REVIEW ARTICLE

Infantile nystagmus syndrome: clinical characteristics, current theories of pathogenesis, diagnosis, and management

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ABSTRACT • RÉSUMÉ

Infantile nystagmus syndrome (INS) is an important clinical diagnosis because it is a common presenting sign of many ocular, neurologic, and systemic diseases. Although INS has been studied for more than a century, its diagnosis and treatment remains a challenge to clinicians because of its varied manifestations and multiple associations, and its pathogenesis continues to rouse considerable scientific debate. Fueled by these challenges, recent basic research and clinical investigations have provided new insights into INS. New genetic discoveries and technological advances in ocular imaging have refined our understanding of INS subtypes and offer new diagnostic possibilities. Unexpected surgical outcomes have led to new understanding of its pathogenesis based on novel hypothesized pathways of ocular motor control. Comparative studies on nonhuman visual systems have also informed models of the neural substrate of INS in humans. This review brings together the classic profile of this disorder with recent research to provide an update on the clinical features of INS, an overview of the current theories on how and why INS develops, and a practical approach to the diagnosis and management of INS.

Le diagnostic clinique du nystagmus infantile (NI) est important parce que ce syndrome est un signe courant de nombreuses maladies oculaires, neurologiques et systémiques. Bien qu'on étudie le NI depuis plus d'un siècle, son diagnostic et son traitement restent des défis pour les cliniciens, en raison des manifestations variées du syndrome et de ses multiples associations, et sa pathogénèse continue d'alimenter le débat scientifique. Inspirés par ces défis, des chercheurs ont mené récemment des travaux de recherche fondamentale et des études cliniques qui ont approfondi la connaissance du NI. Des découvertes en génétique et les progrès de l'imagerie oculaire ont amélioré la compréhension des sous-types de NI et offrent de nouvelles possibilités de diagnostic. Des résultats chirurgicaux inattendus ont débouché sur une compréhension nouvelle de la pathogénèse, fondée sur des hypothèses inédites quant au contrôle oculomoteur. Des études comparatives portant sur des systèmes visuels non humains ont aussi permis d'élaborer des modèles du substrat neuronal du NI chez l'humain. Cette étude fait la synthèse du profil classique du désordre et des travaux récents; elle fait le point sur les caractéristiques cliniques du NI, fournit un aperçu des théories tentant d'expliquer comment et pourquoi le NI se développe et présente une approche pratique du diagnostic et de la gestion du syndrome.

Ocular nystagmus is an involuntary oscillation of the eyes that disrupts steady fixation. Each cycle of nystagmus is initiated by a slow eye movement away from fixation, followed by a corrective eye movement in the opposite direction back toward fixation. If both the initiating and corrective eye movements are slow, the nystagmus is termed "pendular nystagmus," and it appears as a smooth to-and-fro motion of the eyes. If the corrective eye movement is fast (i.e., a saccade), it is termed "jerk nystagmus," and the eyes appear to beat in one direction. Although the fundamental cause of nystagmus is the slow phase, which moves the eyes off target, by convention, jerk nystagmus is named according to the direction of the corrective fast phase.[1]

In many situations, nystagmus is physiologically evoked to maintain clear vision. For example, during head rotations that occur frequently in daily activities, the vestibulo-ocular and optokinetic systems are activated to induce slow-phase eye movements to prevent slip of retinal images off the fovea (which causes degradation of visual acuity), and intermittent saccades serve to keep eye position in a normal working range within the orbit. Although such physiologic nystagmus serves to stabilize retinal images during movement, pathologic nystagmus does the opposite: It destabilizes retinal images of stationary objects, thereby degrading vision.[2]

Most forms of pathologic acquired nystagmus are suggestive of specific anatomic lesions. For example, downbeat nystagmus can be localized to the pontomedullary junction of the brainstem and the flocculus/paraflocculus of the cerebellum,[2,3] pendular seesaw nystagmus is associated with parasellar masses and lesions affecting the mesodiencephalic junction,[4] and horizontal gaze-evoked nystagmus can be localized to the nucleus prepositus hypoglossi-medial vestibular nucleus in the brainstem, as well as the flocculus/paraflocculus of the cerebellum.[1,2] The pathophysiology of infantile nystagmus syndrome (INS), a common type of early-onset nystagmus, is much less certain. In the older literature, it has been variously

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Originally received Feb. 25, 2015. Final revision Jul. 12, 2015. Accepted Jul. 22, 2015

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Can J Ophthalmol 2015;50:400–408
0008-4182/15/$-see front matter
http://dx.doi.org/10.1016/j.jcjo.2015.07.010

Table 1—Classification of Eye Movement Abnormalities and Strabismus definition of infantile nystagmus syndrome

Criteria	Infantile-onset, ocular motor recordings show diagnostic (accelerating) slow phases.
Common associated findings	Conjugate, horizontal-torsional, increases with fixation attempt, progression from pendular to jerk, family history often positive, constant, conjugate, with or without associated sensory system deficits (e.g., albinism, achromatopsia), associated strabismus or refractive error, decreases with convergence, null and neutral zones present, associated head posture or head shaking, may exhibit a "latent" component, "reversal" with optokinetic nystagmus stimulus or (a)periodicity to the oscillation. Candidates on chromosomes X and 6 may decrease with induced convergence, increased fusion, extraocular muscle surgery, contact lenses, and sedation.
General comments	Waveforms may change in early infancy, head posture usually evident by 4 years of age. Vision prognosis dependent on integrity of sensory system.

called "idiopathic motor nystagmus," "sensory nystagmus," and "congenital nystagmus," and this inconsistent nomenclature reflects the incomplete scientific understanding of the disease.[5] Its manifestations and clinical associations are variable and unpredictable, and despite active research, its pathogenesis remains a topic of considerable debate.

In 2001, the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group proposed a classification system to bring consistency and clarity to eye movement and strabismus nomenclature.[5] In this review, we use the CEMAS definition of INS (Table 1), which is a clinical phenotype to be distinguished from other types of early-onset nystagmus such as fusion maldevelopment nystagmus syndrome (formerly known as latent/manifest latent nystagmus), spasmus nutans syndrome, and those that localize to the brainstem or cerebellum. Importantly, the diagnosis of INS does not, in itself, suggest the presence or absence of systemic or ocular disease. The duty, therefore, falls to the clinician to uncover any associated, and sometimes occult, underlying diagnosis.

Clinical Features of Infantile Nystagmus Syndrome

INS is a developmental nystagmus with an onset during the first 6 months of life. It affects between 1 in 1000 to 1500 children, with a 2- to 3-fold male predominance.[6,7] Despite the old name "congenital nystagmus," the oscillations usually begin at 2 to 3 months of age and are rarely present at birth.[2] Clinically, the nystagmus is binocular, conjugate, and predominantly horizontal with a typical frequency of 2 to 4 Hz, and patients old enough to report symptoms rarely complain of oscillopsia.[8,9] Both pendular and jerk waveforms may be observed in the same individual at different times, with the pendular type being more common in early infancy.[9,10] A minority of patients have an associated strabismus, and some exhibit a latent component on monocular occlusion.[9]

On eye movement recordings (Fig. 1), pendular waveforms are often punctuated by brief foveation periods, whereas jerk waveforms have highly characteristic increasing velocity slow phases. The nystagmus often becomes right beating on right gaze and left beating on left gaze, but remains in the horizontal plane on up, down, and lateral gaze (i.e., uniplanar in all gaze positions). A null zone (i.e., a gaze position in which nystagmus is minimal) is common and, if eccentric in location, may be accompanied by an abnormal head posture. The nystagmus intensity (i.e., frequency × amplitude) increases with fixation effort and decreases with convergence, in darkness, and during sleep. INS also shows an apparent reversed optokinetic nystagmus (OKN) response and inverted pursuit (Fig. 2); that is, the fast phases of OKN beat in the same direction as the OKN stimulus, and smooth pursuit movements appear to be initiated in a direction opposite to the actual target movement.[1,2,11]

The prevalence of anterior visual pathway abnormalities in patients with INS has been variously quoted from 38% to 91%.[8,12–14] The abnormalities include media opacities (e.g., congenital cataracts), retinal dystrophies and degenerations (e.g., Leber congenital amaurosis, achromatopsia, congenital stationary night blindness, and congenital toxoplasmosis), optic nerve disorders (e.g., optic nerve hypoplasia and optic atrophy), foveal hypoplasia, aniridia, albinism, and achiasma.[12–14]

In cases in which infantile nystagmus is a feature of another disorder, the inheritance pattern follows that of the associated disease: Aniridia and other PAX6 phenotypes are autosomal dominant, oculocutaneous albinism

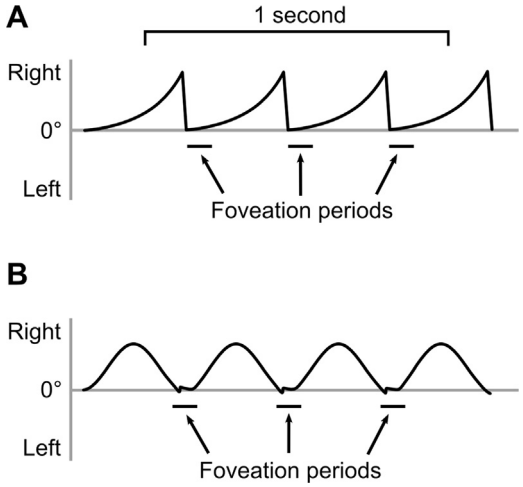

Fig. 1—Schematic diagram of typical infantile nystagmus syndrome (INS) nystagmus waveforms. (A) Jerk-type INS exhibits an increasing velocity slow phase followed by a saccade in the opposite direction. (B) Pendular-type INS has slow-phase movements only, often interrupted by brief foveation periods. (Adapted from Wong.[1])