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REVIEW ARTICLE

Idiopathic infantile nystagmus; Genetics foundation and clinical association

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ABSTRACT

Nystagmus is an involuntary, periodic eye movement caused by a slow drift of fixation of either jerk, pendular, or rotatory form. The clinical and molecular assessment of nystagmus can provide crucial elements for a state-of-the-art differential diagnosis. Herewith, we provide a comprehensive overview of idiopathic infantile nystagmus (IIN), one of the most common forms of IIN that is usually reached out by exclusion of a variety of underlying causes and considered as one of the main leading causes of visual debleating disorders in early childhood.

Keywords: Infantile nystagmus, inherited retinal dystrophy, FRMD7, CASK, GPR143, X-linked, early childhood.

Background

Nystagmus is defined as an involuntary rhythmic ocular oscillation that can be easily seen through direct eye observation. It is a common complaint in the clinical settings that leads to variable degree of reduced visual acuity due to excessive motion of images away from the fovea (1). Patients with nystagmus face a significant negative social stigma due to the consequence of an abnormal head posture or so called torticollis, when the null zone is not at the primary gaze position (2).

Classification

On general, nystagmus can be classified into three main categories depending on the underlying cause: physiologic nystagmus that is mostly evoked by rotation, infantile nystagmus (IIN) that usually appears at birth or shortly thereafter and acquired nystagmus that tends to appear later in life (Table 1). An important feature of all types of nystagmus is that in most cases both eyes move in synchrony however, Infantile form is mainly increased when the patient is fixing or trying hard to read small print. In contrast, acquired nystagmus is less when the patient is fixing a target (2,3). IIN in particular is subdivided into several forms (Figure 1), out of these idiopathic IIN is considered as one of the most common forms of IIN that occurs independently of any ocular or neurological disorders.

Herein, the purpose of this paper is to highlight some recent developments in idiopathic IIN relevant to pediatricians and ophthalmologists with respect to epidemiology, clinical features and assessment, molecular genetics and treatment options.

Epidemiology

IIN has an estimated prevalence of 1.9/10.000 in Leicestershire and Rutland, United Kingdom (4), and usually occurs between birth and 3–6 months of age (5).

Clinical Features

Clinically, IIN is usually characterized by bilateral, conjugate rhythmic oscillations occurring in the horizontal plane of either pendular waveform or jerk waveform with an accelerating slow phase (6,7) (Figure 2A). Patients with IIN will learn over time how to use the foveating saccades, in which there is a slow phase called **foveation periods,** helping these patients to line up the fovea with the targets of interest (8) (Figure 2B). Another characteristic feature of these patients is the tendency to develop abnormal head posture (**torticollis**) when the null zone is not at the primary gaze position and nystagmus has a lower intensity (3).

Inheritance Pattern of IIN

IIN is a heterogeneous disorder that has been described as autosomal dominant (OMIM 164100), autosomal recessive (OMIM 257400), and X-linked (OMIM 31700)

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forms. However, the most common form of inheritance is X-linked, which will be discussed here in detail.

X-linked IIN

A variable degree of penetrance has been shown in females in X-linked IIN pedigrees (9–11). The possible reason for this variability is the skewed X-inactivation in which approximately one-half of the heterozygous females are mildly affected compared to the affected males (12,13).

Table 1. *Classification of nystagmus.*

Physiologic	Infantile	Acquired
• Opto-kinetic • Caloric • Gaze evoked • (Post-) rotatory	• Idiopathic IIN • Ocular/ sensory nystagmus • Latent (type) nystagmus • Spasmus nutans	Anterior optic pathway lesions Dissociated nystagmus Lesions of midbrain, brainstem or cerebellum: • Up-down-beat nystagmus • Gaze paretic nystagmus • Alternating nystagmus • Pendular nystagmus • Dissociated nystagmus in Parinaud syndrome, see-saw nystagmus

To date, three X-linked genes have been identified: *FERM domain-containing 7* (*FRMD7*), *G protein-coupled receptor 143* (*GPR143*), and *calcium/calmodulin-dependent serine protein kinase* (*CASK*). Among these genes, 20%–97% of X-linked IIN cases can be explained by a mutation in the *FRMD7* gene (7,3–19).

FRMD7

FRMD7 is considered the most frequently mutated gene in X-linked IIN, with a detection rate of 20%–97%, as shown in several studies (14,15,17–23). The human *FRMD7* gene (ENSG000001656940) located at Xq26-q27 comprises 12 exons (ENST00000298542) and encodes 714 amino acids (ENSP00000298542). It is a member of the FERM domain family of plasma membrane cytoskeleton coupling proteins. As in most other members, the conserved FERM domain of FRMD7 is located at the N-terminus and is divided into three lobes (F1–F3) that form a cloverleaf structure. This domain is usually responsible for membrane association through interaction with integral membrane proteins and lipids. In contrast to the N-terminus, the C-terminal domain of FRMD7 bears no significant homology to other proteins. FRMD7 also has a central FERM-adjacent (FA) domain that is found in a subset of FERM domain proteins, and which has been found to regulate protein function through modifications such as phosphorylation (24). *In situ* hybridization studies showed that *FRMD7* expression is restricted and localized to certain areas in the brain including the ventricular layer of the forebrain, midbrain, cerebellar primordium, and developing neural retina and optic

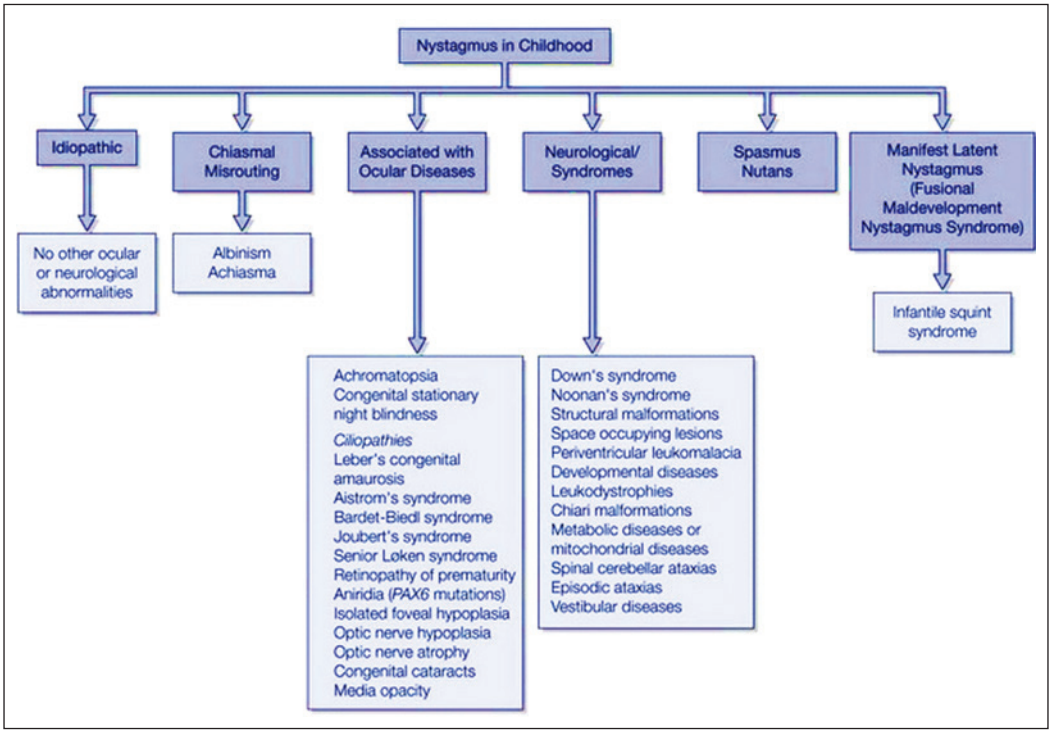

Figure 1. *Classification of infantile nystagmus. Infantile nystagmus can be idiopathic or associated with other ocular diseases such as albinism, retinal, neurological diseases or visual deprivation in early life with spasmus nutans or squint syndrome (26).*

stalk at 56 days post-ovulation (25) (Figure 3). These regions are known to be involved in the motor control of eye movements and gaze stability, suggesting that *FRMD7* plays a role in this process (27).

CASK

Recently Hackett et al. reported mutations in the *CASK* gene in patients with X-linked IIN and mental retardation (28). The human *CASK* gene (ENSG00000147044) maps to Xp11.4, is composed of 27 exons (ENST00000378163) and encodes a multi-domain scaffolding protein of 926 amino acids (ENSP00000367405.1). The CASK protein consists of an N-terminal CAM-kinase domain, two L27 domains, a PDZ domain, an SH3 domain, and a C-terminal guanylate kinase domain (29). It is ubiquitously expressed with a significantly higher expression in the fetal brain (11,24,28). Different domains of the CASK protein interact with more than a dozen different proteins and may be involved in synaptic interaction, protein trafficking, and regulation of gene expression during neural development. Watkins et al. (24) found an interaction between the FRMD7 protein and CASK, suggesting that *FRMD7* mutations could act by disrupting the interaction between FRMD7 and CASK, which is needed to promote membrane extension during neurite outgrowth.

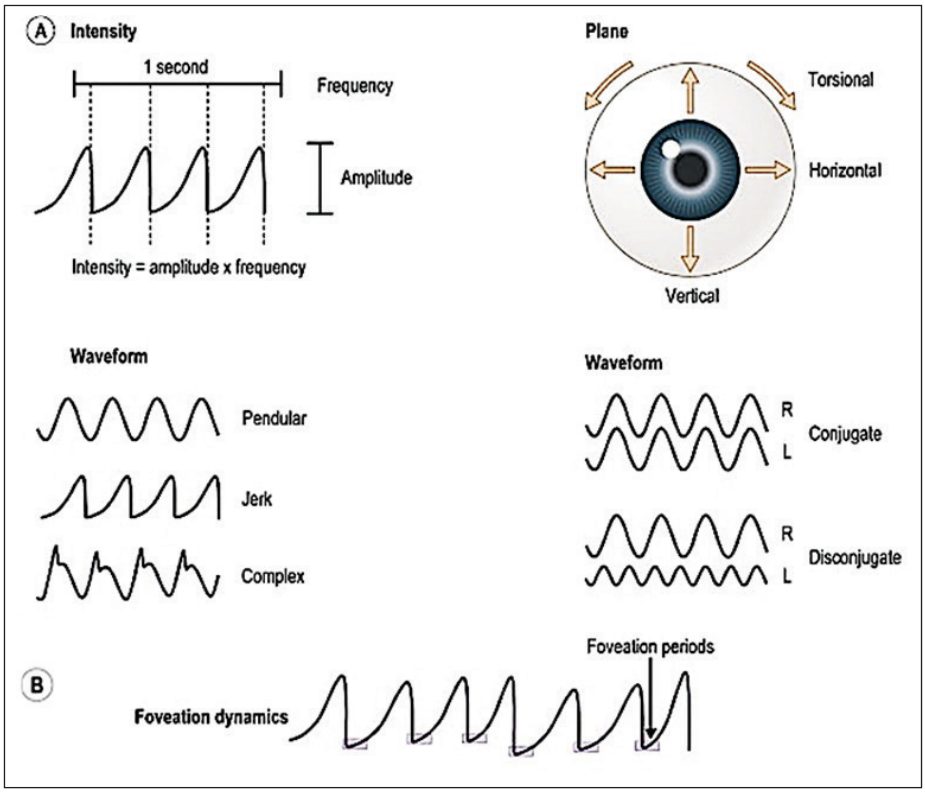

Figure 2. *Eye movement recordings in nystagmus. (A) Representation of the clinical elements for nystagmus waveforms. (B) Representation of the foveation period as a slow phase that allows to line up the fovea with the target of interest.*

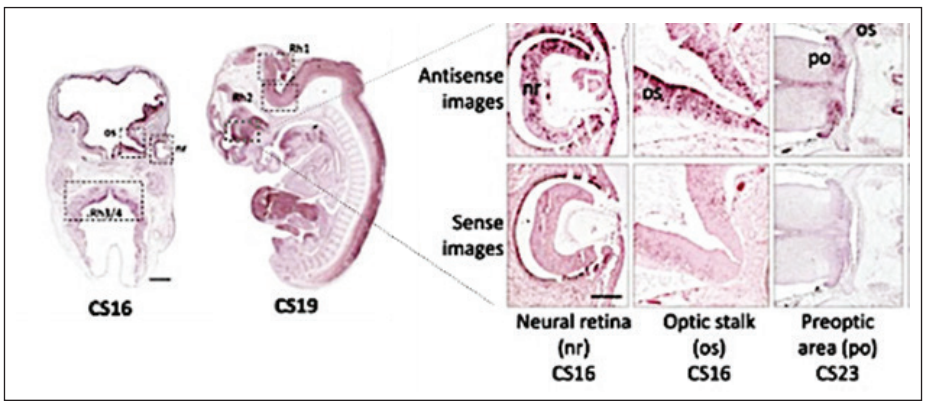

Figure 3. *In situ hybridization showing FRMD7 expression. Expression of FRMD7 in the neural retina and optic stalk can be seen [Adapted from (25)].*

GPR143

GPR143 is a known disease gene for X-linked ocular albinism (OA), invariably characterized by IIN. However, several studies showed its direct correlation with X-linked IIN cases without the classical OA manifestations (20,30–36). The human *GPR143* gene (ENSG00000101850), located at Xp22, is composed of nine exons (ENST00000467482.5) and encodes 404 amino acids (ENSP00000417161.1). The GPR143 protein consists of three cytoplasmic domains with a C-terminus tail domain that contains lysosomal sorting signals for intracellular retention and delivery to lysosomal and melanosomal in melanocytic and non-melanocytic cells, respectively. It is expressed at high levels in the retina, including the RPE, and in melanocytes with a weak expression in the brain and adrenal gland.

Pathophysiology of IIN

The primary pathology behind most forms of IIN can be explained by the failure of early sensorimotor integration that could be affected at the cellular level due to several genetic mutations. In general, this can be divided into afferent (sensory deficit) nystagmus that is presented in most forms of IN and occurs due to visual impairment while efferent nystagmus presented mostly with IIN is due to oculomotor abnormality (26) (Figure 4). Nonetheless, recent studies have shown that the pathology underlying IIN is not only oculomotor, where certain abnormalities in the retina can be observed including foveal hypoplasia, thinning of the retinal nerve fiber layer, and shortening of the cone outer segments (21,24,26).

Differential Diagnosis of IIN

Nystagmus associated albinism

A recent retrospective study by Bertsch et al. (37) showed that albinism accounts for 19% of IN. In general, nystagmus-associated albinism is similar to IIN as it is usually horizontal, conjugate, and associated with torticollis while albinism patients have worse stereopsis, strabismus, and torticollis compared to *FRMD7*-related IIN patients (38).

Nystagmus associated with inherited retinal diseases (IRDs) and low vision

IRDs are considered the second most common cause of IN, with Leber Congenital Amaurosis (LCA) accounting for 14% of the cases while other IRD such as congenital stationary night blindness, achromatopsia, Bardet-Biedl syndrome, Joubert syndrome, and Alström syndrome cause 13% (37). The general characteristic of nystagmus in IRD is similar to IIN while it differs in the association with visual impairment.

Nystagmus associated with neurologic diseases

Nystagmus in neurological conditions is usually asymmetric (dissociated) or unilateral and can be associated with other neurological symptoms such as vertigo, nausea, and headaches. In addition, ocular signs

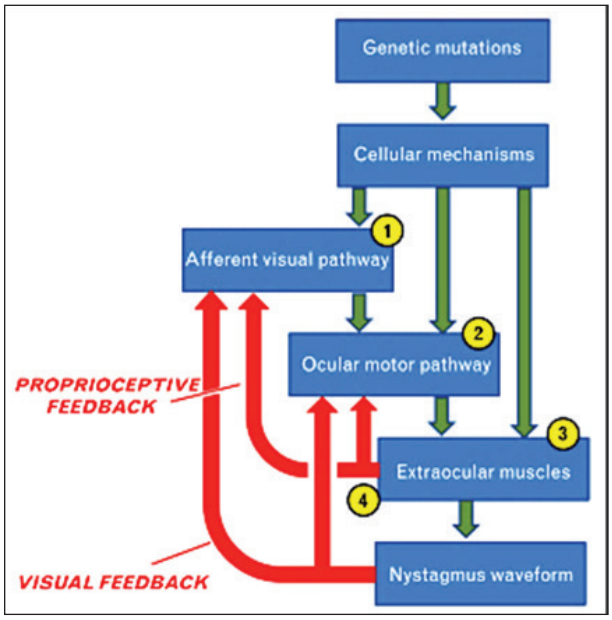

Figure 4. *The sequence of pathophysiology of infantile nystagmus. Genetic mutations are known to underlie changes in cellular function in most IN subtypes, which in turn could affect the developing afferent visual pathway (1), the developing ocular motor system (2), extra-ocular muscle structure and/or motor innervation (3), or feedback from extra-ocular muscle proprioceptors (4) (26).*

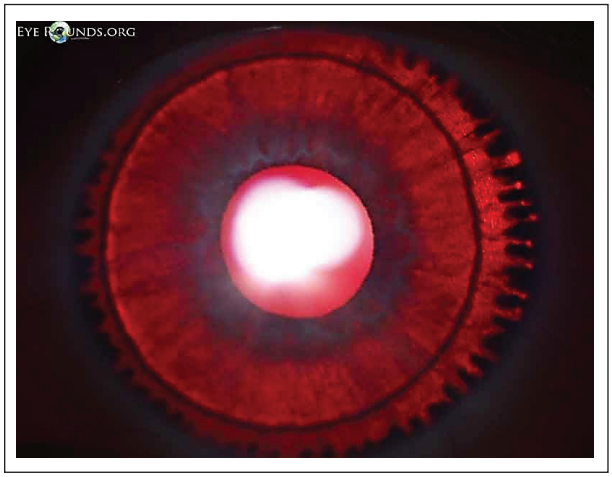

Figure 5. *Slit lamp examination showing diffuse iris transillumination in albinism (from http://www.mrcophth.com/iriscases/iristransillumination.html).*

may be present such as relative afferent pupillary defect, papilledema, and optic atrophy.

Manifest latent nystagmus

The characteristic feature is that this nystagmus is continuously present, mostly horizontal with jerk waveforms, but that it worsens when one eye is occluded.

Spasmus nutans

It is an intermittent, fine, high-frequency, pendular dissociated nystagmus that appears at 1–3 years of

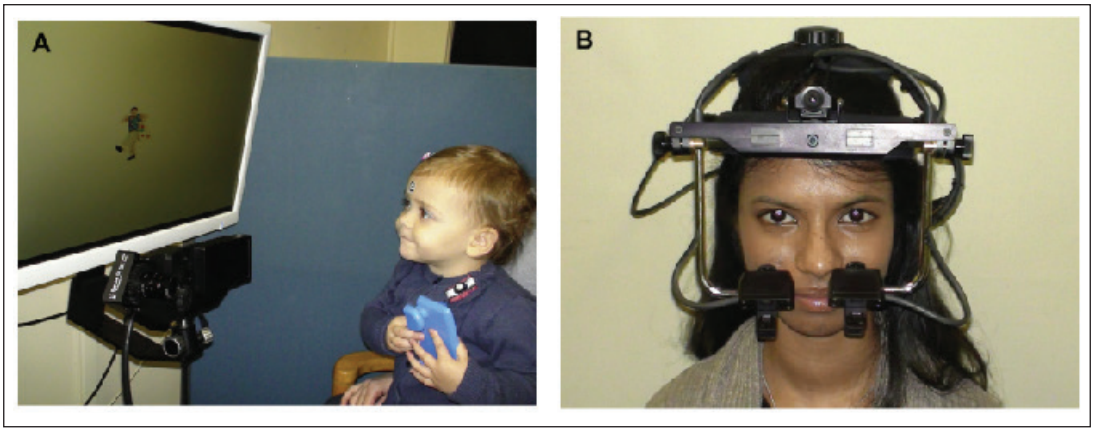

Figure 6. *Eye movement recording instruments. (A) Head free remote eye tracking system (Eyelink 1000, SR Research Ltd, Ottawa, Ontario, Canada). (B) Head-mounted video eye tracker (Eyelink II, SR Research Ltd) (39).*

Figure 7. *The handheld spectral domain OCT. High-resolution and deep tissue imaging with a wide field of view using handheld, contact-free imaging (From http://www.leica-microsystems.com/products/optical-coherence-tomography-oct/details/product/envisu-c-class).*

age and is characterized by a triad of nystagmus, head nodding, and head torticollis (26).

Clinical Assessment of IIN

History

Obtaining a detailed and precise history is the first point in dealing with IN cases. There is often a known family history of this disorder, therefore determining the inheritance pattern is essential.

In addition, the precise age of onset is helpful in differentiating between sensory deficit and IIN forms. An onset within 3–6 months of age, particularly in the setting of gaze-associated variable intensity and torticollis, strongly suggests IIN. Patients with IN due to albinism may have a positive family history and often appear photosensitive. A history of infantile strabismus increases the likelihood of manifesting latent nystagmus. A history of failure to thrive or other signs of developmental delay should prompt immediate investigation. The pattern of nystagmus intensity is helpful in distinguishing IIN from other forms of nystagmus which often increases with fixation effort, attention, or anxiety, and diminishes with convergence in the case of IIN.

Tips and tricks for Nystagmus assessment

Nystagmus waveforms are extremely variable, and their description can also assist in the diagnosis using a number of characteristics (6) (Figure 2):

Plane (direction)

Nystagmus most commonly occurs along the horizontal axis, although nystagmus can also be vertical, torsional, or any combination of these (26).

Amplitude (size) and frequency (cycles per second)

Amplitude and frequency should be assessed in the primary position and with the patient looking to the sides as well as up and down. A reduction of nystagmus can often be seen with the patient in convergence. The intensity can vary with eye position and often there is a position of gaze in which the oscillations are minimal (null point) (26).

Waveform

Nystagmus has been divided into jerk nystagmus that exhibits a quick and slow phase, and pendular nystagmus that is a sinusoidal like oscillation without any obvious quick phase. In jerk nystagmus, the direction of nystagmus is defined by the quick phase of the jerk (e.g. downbeat) (3).

Conjugacy

When the eyes move in tandem, the nystagmus is described as conjugate or associated. Disconjugate or dissociated nystagmus occurs when the eye movements differ in amplitude, frequency, waveform, or when the oscillations of the two eyes are out of phase with each other.

Foveation

Many forms of IN show periods where the eyes move at a lower velocity allowing high visual acuity at the fovea to function.

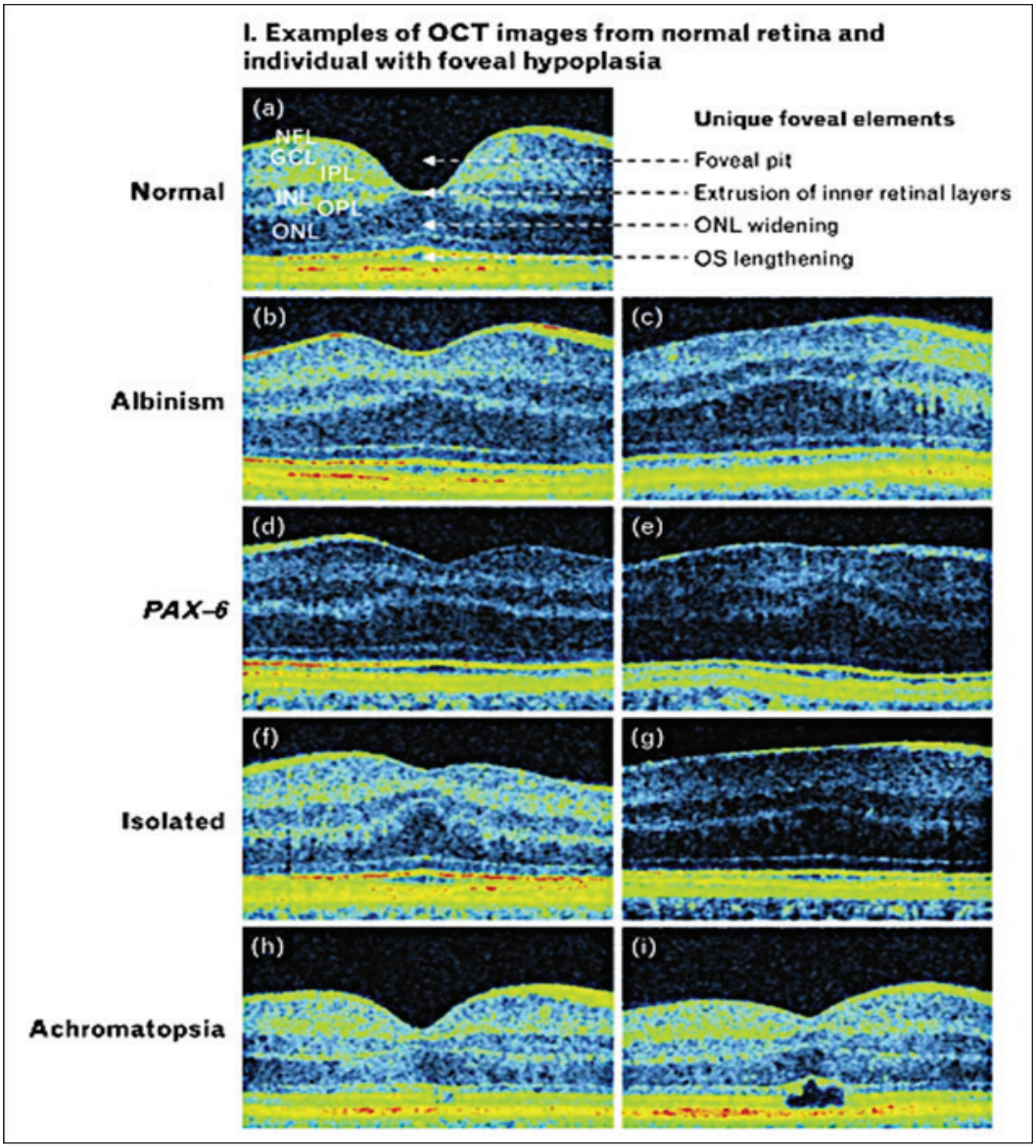

Figure 8. *Characterization of foveal abnormalities in nystagmus subtypes using HH SD-OCT. (A) Normal fovea, with normal foveal elements. (B) and (C) Foveal hypoplasia in albinism. (D) and (E) Foveal hypoplasia associated with PAX6 mutations. (F) and (G) Isolated foveal hypoplasia. (H) and (I) Foveal hypoplasia in achromatopsia (26).*

Dependence on other parameters

The hallmark of IIN is a gaze-dependent, variable intensity resulting in a "null zone" where nystagmus is least marked and where visual acuity is maximized. This often corresponds to adoption of an anomalous head posture and is frequently the stated reason for referral (26).

Ophthalmological examinations

Detailed ophthalmological examinations should be performed for the assessment of a patient with nystagmus.

Best corrected visual acuity (BCVA)

Should be measured using the polarized vectograph to avoid iatrogenic reduction of acuity with occlusion. Individuals with mutations in the *FRMD7* gene have relatively better visual acuity compared to individuals with other forms of IN (39).

Slit-lamp examination

It is recommended to perform slit-lamp examination under dimmed light conditions in order to detect the presence of any degree of iris transillumination that is mostly associated with albinism due to iris hypopigmentation (Figure 5).

Funduscopy

Should be used to document the presence or absence of foveal hypoplasia, optic disc morphology, and any lack of fundus pigmentation that are usually associated with retinal dystrophy.

Eye movement recordings

Nystagmus waveforms can be viewed in detail via eye movement recordings, which can be documented using different methods, including:

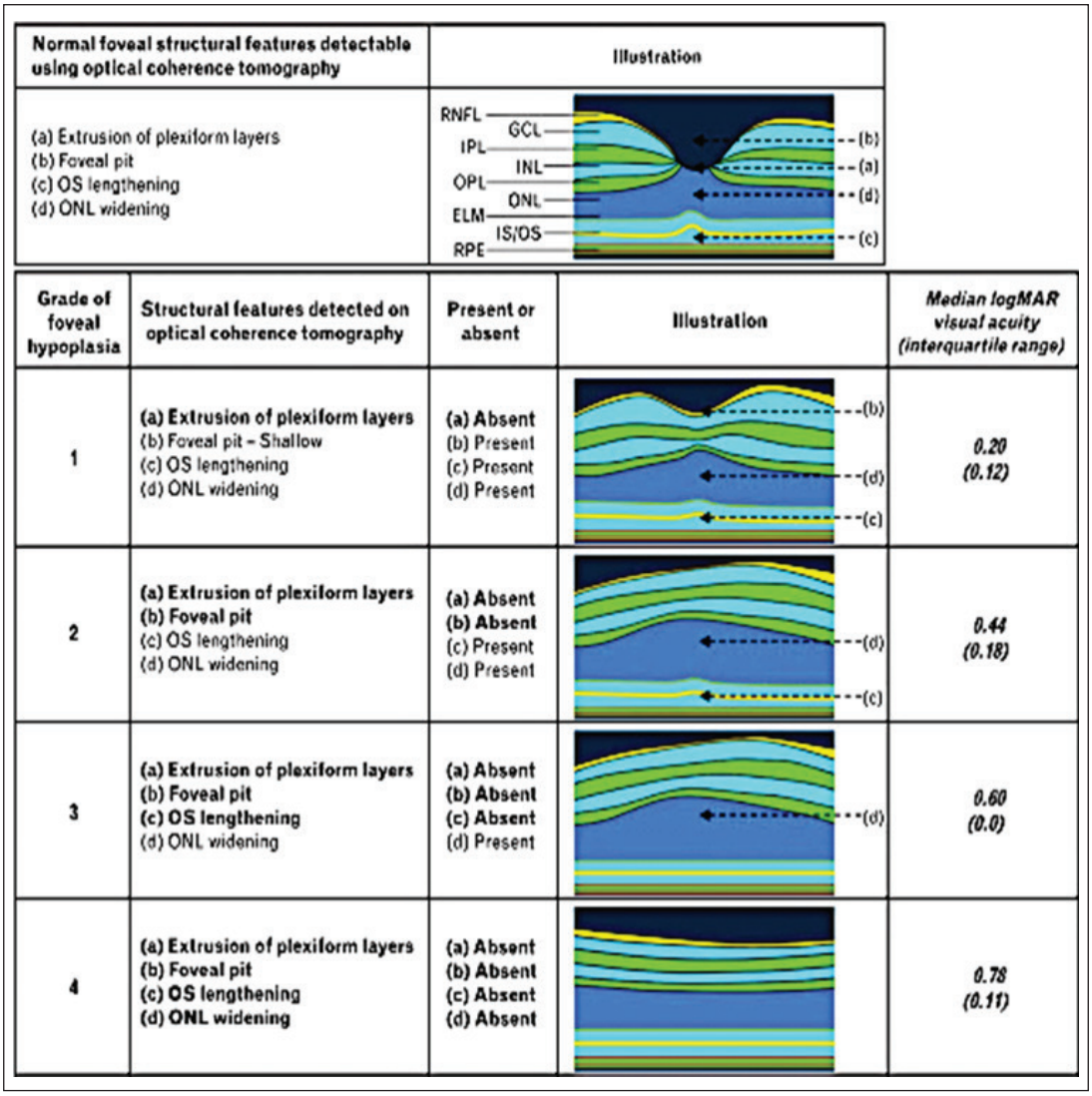

Figure 9. *Structural grading of foveal hypoplasia using HH SD-OCT. Grade 1: Characterized by the presence of a shallow foveal pit, outer nuclear layer (ONL) widening and lengthening of the cone outer segment (OS) while extrusion of plexiform retinal layers is absent. Grade 2. Characterized by absence of the foveal pit and plexiform retinal layers extrusion. Grade 3. Characterized by foveal hypoplasia in grade 2 in addition to absence of the OS lengthening. Grade 4. Characterized by foveal hypoplasia occupying the full thickness (25).*

a) **Head free remote electrooculography** ideal for examination of infants and small children, in which a small target sticker can be placed on the forehead so that head distance can be accurately measured, then the eye tracking system is mounted on the bottom of the computer screen which is being used for the stimuli (Figure 6A).
b) **Head-mounted video eye tracker with scleral search coil** ideal for use in adults provides binocular recordings sampling at 500 Hz (40) (Figure 6B).

Optical coherence tomography (OCT)

The relationship between afferent visual deficits and IN is becoming clearer with high-resolution imaging of the retina, specifically, with hand-held spectral domain OCT (HH SD-OCT) (Figure 7). This device provides reliable measurements in children and allows detailed assessment of the foveal structure in several pediatric eye conditions associated with IN (41). Foveal abnormalities in subtypes of IN have been characterized as shown in Figure 8. Structural grading of foveal hypoplasia using HH SD-OCT is represented in Figure 9.

Electroretinogram (ERG)

Is an essential component in the evaluation of IN, as intrinsic IRD such as LCA, achromatopsia, congenital stationary night blindness, and other disorders might be suspected. The ERG in IIN patients should be within normal values.

Cognitive and visual–cognitive profiling

Recent studies have shown that patients with IIN displays normal neuropsychomotor development and intelligence quotient (IQ), consistent with the absence of central nervous system (CNS) involvement. Thus, the integration of visual–cognitive skills in the overall management plan is essential component and deserve further attention to

differentiate with other different neurodevelopmental disorders (2).

Treatment in IIN

Refractive error correction

The treatment of these patients should begin with a correction of any refractive error to avoid the consequent amblyopia (40). The use of contact lenses is an area of controversy in which Allen et al. (42) reported an improvement in visual acuity and nystagmus particularly in IIN. The improvements in visual acuity with the use of contact lenses compared to spectacles may be attributed to reduced optical aberrations, enlarged retinal image, and increased peripheral visual field. In contrast, recently randomized trial assessing the use of hard and soft contact lenses in IN showed that neither hard nor soft lenses dampen nystagmus as compared to wearing glasses (26).

Pharmacologically

Memantine and gabapentin, drugs with the CNS inhibition effect, are useful agents for patients with nystagmus. Particularly, memantine with its antiglutaminergic effect that inhibit the release of excitatory transmitter glutamate and gabapentin that increase the synaptic concentration of the inhibitory transmitter GABA through voltage-sensitive calcium channels. In adult patients with IIN, both drugs showed a positive effect with improvement in visual acuity, nystagmus amplitude, foveation time, and good tolerability with only mild side effects such as dizziness and tiredness, while no trials have been done in children (43). The trailed treatment dosage of IIN was either up to 2400 mg of gabapentin per day in three divided doses or 20–40 mg of memantine whereas the mechanism behind the improvement of nystagmus is unclear.

Retrobulbar or intramuscular injection of botulinum toxin

It has been demonstrated that the injection of botulinum toxin helped to abolish nystagmus temporarily for six months by muscles weakness, but patient satisfaction has been poor due to adverse effects, such as ptosis or diplopia and the need for reinjection.

Surgical (Anderson or Kestenbaum procedures)

Eye muscle surgery can be performed to shift the null zone of nystagmus into the primary position and to diminish the anomalous head position. Simple tenotomy (disinsertion and reattachment on the original insertion) of all four horizontal rectus muscles has been reported to improve visual function and eye movements in IIN (14).

Cognitive and visual–cognitive profiling

Recent studies have shown that patients with IIN display normal neuropsychomotor development and IQ, consistent with the absence of CNS involvement. Thus, the integration of visual–cognitive skills in the overall management plan is an essential component and deserves further attention to differentiate with other different neurodevelopmental disorders (2).

List of Abbreviations

BCVA	Best corrected visual acuity
CNS	Central nervous system
ERG	Electroretinogram
FRMD7	FERM domain containing protein 7
GABA	Gamma-aminobutyric acid
GPR143	G protein-coupled receptor 143
IIN	Idiopathic infantile nystagmus
IQ	Intelligence quotient
IRD	Inherited retinal diseases
OCT	Optical coherence tomography

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