

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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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

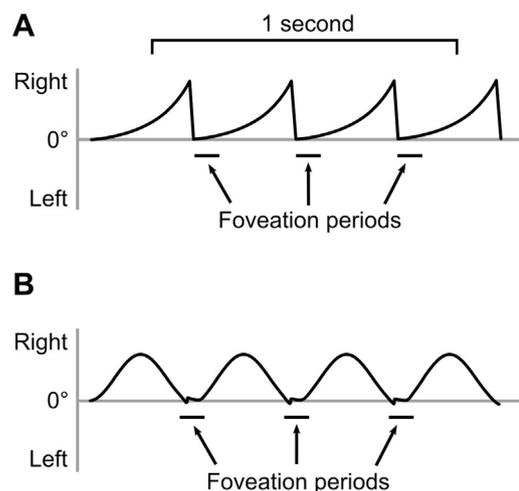


Fig. 1—Schematic diagram of typical infantile nystagmus syndrome (INS) nystagmus waveforms. (A) Jerk-type INS exhibits an increasing velocity slow phase followed by a saccade in the opposite direction. (B) Pendular-type INS has slow-phase movements only, often interrupted by brief foveation periods.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

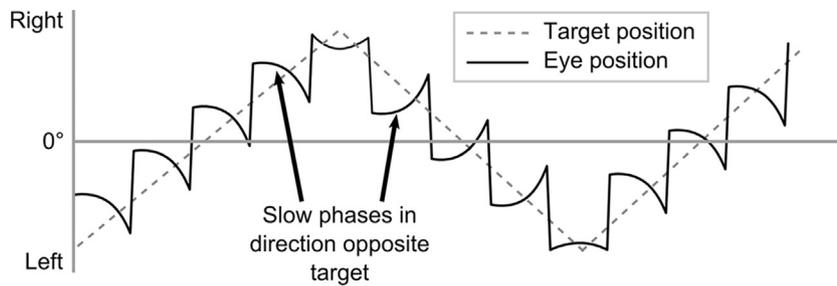


Fig. 2—Schematic diagram of inverted pursuit in infantile nystagmus syndrome (INS). Unlike normal smooth pursuit, slow-phase eye movements occur in the direction opposite target movement.

and achromatopsia are autosomal recessive, and ocular albinism and complete congenital stationary night blindness are X-linked. Of the significant proportion of patients who are without evidence of any other ocular or systemic abnormality (often referred to as idiopathic infantile nystagmus), more than half have a family history of nystagmus.¹² Although autosomal dominant (MIM 164100), autosomal recessive (MIM 257400), and X-linked (MIM 31700) pedigrees have been described, only 1 disease-causing gene, *FRMD7* (Xq26.2), has been identified to date.^{15,16} Mutations in *FRMD7* cause an X-linked idiopathic infantile nystagmus with a penetrance of 100% in males and 53% in female carriers and a phenotype clinically indistinguishable from disease without *FRMD7* mutations.¹⁷ The diagnostic yield of genetic screening for *FRMD7* mutations has been quoted as 20% to 57% in apparent X-linked pedigrees of idiopathic INS and only 3.6% to 7% in singleton cases.^{17,18}

THEORIES OF PATHOGENESIS

Attempts to correlate the range of associated clinical conditions with different eye movement waveforms observed in INS have been met with limited success.⁸ Indeed, different waveforms can be observed in the same individual in different positions of gaze and at different times in the same position of gaze.¹⁹ Instead of using phenotypic classification to gain insight into INS subtypes, some investigators have used a physiology-based approach to seek a unifying defect and common mechanism for the pathogenesis of this clinically heterogeneous disease.²⁰ Theories that have been proposed can be grouped into 2 main categories: those that conceive of INS as resulting from a primary defect in the ocular motor control (i.e., efferent) system, and those that conceive of it as resulting from a primary defect in the visual sensory (i.e., afferent) system.

Infantile nystagmus syndrome as a primary defect of ocular motor control

Because INS is clinically an eye movement disorder, a large proportion of research attention has focused on finding a causative lesion in the ocular motor control pathways. From a systems perspective, ocular motor control

consists of (i) the reflexes responsible for maintaining stable gaze direction (i.e., the fixation, vestibulo-ocular, and optokinetic systems), and (ii) the mechanisms for gaze shifting (i.e., the saccadic, smooth pursuit, and vergence systems). It is not intuitively apparent which of these ocular motor systems is most likely to be defective in INS, and indeed, theories involving many of them have been proposed.^{21–24} Ocular motor models of INS, however, commonly encounter 1 of 2 problems: either they describe a single lesion that does not explain the full constellation of clinical findings, or they account for the clinical findings but require lesions in more than 1 anatomically separate system.²⁵ For example, a computational model based on saccadic system dysfunction accounted for jerk and pendular waveforms, but could not explain the null zone.²¹ Another model based on increased delay in the smooth

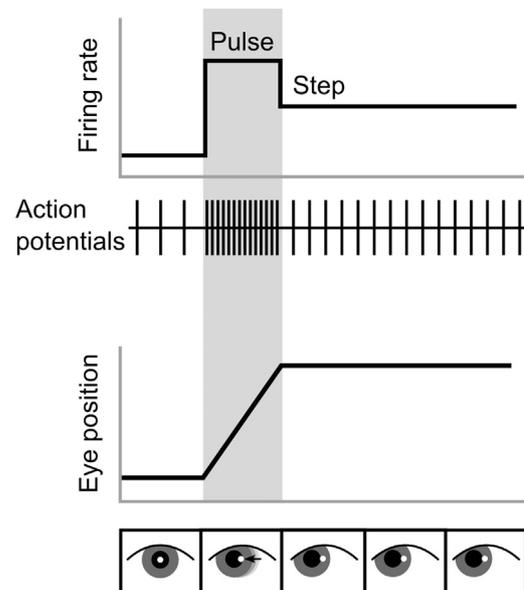


Fig. 3—Pulse-step innervation of extraocular muscles. During an eye movement, motor neurons output a high-frequency burst (i.e., the pulse velocity command) to move the eye from one position to another against resistance of orbital tissues. A higher tonic firing rate (i.e., the step position command) is required to maintain the eye in its new position. The ocular motor neural integrator calculates the step position command from the pulse velocity signal. (Adapted from Leigh et al.²)

pursuit system accounted for pendular, but not jerk, waveforms.²² Interestingly, these ocular motor control systems do converge on a common structure—the ocular motor neural integrator—providing a potential single site of dysfunction to explain the complex phenotype of INS.

The ocular motor neural integrator is a velocity-to-position converter that mathematically integrates an initial eye velocity command to calculate the tonic innervation command required to maintain eye position in a pulse-step paradigm (Fig. 3). Anatomically, the neural integrator for horizontal eye movements—the pathological movement of INS—resides in the nucleus prepositus hypoglossi and medial vestibular nucleus area of the brainstem.² It has been proposed that INS results from a “leaky” neural integrator with an abnormal positive (rather than the normally negative) eye velocity feedback loop.²⁶ Remarkably, when modeled, this abnormal neural integrator is capable of producing a variety of increasing velocity jerk waveforms similar to those recorded from patients with INS. Because the sign of the velocity feedback loop is inverted (i.e., positive rather than negative), this model also accounts for the phenomena of reversed OKN and reversed smooth pursuit initiation observed in INS. Recent refinements on the model that include cerebellar modulation and a variable integrator time constant can produce both pendular and jerk waveforms.²⁵

Another emerging theory of INS as a primary motor disorder points to aberrant extraocular muscle proprioception. This idea came about after it was observed that the Anderson-Kestenbaum procedure (an eye muscle surgery in which horizontal muscles insertions are moved with the aim of shifting the nystagmus null zone to the straight-ahead gaze position; see later Management section) not only shifted the null zone as expected, but it also broadened the null zone and substantially reduced nystagmus amplitude in eccentric gaze (Fig. 4).²⁷ Indeed, a

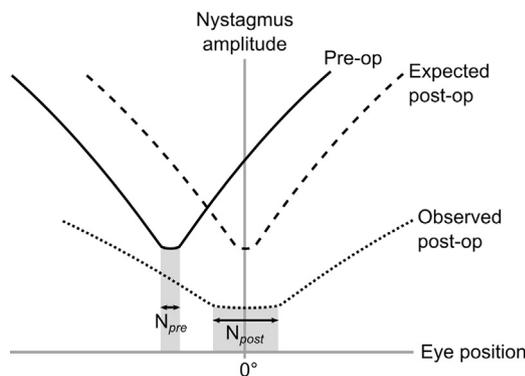


Fig. 4—Effect of Anderson-Kestenbaum procedure on nystagmus amplitude and null zone. The preoperative curve (solid line) shows a null zone (N_{pre}) on left gaze. Surgery is expected to shift the null zone to primary position (expected postoperatively dashed line). The observed postoperative response (dotted line) showed an unexpected broadening of the null zone (N_{post}) and a reduction of nystagmus amplitude in all gaze directions. (Adapted from Dell’Osso et al.²⁸)

simple 4-muscle tenotomy surgery (in which the horizontal extraocular muscle insertions are cut and then reattached in exactly the same position; see later Management section) was also shown to dampen nystagmus intensity in achiasmatic dogs.²⁸

Parallel research identified putative proprioceptive sensory organs, termed *palisade endings*, at the myotendinous junction of nontwitch extraocular muscle fibres in humans.²⁹ Primate studies suggest that palisade ending neurons have a bipolar morphology resembling sensory ganglion cells,³⁰ and that their cell bodies colocalize with motor neurons near their respective ocular motor nuclei.³¹ Indeed, human histologic studies point to a role for this putative proprioceptive loop in INS. Eye muscles in patients with INS have reduced nerve fibre and neuromuscular junction density,³² and their tendinous insertions contain anomalous nerve terminal endings.³³ Interestingly, motor neurons for nontwitch extraocular muscle fibres are also known to receive premotor input from the nucleus prepositus hypoglossi, part of the neural integrator to maintain horizontal gaze.³⁴ The significance of this potential link between proprioceptive disturbance and the neural integrator hypothesis of INS pathogenesis is not known, but it offers fertile ground for further study.^{34,35}

Infantile nystagmus syndrome as a primary defect of the anterior visual pathway

For well more than a century, poor sensory input has been proposed as the causative factor in INS.³⁶ Although the ocular motor control models may account for cases of INS in which no visual sensory defect is apparent, they do not suggest a reason for the strong association with anterior visual pathway disease. Indeed, new imaging techniques demonstrate subtle foveal hypoplasia and optic disc anomalies in patients with INS and *FRMD7* mutations who were previously identified as having normal retinal morphology.³⁷ Furthermore, in normal infant monkeys, visual deprivation creates a robust model of INS, and in infant humans,³⁸ removal of bilateral congenital cataracts within 1 month of nystagmus onset leads to normalization of eye movements.³⁹ On the basis of the strong clinical association with various anterior visual pathway defects, and because purely sensory interventions can cause INS in monkeys and cure it in humans, many have looked to early-onset sensory disease as the cause of INS.

One group proposes that the oscillations of INS are actually the adaptive response of an immature, but normal, ocular motor system to poor foveal function.⁴⁰ Noting that foveal dysfunction causes reduced contrast sensitivity at high spatial frequencies, and citing psychophysical evidence that image contrast is maintained not only by foveal fixation but also by image movement, they argue that nystagmus may be a strategy to maximize visual contrast.⁴¹ Modeling the disease as a nonlinear dynamical system, they show that oscillatory eye movements with increasing velocity waveforms and a null zone is an

optimal strategy to maximize visual contrast. Further, they propose that emergence of this “optimal strategy” during an early critical period of visuomotor development explains why INS is refractory to delayed treatment (e.g., cataract surgery beyond 1 month) and does not occur when similar visual impairment occurs later in life.

A competing hypothesis involves the failed suppression of a phylogenetically ancient primary visual pathway known as the accessory optic system (AOS). The AOS functions as a full-field motion detector⁴² and mediates visual-vestibular interaction in lateral-eyed above-water animals including fish,⁴³ birds,⁴⁴ and lower mammals.^{45–48} An intact AOS with direct retinal input has also been described in monkeys and humans.⁴⁹ Axons from each nasal hemiretina project subcortically to the contralateral nucleus of the optic tract and dorsal terminal nucleus complex (NOT-DTN). Neurons in the NOT-DTN are monocularly driven and show selectivity for nasalward input and a preference for slow-moving stimuli.⁴²

In a case of ontogeny recapitulating phylogeny, the AOS is functional in humans during the first 2 months of life⁵⁰ but is normally suppressed when cortical pursuit pathways mature.^{51,52} This suppression is critical because foveal smooth pursuit, by necessity, creates a full-field optokinetic stimulus in the direction opposite pursuit.⁵³ If the suppression is incomplete and the AOS is allowed to dominate, then activation of smooth pursuit will generate an optokinetic stimulus for the AOS and vice versa, creating the potential for rivalry and functional oscillation between the 2 systems in a positive feedback cycle. Proponents of this theory postulate that degraded visual input caused by a defect in the anterior visual pathway may delay maturation of the cortical pursuit pathway, thereby preventing adequate suppression of the AOS and causing INS.⁵⁴

In addition to a compelling evolutionary link, this model offers an explanation for several unique characteristics of the disorder. The worsening of nystagmus intensity during fixation and visual effort may result from coactivation of and increased rivalry between the foveal pursuit and AOS optokinetic pathways. The presence of a null zone can also be explained: Because activity in each NOT-DTN is monocularly driven by nasalward stimulus in the contralateral eye, when visual input to both NOT-DTN is symmetric, the output will be opposite and nearly equal, resulting in a zone of minimum nystagmus. Furthermore, any visual imbalance between the 2 eyes may cause asymmetric activation of each NOT-DTN and thus account for the commonly observed eccentric null zone.⁵⁴

DIAGNOSIS

The CEMAS definition of INS relies on waveform analysis of eye movement recordings for definitive

diagnosis.⁵ The practicality of eye movement recording as a diagnostic requirement, however, is limited by the availability of necessary equipment and the difficulty of oculography in young children. Furthermore, even on eye movement recordings, there is significant overlap between diagnoses of INS and fusion maldevelopment nystagmus syndrome. In this section, we present a practical approach to the diagnosis of INS.

In any infant or child with abnormal eye oscillations, the nature of the movements needs to be characterized. In particular, nystagmus must be distinguished from saccadic intrusions and oscillations. The critical feature of the former involves slow-phase drifts that move the eye off target, whereas the latter involves fast eye movements that move the eye off target and includes, for example, opsoclonus secondary to neuroblastoma.²

Children in whom early-onset nystagmus has been identified still face a broad differential diagnosis that includes INS, fusion maldevelopment nystagmus syndrome, spasmus nutans syndrome, and other neurologically localizing forms of nystagmus. Even within INS, a wide range of underlying diagnoses must be ruled out. The clinician can navigate through this diagnostic challenge with the aid of a focused patient history, careful clinical examination, and selective ancillary tests.

Patient history

Age of nystagmus onset, history of strabismus, amblyopia, abnormal head posture, suspicion of visual impairment, and family history of nystagmus are essential data. Complications during pregnancy or childbirth, developmental delay, or reports of ataxia, oscillopsia, or headache may indicate a neurologic cause. Conversely, a family history of ocular or systemic disease (e.g., albinism) or visual symptoms such as photophobia, lack of colour vision, or night blindness suggest anterior visual pathway disease. Comorbid amblyopia, infantile esotropia, or trisomy 21 raise the possibility of fusion maldevelopment nystagmus syndrome.^{55,56} Nystagmus onset after age 3 months and other atypical characteristics (e.g., monocular, vertical, or “shimmering” nystagmus) suggest an acquired nystagmus and should heighten suspicion of optic pathway glioma.⁵⁷

Clinical examination

The eyes should be observed in 5 positions of gaze (primary, right, left, up, and down), noting the nystagmus waveform (pendular or jerk), frequency, amplitude, direction and plane of oscillation, and presence or absence of a null zone. Monocular occlusion should also be done to check for latent nystagmus (i.e., a conjugate nystagmus with fast phases directed toward the viewing eye and that reverse direction when occlusion is switched to the other eye). Visual acuity measurements and cover tests are best performed with a +4 D to +10 D lens as an occluder to fog the vision. Occlusion with an opaque object has the

undesirable effect of increasing nystagmus intensity. This may give falsely low measures of visual acuity and mask a subtle strabismus.⁵⁸ Slit-lamp examination for iris transillumination defects is recommended regardless of the child's pigmentation. On funduscopy, special attention should be given to optic disc morphology (e.g., optic nerve hypoplasia or coloboma), signs of foveal hypoplasia (e.g., albinism or aniridia), retinal abnormalities (e.g., Leber congenital amaurosis or achromatopsia), and fundus pigmentation (e.g., albinism).

Signs of INS overlap considerably with those of other types of early-onset nystagmus, but key distinguishing features help to establish the diagnosis. Fusion maldevelopment nystagmus syndrome is associated with an early-onset disruption of binocularity (e.g., infantile esotropia or amblyopia) and does not classically have a null zone.⁵⁹ Spasmus nutans syndrome is associated with torticollis, head nodding, and a "quivering" or "shimmering" nystagmus that is typically pendular, low amplitude, high frequency (usually >10 Hz), and variably conjugate, disconjugate, and asymmetric over seconds to minutes.^{2,5} Gaze-evoked nystagmus is commonly caused by a posterior fossa lesion and may be mistaken for INS with a large, central null zone. The critical distinction can be made by observing the nystagmus on upgaze and downgaze.⁵⁷ If the plane of oscillation changes from horizontal in lateral gaze to vertical on upgaze or downgaze, the nystagmus is not uniplanar, favouring a diagnosis of gaze-evoked nystagmus.

Occasionally, patients demonstrate ocular motor features indicative of more than 1 type of nystagmus. Although parsimony in diagnosis is elegant, the clinician should remember that multiple types of early-onset nystagmus may coexist in the same patient.

Ancillary tests

The choice and order of ancillary tests depend on the clinical presentation. For children with INS in the absence of an obvious cause of vision loss or significant perinatal history suggestive of a neurologic cause, an electroretinogram (ERG) is warranted to rule out retinal dystrophy or degeneration. The diagnostic yield of ERG in such cases is as high as 56%.⁶⁰ If ERG returns a normal result, a brain magnetic resonance imaging (MRI) with contrast is recommended because an optic pathway glioma can masquerade as infantile-like nystagmus or spasmus nutans syndrome in rare cases.^{57,61,62} In contrast, for children who have a significant perinatal history suggestive of a neurologic cause, a brain MRI should be performed to rule out cortical visual impairment (e.g., periventricular leukomalacia in preterm infants, hypoxic ischemic encephalopathy in term infants, traumatic brain injury, infections, or metabolic diseases). If the brain MRI is normal, then an ERG should be ordered. If ocular or oculocutaneous albinism is suspected, genetic testing may be offered, and a multichannel visual-evoked potential that demonstrates chiasmal misrouting is

sometimes helpful to support the diagnosis.^{63,64} Optical coherence tomography often gives valuable information on foveal morphology, but this technique may be limited by eye movement, patient cooperation, and the availability of handheld units necessary for infants.⁶⁵ Routine screening for *FRMD7* gene mutations has a low diagnostic yield and is not recommended as part of the workup for isolated cases of idiopathic INS.¹⁸ It may be considered, however, for patients with a pedigree indicating X-linked inheritance.

MANAGEMENT

The treatment of INS has 3 broad components: management of underlying systemic disease, treatment of associated ocular disease, and symptomatic therapy for nystagmus. Underlying systemic disease such as oculocutaneous albinism or septo-optic dysplasia may require consultation with pediatric or neurology services. For heritable systemic and ocular conditions, referral for genetic counseling should be considered. Even in the absence of an identifiable cause, management should begin with correction of all significant refractive errors, and therapy for amblyopia as needed. Although patching may elicit a latent component, this effect usually subsides with 48 hours of continuous occlusion.⁶⁶ Patching or atropine penalization, therefore, is still recommended for patients with amblyopia and INS, but the frequency and duration of therapy may need to be adjusted.⁵⁸

Asymptomatic, benign forms of early-onset nystagmus do not require specific treatment beyond that outlined earlier. Reassuringly, idiopathic INS and sensory INS with good visual acuity generally become much less obvious as the child becomes older. INS associated with severe visual impairment, however, is usually unremitting.⁵⁷ Further symptomatic treatment is considered in patients who demonstrate a markedly abnormal head posture or reduced visual acuity related to unstable fixation. These issues may be addressed through optical, pharmacologic, and surgical means.

Before reviewing the different treatment options for INS, as well as studies that investigate treatment efficacy, it is important to emphasize that a statistically significant difference does not necessarily mean that a treatment effect is clinically significant. Clinical significance can be defined as treatment efficacy that leads to a change in patient management. A key factor to be considered in assessing clinical significance is *test-retest variability*—the inherent error in visit-to-visit measurements for a given test. For visual acuity, test-retest variability is on the order of 0.14–0.20 logMAR for the gold standard Early Treatment Diabetic Retinopathy Study chart^{67–72} and 0.18–0.33 logMAR for the more commonly used Snellen chart.^{68–70,73} Interpreting visual acuity effect size in this context allows the reader to distinguish between *statistically significant* effects in

the study population (i.e., a significant *p* value) and *clinically meaningful* effects at the individual level (i.e., a change exceeding the threshold of test-retest variability). At a minimum, a treatment outcome needs to exceed its test-retest variability, that is, a visual acuity change of 2 lines (0.2 logMAR), to be considered clinically effective.

Optical

Base-out prisms (7 PD) may be combined with slight myopic overcorrection (−1.00 D) to exploit convergence damping in patients with intact binocular vision.⁷⁴ Prisms can also be prescribed to correct a small amount of face turn. Soft contact lenses are sometimes helpful to reduce prismatic effects in high refractive error and may additionally damp nystagmus via a presumed trigeminal afferent feedback mechanism.^{74,75}

Pharmacologic therapy

Pharmacologic therapy for nystagmus is usually reserved for adults who experience distressing visual symptoms (e.g., oscillopsia). Because such symptoms are rare in early-onset nystagmus, pharmacologic therapy is usually unnecessary.⁷⁶ Several pharmaceuticals that show benefit in other types of acquired nystagmus, however, have been studied for off-label use in INS.⁷⁶ The effects of memantine and gabapentin in INS were studied in a double-blind, randomized controlled trial.⁷⁷ Although both drugs reduced nystagmus intensity, neither demonstrated any effect on visual acuity for sensory INS. For idiopathic INS, gabapentin had no effect, and memantine improved visual acuity by only 0.15 logMAR (not exceeding test-retest variability of at least 0.2 logMAR). Oral and topical carbonic anhydrase inhibitors show some promise, but more study is needed. A case study of 1 patient suggested oral acetazolamide may improve foveation characteristics, but unfortunately visual acuity changes were not reported.⁷⁸ A small (*n* = 5) prospective crossover study of topical brinzolamide showed improved waveform characteristics, but only a 0.12 logMAR improvement in visual acuity.⁷⁹

Surgical treatment

Surgical treatment of INS is considered primarily to correct significant torticollis associated with an eccentric null zone.⁸⁰ The Anderson–Kestenbaum procedure involves paired recessions and resections of antagonist rectus muscles in each eye to shift the null zone into primary position. It can effectively treat abnormal head posture and decrease nystagmus intensity in primary position. Hypothesized improvements in binocular visual acuity from nystagmus damping, however, are not borne out in prospective studies.^{80–83}

Another surgery, Cüppers artificial divergence procedure, uses bilateral medial rectus recessions to create an exophoria in patients who have good binocular function and whose nystagmus is damped by convergence.

Evidence is limited, but prospective case series document improvement in abnormal head posture and broadening of the null zone among most patients, but minimal or no increase in visual acuity.^{83–85}

The surgeries may be combined with each other and with conventional strabismus surgery to correct manifest deviations on a case-by-case basis. In addition, a 4-muscle tenotomy procedure resembling the Anderson–Kestenbaum procedure could be performed.²⁸ This procedure involves disinserting and reattaching the 4 horizontal rectus muscles to their original insertions with the aim of reducing nystagmus intensity via a putative proprioceptive pathway (Fig 4). Although improvement in foveation characteristics and small visual acuity gains have been reported, only a few individual patients had visual acuity improvement that exceeded test-retest variability.^{86,87} Larger-scale studies are needed to evaluate its effects and clinical significance.

CONCLUSION

INS is a protean clinical entity with numerous associated anterior visual pathway problems, some obvious, some occult. The identification of INS is therefore not the end of the diagnostic path, but the beginning of a process to seek out underlying disease. Indeed, the practical importance of this process will only grow as new treatments, such as gene therapy for inherited retinal degenerations, become more widespread.⁸⁸ Regardless of future innovations, treatment for nystagmus in children always begins with the mainstays of pediatric ophthalmology: refractive correction and therapy for amblyopia, as necessary. Torticollis and visual symptoms can then be addressed further with selective application of optical, surgical, and sometimes pharmacological therapies as outlined earlier.

Despite more than 100 years of investigation, considerable controversy remains over the pathogenesis of INS. Some argue it is a primary disorder of the ocular motor control system, noting that a visual sensory defect, although common, is not a prerequisite for the nystagmus to develop. Others maintain that a visual sensory deficit is the instigating factor and hypothesize that the visual defect is merely subclinical in those without an apparent cause for decreased vision. Still another possibility exists: Perhaps INS is a heterogeneous group of diseases, some primarily ocular motor, others primarily visual sensory, that converges on a common clinical phenotype.

Although the question of INS pathogenesis remains unresolved, the search for answers has yielded intriguing insights. Unexpected broadening of the null zone after the Anderson–Kestenbaum procedure led to the recognition of a previously unknown proprioceptive pathway. The potential role of the ancient AOS has also drawn fascinating links to our evolutionary past, highlighting the legacy of phylogeny in our own growth and development. Until a unifying

theory is articulated and supported by definitive scientific evidence, research to understand and overcome this visual system disorder will continue and, in the process, contribute to our understanding of the world in unexpected ways.

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