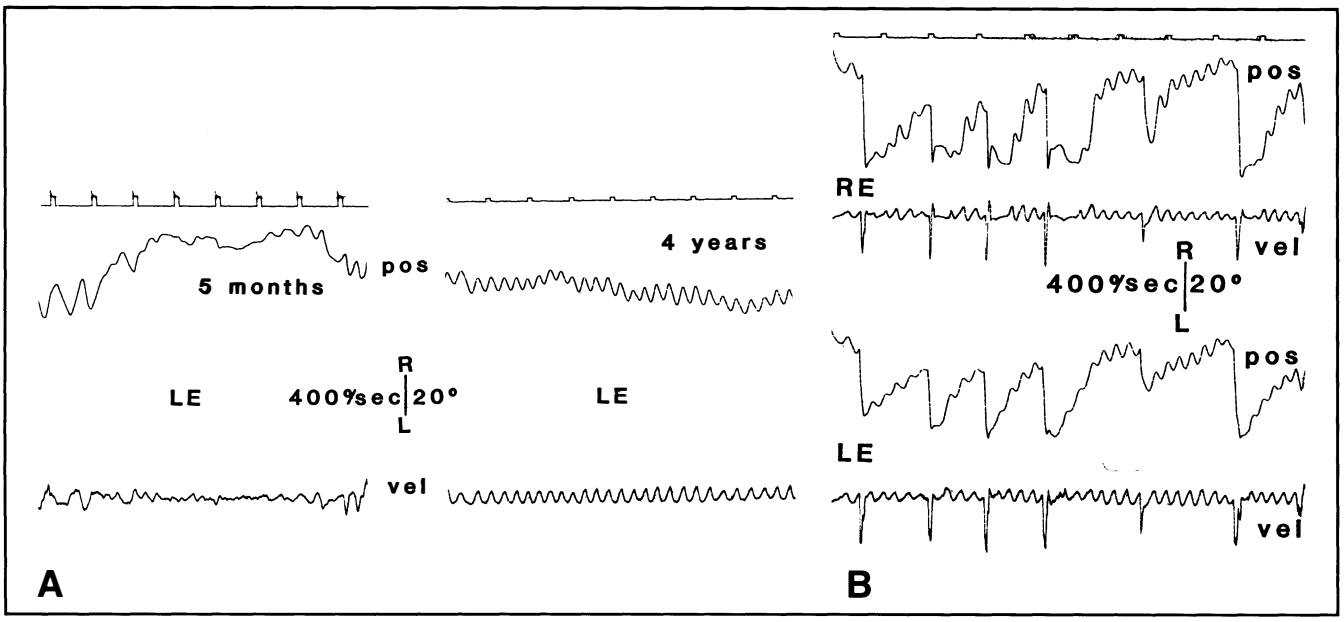

Figure 4. Eye position (pos) and velocity (vel) records of subject II-6. (A) The left eye (LE) at ages 5 months and 4 years. Calibration values apply to the 4-year record. (B) Both the right eye (RE) and LE, showing the conjugate gaze-holding failure produced by attempts at left lateral gaze (from the 4-year recording). The drifts toward primary position contained CN waveforms.

at 5 months, 720 to 1,000 msec at 4 years, and 500 to 850 msec at 7 years. No periods of extended foveation were seen in any of the records, and no nulls could be documented; there was no latent component.

During the last recording session (at age 7), we also tested the effects of stimulating her forehead with vibratory stimuli at 48 and 108 Hz. For stimulation above the right eye, reductions in peak-to-peak CN amplitude were 42% and 60% in the right eye and 12% and 34% in the left for the respective stimulation frequencies; no effect on gaze holding was seen.

Subject II-8. Subject II-8 was recorded at ages 2 months and 3 years. He had the same two CN waveforms (pendular and asymmetric pendular) during both recordings. Figure 5 demonstrates that at 2 months they were not yet well developed; at both ages, gaze-holding failure was evident when lateral gaze was attempted (leftward saccades 1 through 3 and 1 through 6). As both tracings show, CN was superimposed on the decreasing-velocity drifts that lasted several seconds. The time constants of the gaze-holding failure ranged from 500 to 800 msec at 2 months and 300 to 730 msec at 3 years. At 2 months his CN was a 1-Hz, high-amplitude pendular nystagmus; by 3 years it had developed into a 3- to 4-Hz, low-amplitude (1° to 3°) waveform that at times was damped (<0.5°) for periods of up to 1 second (see figure 5). His age precluded the determination of either slight gaze or convergence nulls, if present; none were evident clinically.

Clinically unaffected relatives. We also recorded the eye movements of the father (subject I-1),

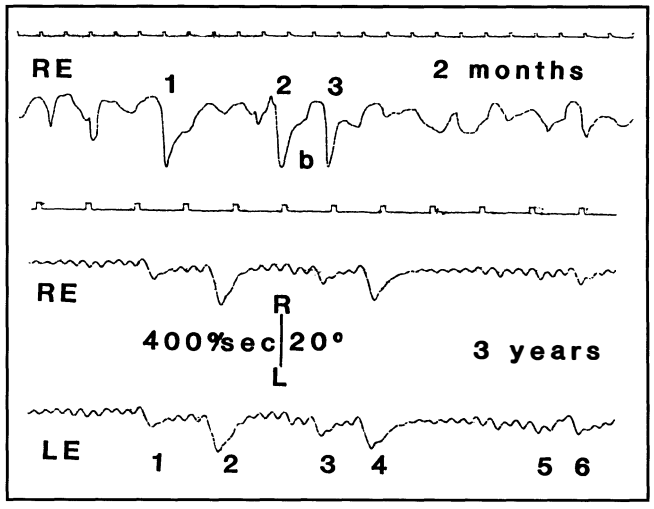

Figure 5. Eye position record of the right eye (RE) of subject II-8 at age 2 months and of both the RE and left eye (LE) at age 3 years. The gaze-holding failure is shown with attempted left gaze (saccades 1 through 3 in the 2-month and 1 through 6 in the 3-year records). Note the different time scales of the two records. Calibration values apply to the 3-year record. In both records, the drifts contained CN waveforms.

mother (subject I-2), and two clinically unaffected siblings (subjects II-3 and II-5). This was done to determine whether there were saccadic instabilities present. It has been reported that square-wave jerks (SWJ) and square-wave oscillations (SWO)[25] may be found in the clinically unaffected relatives of those with CN.[26,27] The mother's eye movements were normal and contained only 1.4 SWJ per

minute while she was fixating a target in primary position. Both parents and the two unaffected siblings maintained gaze at ±15° without the centripetal drifts seen in the affected siblings. The father exhibited 23.7 SWJ per minute, subject II-3 had 12.6 SWJ per minute, and subject II-5 had 6.4 SWJ per minute. Their average SWJ amplitudes ranged from 1° to 2°, from 0.5° to 2°, and from 0.5° to 3°, respectively. The intersaccadic intervals of the SWJ varied from 200 to 400 msec in all three. Fixation at ±15° yielded similar values for each. In addition, all three occasionally had square-wave pulses (SWP), previously called "macro square-wave jerks,"[28] in conjunction with SWJ and runs of SWO; their amplitudes were the same as those of the SWJ. The intersaccadic intervals during the SWO varied between 400 and 900 msec. A common finding was a SWO consisting of three saccades separated by these long intervals.

We also noted, in the father, a *uniocular* (left eye), convergent drifting in left gaze. The records of subject II-5 contained disconjugate (right eye > left eye), convergent drifting in conjunction with small corrective saccades, giving rise to a low-amplitude (2° to 3° peak-to-peak), low-frequency (0.3-Hz) jerk, dissociated nystagmus. In both cases, the movements were superimposed on the SWJ.

Discussion. *Visual acuity.* The visual acuity of the siblings with CN was less than we expected for idiopathic CN (20/20 to 20/80, in our experience). This could be due to a primary afferent visual abnormality or to the relative absence of foveation periods they exhibited. We found no evidence of the former (or of albinism) and conclude that the absence of well-developed foveation periods was the main factor in the lowered acuity.

Congenital nystagmus waveforms. The CN waveforms we recorded from subject II-6 at age 5 months and from subject II-8 at age 2 months did not contain the adaptations commonly found to extend foveation; these were found in their older siblings (subjects II-1 and II-4). Although the absence of well-developed foveation periods is not unusual in infancy,[29] it was remarkable in the case of subject II-6. This subject did not develop better waveforms, as documented from the recordings at ages 4 and 7 years. This finding suggests that the coexisting gaze-holding failure may have had a detrimental effect on the development of the fixation subsystem of this subject. Although subject II-8 did not develop better waveforms, he exhibited reduced CN amplitude and better control of the bias of his CN by age three. Due to that bias in his pendular CN, target foveation was accomplished at the peaks of the waveform, when eye velocity went through zero. Subject II-4 exhibited triangular waveforms, which do *not* allow for extended target foveation; this is rare for someone of his age. Subjects II-1 and II-4 did develop some good waveforms when fixating in primary position. All four siblings had both pendular and asymmetric pendular waveforms, demonstrating the effects of inheritance on CN waveform.[30]

In individuals with CN, as gaze is directed away from the null region, changes in both the amplitude and waveform of the oscillation are common, with the direction of jerk waveforms corresponding to the direction of gaze (with respect to the null). Despite these changes, the desired gaze angle is maintained to allow target foveation during the period of extended foveation in each nystagmus cycle. However, since these individuals had both hereditary CN and gaze-holding failure, it allowed us to compare their CN waveforms at primary position with those at lateral gaze angles, where the latter condition takes effect. We found that near primary position, when the effects of gaze-holding failure are minimal, the waveforms reflected those of individuals with CN and no gaze-holding failure. At lateral gaze angles, however, the waveforms lacked periods of extended foveation. Since the fixation systems of these subjects were able to extend foveation near primary position, we attribute the lack of extended foveation to the increased postsaccadic (ie, initial slow-phase) velocities present at lateral gaze angles due to the gaze-holding failure.

The neural integrator hypothesis. Normal individuals can maintain eccentric gaze, implying that the neural integrator's output is able to hold a tonic level. One way to conceptualize the neural integrator is by positive feedback around the leaky integrator. If the value of this feedback were too high, the output would rise exponentially and the eyes would move farther into lateral gaze.[6] Although this scheme is simplistic (for example, the stability of the integrator is very sensitive to small changes in the feedback loop), a modified version of it, using neural networks, is more robust.[31] Changes in the gain of the feedback loop could be responsible for CN (at least the jerk waveforms), with its characteristic increasing-velocity slow phases.[6] In the dark, maintenance of eccentric gaze depends on an internal signal based on the subject's desired gaze angle. The ability to maintain eccentric gaze angles is idiosyncratic and may result in physiologic end-point nystagmus at angles as small as 20°,[32] or in rebound nystagmus.[33] We did not find a gaze-holding failure at ±15° in either of the parents or in the unaffected siblings despite its appearance in all siblings affected with CN. We chose ±15° to remain below the range where end-point nystagmus begins to appear in normal individuals.

The affected subjects in this study demonstrated gaze-holding failure, suggesting a leaky neural integrator. The range of time constants (300 to 1,450 msec) can be interpreted as a partial failure of the neural integrator; total failure would have resulted in the time constant of the ocular motor plant (approximately 200 msec). The presence of a significant neural integrator leak, rather than its exact time constant, appears to be the relevant consideration affecting the lack of foveation periods in the CN waveforms. When the CN was pendular, we

recorded the expected drifts back to primary position with the pendular CN superimposed on the decreasing-velocity drifts (figure 4B). Since none of the siblings had CN with a latent component (as shown by recordings while fixating monocularly), this was not the dual-jerk latent waveform occurring in latent/manifest latent nystagmus or mixtures of it with CN.[30] The combination, in some of the siblings, of pendular CN and gaze-holding failure was not sufficient to contradict the neural integrator hypothesis of CN genesis since different types of instability might be responsible for the two basic CN oscillations—pendular and jerk.[3,6] However, when the CN was one of the jerk waveforms, we also recorded decreasing-velocity drifts back to primary position with the CN interspaced or superimposed. If the hypothesis is correct that jerk CN is caused by too much positive feedback around the normally leaky neural integrator, this second case should not have occurred. Since the neural integrator cannot be both too leaky and overly compensated by positive feedback, we conclude that jerk CN in these individuals is not caused by too much positive feedback around the neural integrator.

There is no difference in waveforms (implying underlying mechanism) between the CN in this family and idiopathic CN. Although there was a near absence of extended foveation, some siblings did manage to extend foveation in primary position. What made these individuals unique was the addition of the gaze-holding failure to their CN. The former resulted in the poor foveation and associated decrease in visual acuity. Thus, the gaze-holding failure, coexisting with a CN indistinguishable from common idiopathic CN, is strong evidence against (ie, these are counter examples to) the neural-integrator hypothesis for the genesis of CN. We regard the alternative, that there was a totally different ocular motor deficit in only these subjects, as improbable. Deficits in different anatomic sites may have the same mechanistic effect (eg, if they are in the same feedback loop) and thereby produce CN. However, we feel that the most parsimonious explanation for the specific oscillations of CN in all affected individuals is a single motor deficit that differs only in its magnitude and variation with: gaze or convergence angle; and pursuit, optokinetic or vestibulo-ocular velocity. Such an explanation can account for all the clinical variation seen among subjects.

Fixation reflexes. The development of the fixation reflex requires visual input that, among other things, is necessary to calibrate the neural integrator.[31,34] The waveforms of CN (both pendular and jerk) lend themselves to distortion by the normal fixation reflex that operates to maintain target foveation. Figure 6 schematizes nystagmus with pendular, increasing-velocity, linear, and decreasing-velocity slow phases. The effects of waveform distortion produced by the fixation system are also shown for each waveform. We hypothesize that the low (at or near zero) postsaccadic velocities and

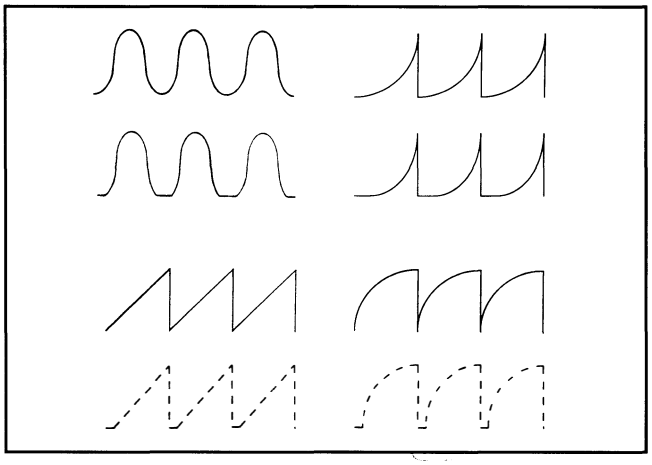

Figure 6. Drawings of pendular (top left), increasing-velocity (top right), linear (bottom left), and decreasing-velocity (bottom right) types of nystagmus appear in the upper tracings of each pair. The lower tracings of each pair illustrate the distortion of these waveforms produced by the fixation subsystem's attempt to extend foveation. The dashed waveforms have not been recorded in adult-acquired nystagmus (see text).

accelerations of CN waveforms, in combination with the foveal target image position, satisfy the basic conditions for the operation of the fixation subsystem. That is, the fixation subsystem will be unable to alter the eye motion to maintain fixation when the target image is not on the fovea or is not moving with a velocity or acceleration below some minimal threshold value. We have never recorded (nor found published examples of) extended-foveation periods on the waveforms of nystagmus acquired in adulthood that exhibit either linear or decreasing-velocity slow phases. Both of these types of waveforms have slow phases with initial velocities that may exceed the upper bounds of the fixation subsystem; both also have velocity discontinuities that result in high accelerations. For example, we documented[35] one case of a posterior fossa tumor present since birth (or early infancy) in which the patient's jerk nystagmus had linear slow phases and there were occasional beats that exhibited periods of extended foveation. In that case, the recordings support the interpretation that the fixation system suppressed some of the slow phases. Thus, the waveforms shown dashed in figure 6 are either rare (linear slow phases) or nonexistent (decreasing-velocity slow phases); we interpret that as an indication that the initial slow-phase velocities (or accelerations) in acquired nystagmus are usually too great for the fixation subsystem to extend foveation and, in so doing, distort the waveforms. Further, the plasticity present in early infancy may play an important role in the development of the fixation reflexes necessary to produce extended periods of foveation when nystagmus is present. However, no improvement in gaze holding was present in the affected siblings of this family as their ocular motor systems developed. Thus,

they had little or no ability to plastically change the gain of the neural integrator and overcome the leak. This inability cannot be attributed to the CN because most individuals with CN do exhibit precise fixation at lateral gaze angles (ie, their neural integrators are well calibrated).

In summary, the four affected subjects in this study had CN waveforms in combination with gaze-holding failure—a previously unreported phenomenon. The initial postsaccadic velocity of centripetal drifts was sufficient in these subjects to preclude the development of foveation periods in the CN waveforms when the subjects were fixating at lateral gaze angles, but, as figure 3A suggests, foveating periods appeared to be possible near primary position. We attribute this to the near-zero initial drift velocities present at these small gaze angles. Thus, although the fixation subsystems of both normal individuals and those with CN can hold images steady on the fovea for significant periods of time, they may be able to do so only if there are no forces driving the eyes away from the target with drift velocities greater than a few degrees per second. Normally, the waveforms of CN slowly accelerate away from the target from zero (the eye motion having just reversed direction) or near-zero velocity and the normal fixation reflexes can extend foveation, producing the waveforms with extended-foveation periods that are commonly recorded. In these subjects, the gaze-holding failure appears to have precluded extended foveation except at near-primary gaze angles. At lateral gaze angles, there were no periods when the target image remained on the fovea with low drift velocities. These findings suggest that the fixation subsystem may only be able to maintain the position of foveal images with low drift velocities and accelerations. This may be modeled using input position, velocity, and acceleration nonlinearities whose outputs are zero above yet-to-be-determined input threshold values and whose gains are unity within their operating ranges.

Afferent stimulation. Stimulation of the ophthalmic division of the trigeminal nerve reduces CN in some subjects.[36,37] In subject II-6, at age 7, we recorded a reduction in CN amplitude when vibratory stimuli (especially at 108 Hz) were applied to the forehead. A similar, clinically visible reduction was videotaped (but not recorded) for subject II-4. This effect on the CN, but *not* on the gaze-holding failure, suggests that either the sites of origin of the two are not the same or they are differentially affected by vibration.

Clinically unaffected relatives. Our recordings of clinically unaffected relatives, including the father of the subjects, confirmed the findings of Shallo-Hoffmann et al[26,27] that relatives may exhibit saccadic instabilities. As figure 1 shows, the father (I-1) had saccadic instabilities that were passed on to clinically unaffected siblings II-3 and II-5; it is possible that siblings II-2, II-7, and II-9 (unavailable for recording) had saccadic instabilities. The appearance of saccadic instabilities linked with CN has been documented in recordings from an infant with saccadic oscillations and intrusions preceding the later development of CN.[38] In addition to SWJ and occasional SWO, which were seen in clinically unaffected relatives, we also found SWP; these are usually a sign of neurologic disease.[25,39,40] Studies of SWJ in normal individuals[41-43] differ in their conclusions on what should be considered abnormal (9 to 15 per minute, with amplitudes of 2° to 4°); SWO were also shown. We consider frequent SWJ, SWO, and SWP to be specific indicators of fixation instability and combinations of them to be "abnormal" despite both the lack of clinical problems associated with them and the existence of normal subjects with SWJ frequencies higher than the above ranges. The intersaccadic intervals we found in the SWO were greater than the normal values of 200 to 300 msec usually seen in SWJ and reported for SWO in progressive supranuclear palsy.[25] They were, however, consistent with the SWO shown in previous studies[26,27,44] of clinically unaffected relatives of CN subjects.

Genetics. Three distinct ocular motor abnormalities were present in this family: saccadic intrusions and oscillations, gaze-holding failure, and CN. The mode of inheritance of the saccadic abnormalities appears to be autosomal dominant (figure 1) (subjects I-1, II-3, and II-5). Several modes are possible for the gaze-holding failure and the CN. First, the same genetic abnormality may have been responsible for all three defects, but subjects I-1, II-3, and II-5 may have been able to suppress the gaze-holding failure and CN. In this mode, the transmission for all three conditions is autosomal dominant with variable expressivity. Second, the appearance of gaze-holding failure and CN in some of the siblings in the second generation may reflect genetic "anticipation," in which the genetic abnormality undergoes a transformation in the second generation that results in more severe dysfunction. Again, the transmission is autosomal dominant. Third, the gaze-holding failure alone may reflect the effect of the dominant gene, and the CN that accompanied it in each of the four siblings (subjects II-1, II-4, II-6, and II-8) may reflect the propensity for horizontal instability (in the form of CN) seen with a variety of congenital afferent visual defects. That is, any condition (sensory or motor) that interferes with early visual and ocular motor development may facilitate the development of CN in an ocular motor system with a preexisting propensity for oscillation. In this mode, the transmission of the saccadic instabilities is autosomal dominant, with more severe expression in the second generation causing the gaze-holding failure. The CN is facilitated in those in whom the horizontal system is near oscillation and other deficits are present during early development.

The observation that not all siblings in this family developed CN is consistent with the known lack of a direct cause-and-effect relationship between

afferent visual defects and the development of CN in all subjects. The gaze-holding failure, present in all affected siblings but absent in both the parents and the clinically unaffected siblings we tested, remains a unique association in this family.

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