Special Communication

A Unifying Neurologic Mechanism for Infantile Nystagmus

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Lateral-eyed afoveate animals use the subcortical accessory optic system to generate accurate responses to full-field optokinetic input. When humans rotate their eyes to pursue a moving target, the visual world sweeps across their retinas, creating a contraversive optokinetic stimulus. Humans have developed a cortical foveal pursuit system that suppresses the perception of this full-field optokinetic motion during active pursuit. When foveal vision is slow to develop in infancy, this phylogenetically old optokinetic system, which is normally operative in the first 2 months of human life, continues to be ontogenetically expressed. Hypothetically, the incursion on cortical pursuit of the antagonistic motion stimulus from this subcortical optokinetic system facilitates development of the unstable oscillatory activity of the eyes that characterizes infantile nystagmus.

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Infantile nystagmus is conjugate oscillation of the eyes that may appear in isolation but more often appears in conjunction with afferent visual deficits, such as aniridia, albinism, optic nerve hypoplasia, congenital retinal dystrophies, isolated foveal hypoplasia, congenital cataracts, and achiasma. Infantile nystagmus is defined by the following general features[1-3]:

1. a predominantly horizontal pendular or jerk nystagmus;
2. onset occasionally at birth but usually at age 2 to 3 months;
3. unlike vestibular nystagmus, infantile nystagmus stays horizontal in upgaze;
4. nystagmus often damps during near fixation;
5. absence of oscillopsia, vertigo, or imbalance;
6. central or eccentric null position;
7. apparent inversion or "reversal" of optokinetic nystagmus in approximately two-thirds of cases;
8. increase in the oscillation during attempted fixation or pursuit;
9. presence of foveation periods on eye movement recordings; and
10. absence of neurologic abnormalities outside of the visual system.

At least 50% of patients with infantile nystagmus have associated maldevelopment of the retinas or optic nerves.[4-6] Patients without detectable visual system deficits often show X-linked or autosomal dominant inheritance of infantile nystagmus.[7,8] A gene (*FRMD7*; OMIM: 300628) with strong expression in the developing neural retina has been identified as a cause of X-linked infantile nystagmus.[9-11] Eye movement recordings show a number of waveforms that have in common short foveation periods that follow each refixation movement.[1] Although neuronal misdirection of the anterior pathways through the chiasm can facilitate the development of infantile nystagmus in patients with albinism and achiasma, most patients with infantile nystagmus have normal hemispheric visual-evoked potentials, indicating that chiasmal misdirection is not necessary to generate this oscillation.[12,13]

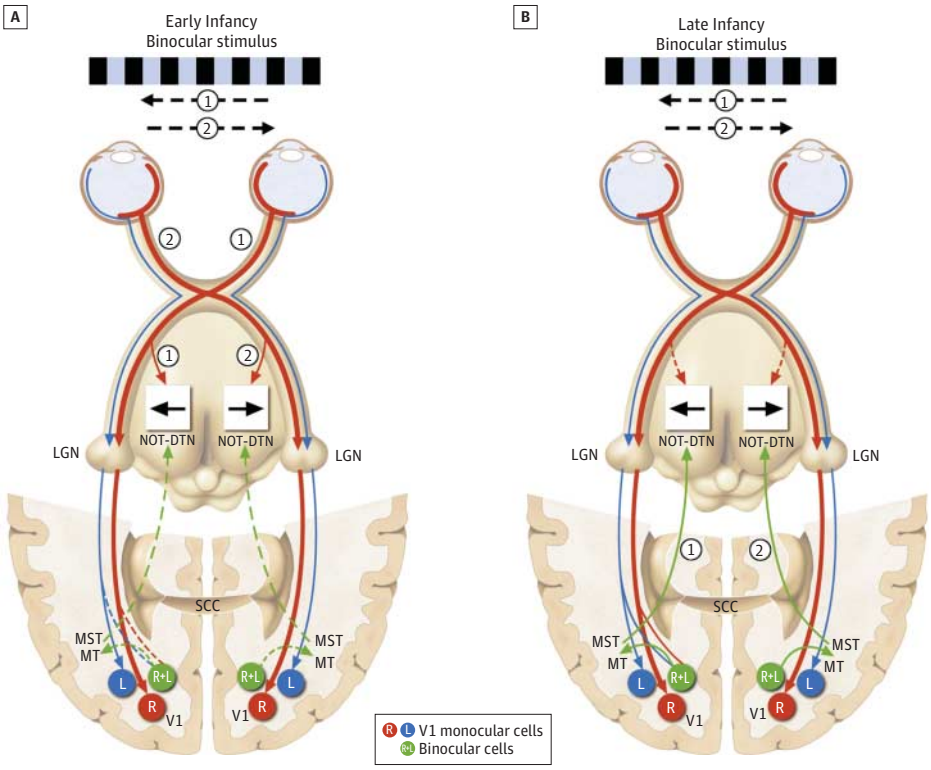
We have come to see infantile and latent nystagmus as existing on a clinical and neuroanatomic continuum. In humans, infantile strabismus creates a dissociated form of binocular vision in which the 2 eyes are subjected to unequal visual input. When cortical binocular vision fails to develop in infancy, we hypothesize that the ocular motor disturbances of infantile strabismus correspond to subcortical binocular visual reflexes that are operative in lateral-eyed animals.[14] Dissociated eye movements, such as latent nystagmus, manifest when the nascent binocular cortical pursuit pathways fail to suppress monocularly driven subcortical optokinetic pathways that are modulated by the nucleus of the optic tract and the dorsal terminal nucleus (NOT-DTN) of the accessory optic system (AOS).[15,16] It therefore seems reasonable to question whether infantile nystagmus, a binocular oscillation often associated with reduced central vision in both eyes, could similarly arise from an atavistic resurgence of this subcortical visual system.

We propose that abnormal development of binocular foveal vision allows the AOS, a primitive subcortical "pursuit" system, to remain expressed in humans and that the inherent antagonism between the cortical and subcortical pursuit systems is manifested in the form of infantile nystagmus. We use the term *isolated* instead of *idiopathic* (ie, unknown cause) infantile nystagmus because the latter is incorrect as well as misleading (ie, nystagmus in patients with associated sensory deficits is not caused by those deficits; correlation—even time-locked correlation—does not equal causality). The direct cause of infantile nystagmus has been attributed[17,18] to the normally oscillating part of the smooth pursuit system. Ocular motility studies[1-3] have shown the nystagmus exhibited by patients with and without associated visual sensory deficits to be identical. Because infantile nystagmus is a single entity with a known cause, there is no foundation for arbitrarily describing the nystagmus of one subset of patients as idiopathic.

What Is the AOS?

As detailed in a recent publication,[16] the AOS is a primary visual system receiving direct visual information from the retina via one or more accessory optic tracts.[19] The AOS is responsible for

Figure 1. Depiction of the Brain, as Viewed From Above, Showing Normal Cortical and Subcortical Projections During Early Human Development



A, Early in infancy, horizontal optokinetic stimuli (shown as leftward or rightward motion) from each nasal retina are transmitted via a subcortical pathway to the contralateral nucleus of the optic tract-dorsal terminal nucleus (NOT-DTN) of the accessory optic system (solid red arrow), which is directionally sensitive to ipsiversive motion (ie, nasalward for the contralateral eye). During this early stage of development, the cortical pursuit pathways (shown as corticofugal projection from the middle temporal area–medial superior temporal area [MT-MST] to the ipsilateral NOT-DTN) have not yet become functional (interrupted green arrows). B, Later in infancy, horizontal optokinetic responses become encephalized, binocular cortical pursuit pathways become fully operational (solid green arrows), and subcortical optokinetic pathways regress (interrupted red arrows). L indicates left eye monocular cells; LGN, lateral geniculate nucleus; R, right eye monocular cells; R+L, cortical binocular cells; SCC, splenium of the corpus callosum; and V1, primary visual cortex. Based on the model proposed by Hoffmann.[32]

visuovestibular interaction in afoveate animals.[20-22] Its retinal input is derived from ON-type direction-sensitive ganglion cells. The AOS neurons have large receptive fields (averaging approximately 40° vertically and 60° horizontally), are direction selective, and have a preference for slow-moving stimuli.[19,22-25] The AOS processes information about the speed and direction of movement of large textured parts of the visual world.[20,23,24] After accounting for an eye movement–generated slip (efference copy), the AOS signals motion as a function of slip of the visual world over the retinal surface and generates corrective eye movements to stabilize the retinal image.[20,23,24] As an analyzer of world motion, the AOS subserves visual proprioception in the afoveate animal.[20,23,24] Ontogenetically, the function of this subcortical optokinetic system antedates full maturation of the vestibuloocular reflex in lower vertebrates.[26,27]

The AOS is involved in determining self-motion and is uniquely organized in a vestibular coordinate system.[20,23,24] Experimental studies by Simpson and colleagues[20,23,25] indicate that visual and vestibular signals that produce compensatory eye movements are organized about a common set of axes derived from the orientation of the semicircular canals. Because the AOS is directionally sensitive to low-velocity movements, whereas the vestibular system typically responds to movements of higher velocity, the AOS and vestibular labyrinths form 2 complementary systems to detect self-motion and promote image stabilization so that objects in the visual world can be quickly and accurately analyzed.[19,20,24,25] The AOS exists in all vertebrate classes,[20,28-30] including humans.[31] In human infancy, the AOS is believed to generate full-field subcortical optokinetic responses within the first 2 months of life before normal binocular cortical pursuit pathways supersede this phylogenetically ancient subcortical system (**Figure 1**).[32-36]

Role of the AOS in Infantile Nystagmus

Full-field optokinetic nystagmus and foveal pursuit are diametrically opposed ocular motor functions—you have to turn one off to have the other.[36] Failure to do so produces a discordance wherein activation of one system provides visual feedback that reactivates the other system in a positive feedback manner. The following clinical and experimental evidence support this mechanism as the substrate for the horizontal oscillations of infantile nystagmus.

Pendularity

The pendular nature of infantile nystagmus may reflect the balanced antagonism of these hierarchical optokinetic systems. Pendular pursuit oscillations result from negative feedback and excessive time delay in the internal pursuit feedback loop. Most of the control systems in nature (as well as those constructed by man) use negative feedback (part of the output is fed back to subtract from the input). This system produces a stable, time-invariant control structure. However, when there is an increased delay in that feedback pathway, the resulting phase shift in the feedback signal causes an effective reversal in its sign. For example, a 180° phase delay in a

sine wave results in the positive portion coinciding with the original negative portion. Because the feedback is negative by design (ie, the feedback signal is multiplied by −1), that delayed positive portion becomes negative and it sums with the undelayed negative portion of the original signal. This signal continues to grow with each cycle. The result is an oscillation similar to that produced in auditorium microphone and speaker systems when the volume (gain) is too high for the short, built-in time delay from microphone to speaker. In infantile nystagmus, the antagonistic pursuit signals produced by coexpression of the cortical pursuit system and the subcortical AOS (which functions as an afoveate full-field pursuit system) may provide the substrate for the underlying pendular oscillation. Saccadic refixation movements get secondarily superimposed to provide the variable waveforms that have been identified within the oscillation.[1]

Directionality

Infantile nystagmus manifests clinically as a predominantly horizontal conjugate nystagmus. This trajectory may reflect the antagonism between the subcortical NOT-DTN (which generates monocularly driven optokinetic responses) and the middle temporal area and medial superior temporal area (MT-MST) within the visual cortex, which generates binocular horizontal pursuit movements. In monkeys, MST generates optokinetic responses that are largely visuovestibular in origin[37,38] and maximally responsive to side-to-side full-field optic flow.[39,40] This intrinsic directional sensitivity could explain why infantile nystagmus is usually maximal in the horizontal plane, reflecting delayed (in isolated cases) or deranged (in the cases with structural abnormalities within the eye or neuronal misdirection) maturation of the horizontal pursuit pathways involving MT-MST in the visual cortex. This predominant mismatch between horizontal cortical and subcortical motion pathways could also explain how the oscillation of infantile nystagmus maintains its horizontal trajectory in upgaze, unlike in vestibular nystagmus. The rare patients with vertical or oblique nystagmus[41,42] need further study to better understand how our hypothesis may apply to them.

Foveation Periods

Unique to infantile nystagmus is its association with brief foveation periods following saccadic refixation.[43-45] These foveation periods utilize the preserved ability of the fixation and cortical pursuit systems to stabilize the eyes on target until an incursion of the subcortical optokinetic signal modulated by the AOS succeeds in derailing these functions. During foveation periods, ocular motor functions, such as fixation, pursuit, and the optokinetic and vestibuloocular reflexes, continue to function robustly in infantile nystagmus despite the superimposition of a pendular oscillation.[43-45]

Absence of Oscillopsia

The absence of oscillopsia during normal eye movements arises from an efference copy that reconstructs target and world motion so that the perception of either is not influenced by the sweeping of the visual world across the retinas.[46-48] The absence of oscillopsia in infantile nystagmus requires an online efference copy to correct for a constantly changing (in amplitude and waveform) oscillation.[46-48] There is some evidence[24] that efference copy may be embedded within the functioning AOS. This would explain why rare patients who first express infantile nystagmus in their adolescence do not invariably experience oscillopsia.[49]

Null Position

Infantile nystagmus is often associated with an eccentric horizontal null position leading to a gaze preference. In infantile nystagmus, this null position is the binocular equivalent of the monocular optokinetic bias that defines latent nystagmus. In the presence of infantile esotropia, the visuovestibular-optokinetic imbalance that drives latent nystagmus is modulated by the differential activity of each NOT-DTN, which is sensitive to nasally directed input from the contralateral eye.[50] In the setting of infantile nystagmus, this model would predict that any superimposed binocular visual imbalance could generate a horizontal null position without strabismus via asymmetrical activation of the NOT-DTN.

Time of Onset

Infantile nystagmus is usually noted between the second and third months of life.[4] The developmental time course of infantile nystagmus overlaps that of infantile esotropia in that both conditions first appear during early infancy when binocular cortical pursuit pathways normally mature sufficiently to overtake the subcortical optokinetic system. During the first 2 months of human life, cortical pursuit pathways have not fully matured, and full-field optokinetic eye movements are attributed to subcortical visual systems, such as the NOT and the AOS.[34,35] Ontogeny recapitulates phylogeny as the emergence of infantile nystagmus coincides with the developmental maturation of the cortical pursuit pathways, which fail to exert their predominance over the subcortical optokinetic pathways in the first 2 months of life. When maturation of these cortical pathways is delayed or deranged, the subcortical pathways continue to function, with the persistent antagonism between these 2 systems expressed in the form of infantile nystagmus. The fact that antagonism cannot be established in children with cortical visual loss demonstrates how an intact visual cortex is necessary for infantile nystagmus to develop.[51-53] Once the visual cortex has developed, the subcortical optokinetic pathways normally cease to function, which explains why infantile nystagmus does not arise when central binocular visual loss develops after early infancy.[53]

This explanation does not account for cases of infantile nystagmus that have been noted to appear at birth because the cortical pursuit system is not yet operational.[33-35] Animal models[54-57] suggest that genetic mutations can invert the directional sensitivity of the subcortical AOS to allow this oscillation to be expressed. Inversion of the retinal slip, the error signal of the subcortical optokinetic feedback loop, has been demonstrated in an albino rabbit[54] and in achiasmatic zebrafish belladonna mutant,[55-57] which shows nystagmus in light with waveform characteristics superficially resembling infantile nystagmus. Inversion of the subcortical error signal within the AOS could produce an unstable feedback mechanism that would tend to increase retinal slip.[57] That result would allow infantile nystagmus to manifest as the cortical pursuit system matures and would preclude accurate calibration of pursuit damping. When mutational effects are localized to the subcortical optokinetic system, electrophysiologic symmetry may be preserved within the visual cortex. Conversely, some infants with normal vision exhibit a transient nystagmus that disappears as the visual system matures in the postnatal period,[58] perhaps reflecting an atavistic expression of the normal AOS before it is inactivated as normal connections from cortical pursuit pathways become established. There is always the alternative that, in cases of isolated infantile nys-

tagmus appearing at birth, pursuit-system damping calibration is precluded by some other factor (eg, genetic) independent of sensory loss or AOS directional inversion.

Association With Seesaw Nystagmus

Eye movement recordings have shown that infantile nystagmus is accompanied by a subclinical seesaw nystagmus.[59] Seesaw nystagmus is a cyclovertical oscillation of the eyes that has been attributed to reactivation of the lateral and medial terminal nuclei within the AOS.[60] Because torsional eye movements are not generated within the visual cortex,[50] reactivation of the AOS seems necessary to explain the coexistent cyclovertical component of this oscillation. In rare infantile nystagmus cases with achiasma or hypochiasma, a clinically visible seesaw nystagmus is also present.[61]

Reversed Optokinetic Nystagmus

Despite their apparent reversal, the optokinetic responses in infantile nystagmus are not reversed; affected patients still generate the correct optokinetic responses during each foveation period. These responses are driven by the (still intact) cortical pursuit system.[44] So-called *reversed* horizontal optokinetic responses in infantile nystagmus are attributable to a shift in the null zone brought about by viewing horizontal optokinetic targets.[62,63] Underlying this dynamic null shift may be the breakthrough responses of the AOS to full-field optokinetic stimuli that are reactivated by the fully functioning pursuit system.

Optokinetic motion is known to displace the resting position of eyes in the direction of the fast phase.[64] For example, rightward-moving optokinetic targets would displace the eyes to the right, simulating right gaze and generating a right-beating nystagmus. This binocular displacement would produce the appearance of a reversed optokinetic nystagmus because the shift in gaze position to the right is equivalent to a displacement of the null position to the left.[53] In this scenario, the optokinetic shift in gaze position to the right tells the (still active) AOS that the world has rotated to the left, reinforcing a right-beating nystagmus.

Augmentation by Fixation and Pursuit

In contradistinction to peripheral vestibular nystagmus, the intensity of infantile nystagmus increases during visual activity involving fixation or pursuit.[65-67] Thus, daydreaming in the light will diminish infantile nystagmus, whereas any active gaze effort in the dark will evoke it.[68] The fixation system works synergistically with the pursuit system and helps it to function smoothly by correcting for small position errors. When fixation and pursuit are activated by attention to the external visual world, infantile nystagmus intensifies because of increased antagonism between the cortical and subcortical optokinetic inputs.

Association With Congenital Visual Loss

Approximately half of the cases of infantile nystagmus are accompanied by structural or electrophysiologic derangements involving central foveal vision in both eyes.[4-6] The common denominator in these disorders is binocular maldevelopment of central foveal vision subserving high-frequency contrast sensitivity. When present from birth, these derangements preclude the normal development of cortical foveal pursuit and promote persistent expression of the subcortical optokinetic pathways driven by the NOT-DTN. Animal models[54-57] demonstrate that albinism and achiasma can also alter the trajectories of the subcortical optokinetic pathways.

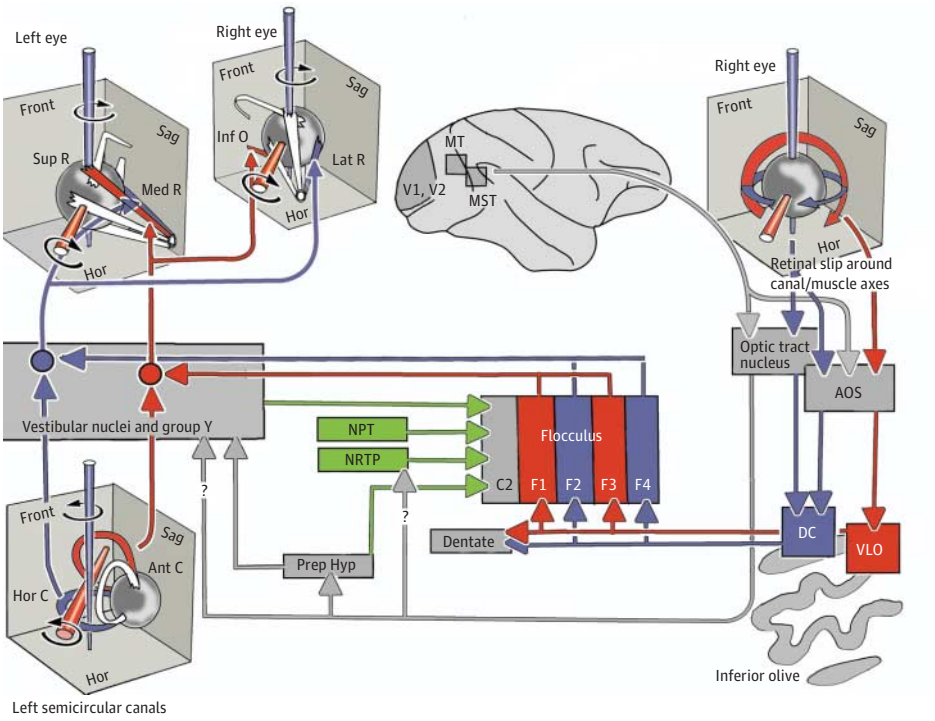
Hereditary forms of infantile nystagmus are commonly associated with no other detectable visual system abnormalities. However, a study by Weiss and Kelly[69] found that patients with isolated infantile nystagmus showed delayed development of normal grating acuity responses. This finding suggests that patients with apparently isolated infantile nystagmus may have a genetically determined maturational delay in binocular development of cortical vision. Developmental retardation in the maturation of cortical pursuit during the necessary time window could lead to persistent activation of the subcortical optokinetic system and promote the expression of infantile nystagmus. If a perturbation in developmental timing alone is sufficient to permit the AOS to generate subcortical optokinetic responses, this temporal delay could explain the occurrence of infantile nystagmus in patients who ultimately develop otherwise normal visual systems. In these infants, genetic mutations or developmental perturbations that delay the normal bilateral maturation of cortical (foveal) pursuit pathways could be sufficient to allow the subcortical optokinetic system to remain functional.

Superimposition of Latent Nystagmus

Infantile nystagmus syndrome and latent nystagmus (also termed *fusion maldevelopment nystagmus syndrome*)[70] exist on a continuum wherein early loss of vision in both eyes (eg, from bilateral congenital cataracts or bilateral optic nerve hypoplasia) precipitates infantile nystagmus, whereas early visual loss in one eye (eg, from a unilateral congenital cataract or unilateral optic nerve hypoplasia) gives rise to a manifest latent nystagmus.[71] Furthermore, infantile nystagmus is often accompanied by a superimposed latent nystagmus[72] causing visual acuity to be further degraded under conditions of monocular testing.[73] Like infantile nystagmus, latent nystagmus has a torsional component and requires persistent activation of subcortical optokinetic pathways for its expression.[50] Latent nystagmus is generated by nasalward motion input to the NOT-DTN of the AOS from the contralateral eye.[50] Latent nystagmus reflects a monocular optokinetic predominance in the nasal direction that is mediated subcortically by the NOT-DTN (a part of the AOS) within the mesencephalon.[15,50,74] This monocular, subcortical, nasotemporal optokinetic asymmetry is normal in lateral-eyed animals but suppressed in humans with cortical binocular vision.[75]

Whereas latent nystagmus represents a *unilateral* activation of nasally directed subcortical optokinetic pathways, infantile nystagmus signals a *bilateral* activation of subcortical optokinetic pathways. This interrelationship explains how binocular central visual loss from birth gives rise to infantile nystagmus, whereas monocular visual loss from birth gives rise to esotropia with latent nystagmus. It also predicts that latent nystagmus should be superimposed on infantile nystagmus when strabismus coexists. This framework allows us to cross-correlate these 2 oscillations and conceptualize them as involving the same neurologic pathways along a continuum of top-down (cortical-subcortical) optokinetic imbalance in infantile nystagmus and side-to-side (binocular) optokinetic imbalance in latent nystagmus. Infantile nystagmus could be considered the binocular form of latent nystagmus. The waveform differences arise from the functional sites affected by these imbalances (a tonic imbalance in the visuovestibular system resulting in latent nystagmus

Figure 2. Diagram of Cortical and Subcortical Optokinetic Pathways Mediating Infantile Nystagmus



We propose that *cortico-mesencephalic-cerebellar* pathways involving the middle temporal area–medial superior temporal area (MT-MST), the accessory optic system (AOS), the nucleus of the optic tract, and the flocculus of the cerebellum generate this horizontal oscillation. Pathways for horizontal eye movements are shaded blue, pathways for movements around an oblique horizontal axis are shaded in red, and mossy fiber pathways (unrelated to the climbing fiber pathways mediating the AOS) are shaded in green.
Ant C indicates anterior canal; C2, F1, F2, F3, and F4, layers within the cerebellar flocculus; DC, dorsal cap; Front, frontal plane; Hor, horizontal plane; Hor C, horizontal canal; Inf O, inferior oblique muscle; Lat R, lateral rectus muscle; Med R, medial rectus muscle; MT, middle temporal area; MST, middle superior temporal area; NPT, nuclei of the paramedian tracts; NRTP, nucleus reticularis tegmenti pontis; Prep Hyp, nucleus prepositus hypoglossi; Sag, sagittal plane; Sup R, superior rectus muscle; V1, V2, cortical areas; and VLO, ventrolateral outgrowth. Question marks indicate disputed projection of the nucleus of the optic tract to the vestibular nuclei and the NRTP. Modified from Voogd et al.[83]

and an interference with the calibration of the pursuit-system damping causing infantile nystagmus).

Involvement of Cerebellar Pathways

The responses of the AOS are modulated by the flocculus within the vestibulocerebellum. Experimental findings from numerous studies[76] implicated an integral role for the cerebellum in the modulation of infantile nystagmus. High-resolution magnetic resonance imaging using voxel-based morphometry has found that gray matter volume increases within cortical area V5/MT, the fusiform gyrus, and the vestibulocerebellum. These changes may relate to the antagonism between cortical pursuit and the subcortical AOS, the effort involved in maintaining fixation, or both.

In situ hybridization studies[9,77,78] on the embryonic human brain have shown that the *FRMD7* mutation that characterizes X-linked infantile nystagmus is expressed in the developing forebrain, midbrain, cerebellum, primordium, spinal cord, and neural retina. Barreiro et al[79] modeled the ocular motor system and concluded that infantile nystagmus could result from adaptive cerebellar mechanisms. Yoshida et al[80] found that mutant mice deficient in the glutamate receptor δ_2 subunit, which have limited plasticity of synapses onto Purkinje cells, also have oscillations of approximately 10 Hz in Purkinje cell responses and eye movements that resemble pendular infantile nystagmus.

Finally, periodic alternating nystagmus is modulated by the nodulus of the vestibulocerebellum and requires the coexistence of a visual deficit and a vestibular malfunction.[81,82] Thomas et al[10] showed that periodic alternating nystagmus occurs predominantly with missense mutations in *FRMD7* and concluded that this is most likely related to instability of the optokinetic-vestibular systems. Perhaps efferent activity from the cerebellar flocculus modulates the slow eye movements of infantile nystagmus while the cerebellar nodulus and uvula give rise to periodic alternating nystagmus. These findings do not imply that infantile nystagmus is anatomically localized within the cerebellum but that the vestibulocerebellum actively participates in generating this oscillation (**Figure 2**).[83]

Theories of Causation

Other causational theories for infantile nystagmus have invoked atavistic evolutionary mechanisms to explain the oscillation. Yee

et al[84] examined the role of the subcortical AOS in humans and concluded from their optokinetic measurements that infantile nystagmus must be due to an inherent defect in the subcortical optokinetic system. Dell'Osso[85] rebutted this conclusion and pointed out that the apparent full-field optokinetic defects could be attributed to the nystagmus itself rather than to an inherent defect in the subcortical optokinetic system. Kommerell and Mehdorn[86] ascribed infantile nystagmus to a primary defect in the optokinetic system, which can no longer maintain retinal slip control. Kommerell[87] and Kommerell et al[88] inferred that, because patients with infantile nystagmus can differentiate velocities of optokinetic stimuli, the defect cannot be in the retinocortical pathway and must be between the cortex and the ocular motor centers in the brainstem. Optican and Zee[89] reproduced some of the waveforms of infantile nystagmus by using a computer model to create a reversal in the sign of the velocity pathway to make the neural integrator unstable. However, the demonstration of simultaneous decelerating (due to a leaky neural integrator) and accelerating (due to infantile nystagmus) slow eye movements in a family who had both deficits disproved the hypothetical explanation.[90] Jacobs and Dell'Osso[17] modeled infantile nystagmus as attributable to an intrinsic instability in the foveal pursuit system. According to this model, evolution has necessarily designed the cortical pursuit system to operate on the threshold of oscillation to provide minimal response time without instability.[18] Given that the normal horizontal pursuit system is intrinsically underdamped, it is almost guaranteed that some individuals will fail to achieve the delicate balance between quasi-instability (underdamped) and total instability (undamped), manifesting as infantile nystagmus.

Harris and Berry[91,92] have proposed that contrast sensitivity to low spatial frequencies is enhanced by motion of an image across the retina and that the best compromise between moving the image and maintaining the image on the fovea (or its remnant) is to oscillate the eyes with jerk nystagmus with increasing velocity waveforms, as is seen empirically in infantile nystagmus. During infancy, "evolution would need to tread a fine line by programming the development of ocular motor control in tandem with foveal maturation to maximize visual contrast without causing nystagmus."[92(p68)] Accordingly, loss of high spatial-frequency information (whether caused by foveal, optic nerve, or optical aberrations) could lead to an atavistic resurgence of low-frequency peripheral retinal visual mechanisms that enhance their function during oscillation of the eyes.[92]

Our hypothesis reconciles these aforementioned theories by proposing that the absence of timely maturation of high-frequency (foveal) motion sensitivity, by whatever cause, must secondarily delay development of high-frequency cortical pursuit pathways, lifting the developmental brakes on the peripheral retinal motion input to the AOS to precipitate infantile nystagmus. In this setting, persistent activation of a normal AOS could be responsible for the abnormal retinal slip control postulated by Kommerell and Mehdorn.[86] Although an abnormal AOS may contribute to infantile nystagmus in patients with albinism or achiasma (as well as in those infants that have nystagmus at birth), the preponderance of evidence points to a persistent activation of a normal AOS that disrupts retinal slip control during attempted fixation and foveal pursuit. This hypothesis explains how the saccadic, pursuit, and optokinetic systems can continue to function normally in infantile nystagmus despite the superimposed aberrations that this oscillation generates. It also assigns a specific neuroanatomic correlate to the ocular motor control systems that have long been suspected to generate infantile nystagmus. By virtue of this analysis, it becomes clear that infantile nystagmus arises from a neuroanatomically dispersed system of cortico-mesencephalic-cerebellar feedback loops (Figure 2).[83]

Conclusions

We hypothesize that infantile nystagmus signals a breakdown in the armistice between subcortical and cortical optokinetic pathways during early development. Neuroanatomically, infantile nystagmus arises from a discordance between the foveate smooth pursuit modulated by the visual cortex and the afoveate full-field optokinetic system modulated by the AOS. Under conditions of normal visual development, cortical smooth pursuit overrides and suppresses the contradirectional optokinetic input that is generated by the AOS after the first few months of life. However, delayed or diminished development of central foveal vision may unleash the fundamental antagonism between subcortical optokinetic pathways and cortical pursuit, causing infantile nystagmus to be expressed. Because the AOS functions as a subcortical pursuit system in afoveate animals, its reactivation in humans explains the paradox that infantile nystagmus is inherent to the pursuit system, yet pursuit gain remains normal.

Through the prism of evolution, infantile nystagmus can be seen as a clinical expression of the fundamental antagonism between the subcortical optokinetic system and the cortical foveal pursuit system. Because these visual motion detection systems need to be coordinately expressed for infantile nystagmus to arise, this palindromic oscillation does not develop in afoveate lateral-eyed animals or in humans with cortical visual loss. In isolated cases, infantile nystagmus may reflect slow development of central foveal vision, which impedes maturation of cortical pursuit and allows the AOS to establish a foothold and exert its influence. Based on this model, it seems plausible that isolated infantile nystagmus could also arise from a genetic failure to inactivate the AOS even in the absence of abnormal foveal visual development.

Finally, we have proposed a hypothetical framework wherein 2 distinctly different types of oscillations (infantile nystagmus and latent nystagmus) may be linked. Although each has its own direct motor cause (uncalibrated pursuit damping or tonic visuovestibular imbalance, respectively), they share a common root. That possibility is supported by the following observations: infantile nystagmus may exhibit a latent component; infantile nystagmus may coexist with latent nystagmus; the "null" that is characteristic of infantile nystagmus is hypothesized to arise from the same Alexander law variation of slow-phase velocity that governs latent nystagmus; and the low-amplitude, high-frequency pendular oscillation of NOT-DTN nystagmus is often found superimposed on both infantile and latent nystagmus waveforms. As with all hypotheses, novel experiments in animals and humans will be required to either disprove or support our proposed framework.

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