

INVITED REVIEW ARTICLE

Nystagmus in Childhood



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Received Feb 11, 2014; accepted Feb 24, 2014
Available online 31 July 2014

Key Words

abnormal head posture;
albinism;
eye movement recordings;
head posture;
idiopathic infantile nystagmus;
manifest latent nystagmus

Nystagmus is an involuntary rhythmic oscillation of the eyes, which leads to reduced visual acuity due to the excessive motion of images on the retina. Nystagmus can be grouped into infantile nystagmus (IN), which usually appears in the first 3–6 months of life, and acquired nystagmus (AN), which appears later. IN can be idiopathic or associated to albinism, retinal disease, low vision, or visual deprivation in early life, for example due to congenital cataracts, optic nerve hypoplasia, and retinal dystrophies, or it can be part of neurological syndromes and neurologic diseases. It is important to differentiate between infantile and acquired nystagmus. This can be achieved by considering not only the time of onset of the nystagmus, but also the waveform characteristics of the nystagmus. Neurological disease should be suspected when the nystagmus is asymmetrical or unilateral. Electrophysiology, laboratory tests, neurological, and imaging work-up may be necessary, in order to exclude any underlying ocular or systemic pathology in a child with nystagmus. Furthermore, the recent introduction of handheld spectral domain optical coherence tomography (HH SD-OCT) provides detailed assessment of foveal structure in several pediatric eye conditions associated with nystagmus and it can be used to determine the underlying cause of infantile nystagmus. Additionally, the development of novel methods to record eye movements can help to obtain more detailed information and assist the diagnosis. Recent advances in the field of genetics have identified the *FRMD7* gene as the major cause of hereditary X-linked nystagmus, which will possibly guide research towards gene therapy in the future. Treatment options for nystagmus involve pharmacological and surgical interventions. Clinically proven pharmacological treatments for nystagmus, such as gabapentin and memantine, are now beginning to emerge. In cases of obvious head posture, eye muscle surgery can be performed to shift the null zone of the nystagmus into the primary position, and also to alleviate neck problems that can arise due to an abnormal head posture.

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1. Introduction

Nystagmus is defined as an involuntary rhythmic oscillation of the eyes, and it can be confirmed relatively easily through direct observation of eyes and/or eye movement recordings. Nystagmus is commonly encountered in clinical practice and leads to reduced visual acuity due to the excessive motion of images on the retina, and also the movement of images away from the fovea.¹ The prevalence of nystagmus in the general population is estimated to be 24 per 10,000 population with a slight predilection toward European ancestry.² The prevalence of infantile nystagmus is 14 per 10,000.²

Nystagmus can be grouped into infantile nystagmus (IN), which usually appears in the first 3–6 months of life, and acquired nystagmus (AN), which appears later. For those who have infantile nystagmus (IN), this can be idiopathic or associated to another eye disease, such as retinal disease, albinism, low vision, or visual deprivation in early life (due, for example, to congenital cataracts or optic nerve hypoplasia). Nystagmus can also be part of neurological syndromes and neurologic diseases (Figure 1).³ In IN associated with other eye diseases, vision is not only affected by the excessive motion of the image on the retina caused by the nystagmus, but also by a defective visual system.⁴ Mechanisms underlying IN are not very clear. Numerous hypotheses and models have been proposed to explain the ocular oscillations observed in IN, usually highlighting various elements of the ocular motor circuitry as the direct cause.⁵ However, the clear association between IN and the many sensory anomalies that lead to sight loss during visual development imply an afferent cause to many IN forms.⁶

Acquired nystagmus can result from a range of neurological disorders, of which the most common are multiple

sclerosis, disease of the vestibular apparatus and innervations, insult to the nervous system caused by stroke, tumors, or trauma, and as a result of drug toxicity.⁷ In general, the mechanisms underlying AN are better understood than those behind IN. AN is commonly associated with lesions to the subcortical ocular motor circuitry.⁸ Consequently, detection and diagnosis of diseases associated with AN are greatly assisted by neuroimaging methods.

Nystagmus can be distressing for both those with IN and AN. Nystagmus leads to deterioration in visual acuity and motion sensitivity mainly because of deterioration in foveal vision, when images move across the retina rapidly.⁹ Nystagmus can also have a significant psychological and social impact.¹⁰ Although patients with IN and AN both have reduced vision, patients with AN tend to suffer from oscillopsia (the illusion of constant movement of the surroundings) and hence may be more troubled by the condition.¹¹ Patients with IN do not usually suffer from oscillopsia. Two hypotheses have been suggested to explain the mechanism behind the suppression of oscillopsia. The first is the “sampling theory”, by which the information from the most stable retinal images during the foveation periods can be used to establish a stable image, whereas the rest of the nystagmus cycle is ignored.¹² The second hypothesis is the “remapping theory” whereby an efference copy signal of the nystagmus waveform is used to cancel the effects of motion.¹³ This is probably the most likely theory because vision during the fast phases of the nystagmus cycle has been documented which argues against sampling. Finally, a recent Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI) study in a patient with infantile nystagmus during maximal nystagmus showed a metabolic downregulation of the area MT/V5 bilaterally, the most important part of the visual cortex for visual motion

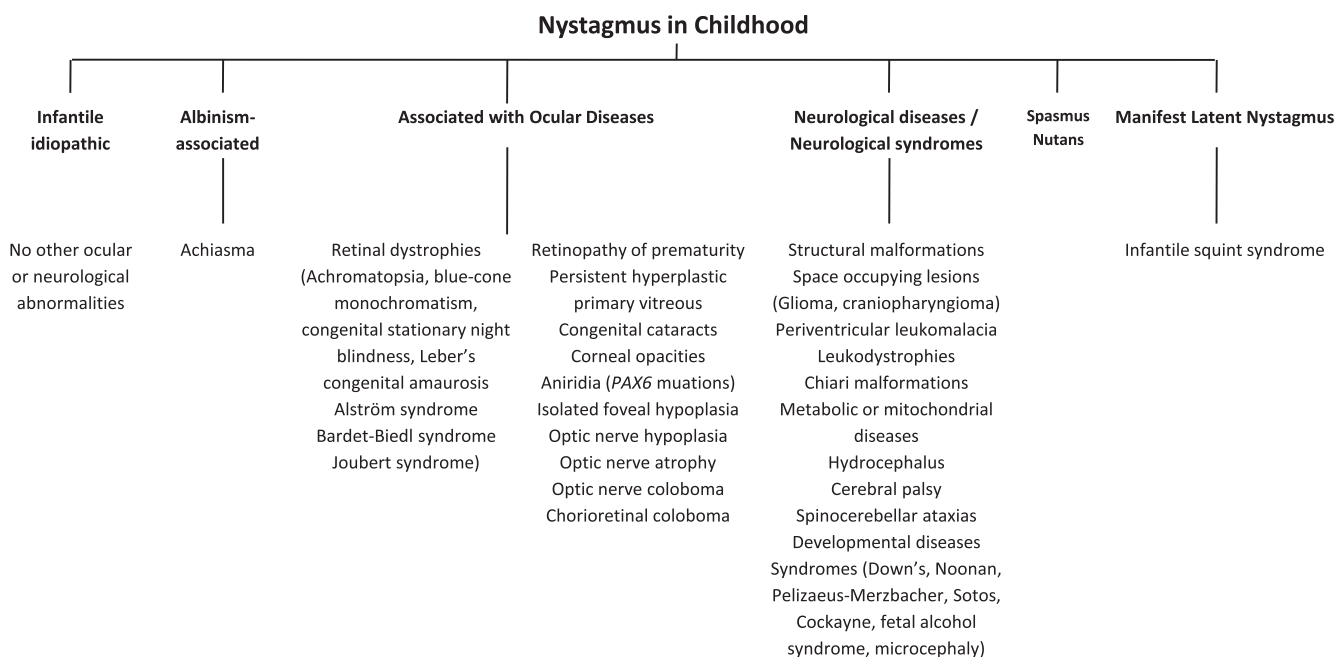


Figure 1 Classification of childhood nystagmus. *Note.* From “The pharmacological treatment of nystagmus: a review”, by R.J. McLean and I. Gottlob, 2009, *Expert Opin Pharmacother*, 10, p. 1805–16. Copyright 2009, Informa UK Limited. Adapted with permission.

processing.¹⁴ The authors suggested that the relative decrease in metabolic activity in this network of visual-motion processing represents the functional correlate for the clinical absence of oscillopsia in patients with a congenital pendular nystagmus (Figure 2).¹⁴

It is important to differentiate between infantile and acquired nystagmus. This can be achieved by considering not only the time of onset of the nystagmus, but also the waveform characteristics of the nystagmus. Nystagmus waveforms can be viewed in detail via eye movement recordings, which can be documented using different methods, such as electrooculography, the scleral search coil, and video eye-tracking devices (Figure 3A and B).¹⁵ Nystagmus waveforms are extremely variable (Figure 4).¹⁶ They can be described using a number of characteristics which can also assist in the diagnosis.¹⁷ (1) Plane: nystagmus most commonly occurs along the horizontal axis, although nystagmus can also be vertical, torsional, or any combination of these, such as seesaw nystagmus (vertical with torsional) or cyclorotatory nystagmus (horizontal with vertical).¹⁸ (2) Amplitude (size) and frequency (cycles per second):¹⁹ amplitude and frequency should be assessed in primary position and with the patient looking to the sides as well as up and down. Often a reduction of nystagmus can be seen with the patient fixing at near (in convergence). Nystagmus intensity can vary with eye position and often there is a position of gaze in which the oscillations are minimal (null point).¹⁸ (3) Waveform: nystagmus has been divided into jerk nystagmus, which exhibits a quick and slow phase, and pendular nystagmus, which is a sinusoidal like oscillation without any obvious quick phase (Figure 4). In jerk nystagmus, the direction of nystagmus is defined by the quick phase of the jerk (e.g., downbeat).²⁰ The slow phase can have accelerating and decelerating velocities (Figure 4). (4) 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. For example, the amplitude can be larger in one eye in anterior visual pathway pathology and spasmus nutans. Additionally, both eyes may move in opposite directions in spasmus nutans, seesaw nystagmus, or convergence nystagmus in Parinaud syndrome.¹⁸ (5) Foveation: many forms of congenital nystagmus show periods where the eyes move at a lower velocity allowing high-acuity vision at the fovea to function.⁹ (6) Dependence on other parameters: certain types of nystagmus waveform are not constant but vary with time (e.g., intermittent or reverse direction), monocular or binocular viewing, and convergence or eccentricity of gaze. For example, periodic alternating nystagmus is a horizontal jerk nystagmus that goes through cycles of left- and right-beating nystagmus, reversing approximately every 1–2 minutes.¹⁸

2. Infantile nystagmus

2.1. Infantile idiopathic nystagmus

IIN is the most common type of infantile nystagmus, followed by nystagmus associated with ocular disease.² In infantile idiopathic nystagmus (IIN) no underlying eye condition or neurological problems are present. IIN is usually bilateral, conjugate, occurring in the horizontal plane, and of either a pendular waveform or a jerk waveform with an accelerating slow phase, but it may also rarely appear as primarily vertical or even torsional nystagmus.^{17,21} The term “idiopathic infantile nystagmus” is used in preference to “congenital idiopathic nystagmus” as the nystagmus is not always present at birth.²² The onset of IIN is usually between birth and 12 weeks of age.²³ Visual acuity is log-MAR 0.3 (6/12) or better in most patients and nystagmus usually becomes less evident with age.²¹ Strabismus is not common and good stereopsis is often present.

Individuals with IIN develop a “foveation strategy” during visual development in order to improve vision.²⁴ Individuals learn how to use “foveating saccades” to

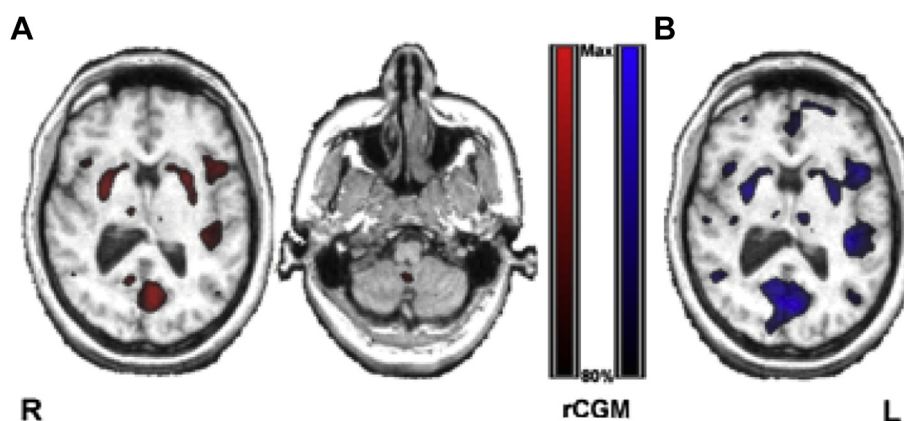


Figure 2 Thresholded regional cerebral glucose metabolism (rCGM) during gaze (A) with maximal pendular nystagmus (red) and decreased metabolism in MT/V5 bilaterally and an increase in the cerebellar nodulus compared to (B) glucose uptake in V1 and MT/V5 while fixating in the null zone. *Note.* From “Visual motion suppression in congenital pendular nystagmus”, P. Schindwein, M. Schreckenberger, and M Dieterich M, 2009, *Ann New York Acad Sci*, 1164, p. 458–60. Copyright 2009. *New York Academy of Sciences*. Reproduced with permission.

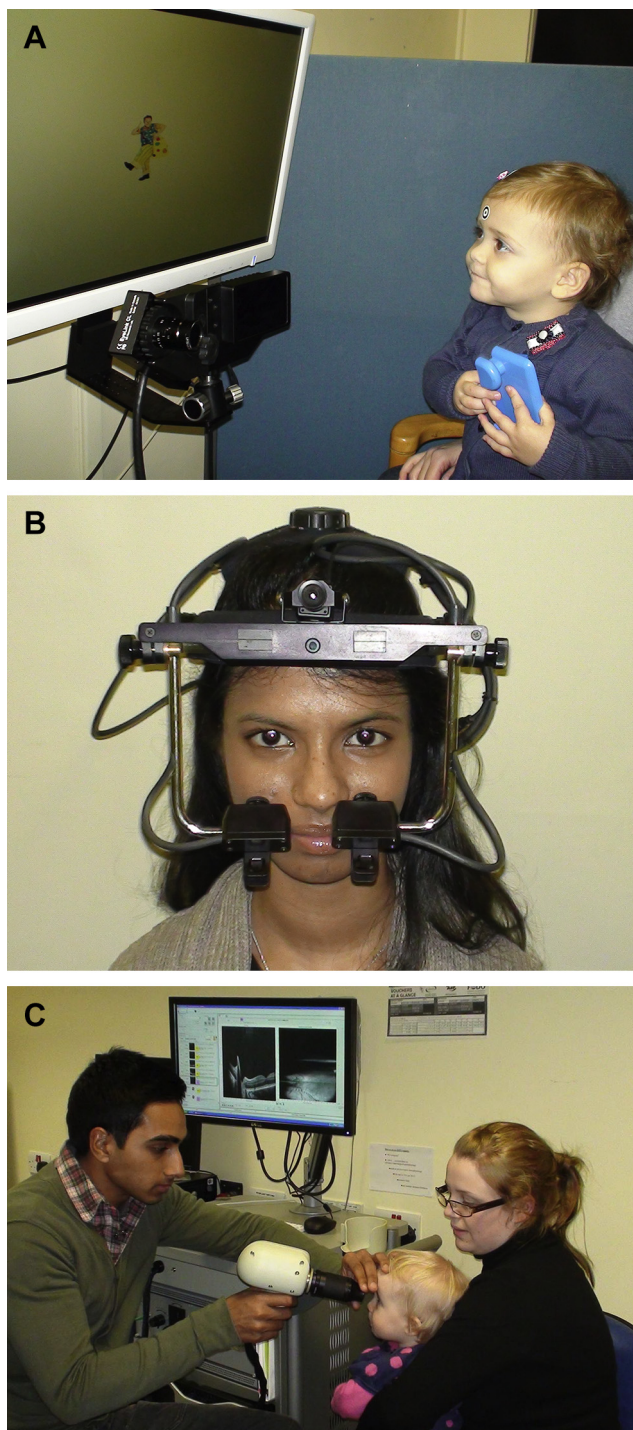


Figure 3 (A) Eyelink 1000, SR Research Ltd, Ottawa, Ontario, Canada, a head free remote eye tracking system which does not require head stabilization. A small target sticker can be placed on the forehead so that head distance can be accurately measured. The eye tracking system is mounted on the bottom of the computer screen which is being used for the stimuli. Ideal for use in infants and small children. (B) Head-mounted video eye tracker (Eyelink II, SR Research Ltd) provides binocular recordings sampling at 500 Hz. (C) The hand-held OCT is performed on a toddler (Bioptigen Inc, Research Triangle Park, North Carolina, USA).

maximize the time periods when the eyes are moving slowly. Individuals use these slow periods (called foveation periods) to line up the fovea with targets of interest.

A study investigating visual acuity development of children with IN syndrome reported that patients with IIN showed mildly reduced visual acuity before 24 months of age and a gradual maturation of visual acuity with age after 24 months, which paralleled with existing normative curves for visual acuity development.²⁵ Indeed, most of the visual acuity test results were within the 95% normative tolerance limit before 48 months of age. After 48 months of age, visual acuity improved, even though only half of the visual acuity test results were within the 95% normative tolerance limits.²⁵

IIN is usually associated with a null region where the nystagmus has a lower intensity. If the null point does not coincide with the primary gaze position, then a head position may be adopted to reduce the nystagmus.²⁶ This can result in a face turn most commonly when the nystagmus is in the horizontal plane. Sometimes patients with horizontal nystagmus also adopt chin up and down positions, the reason for which is poorly understood.²⁷ Patients with IIN can have a strong family history of nystagmus or can be singly affected. The most common mode of inheritance is due to X-linked mutations.²⁸ The cause of IIN is still unknown. A suggested mechanism is the developmental miswiring of the visual system.²⁹ However, there is no consensus concerning the dysfunctional neuronal structures in IIN, with suggestions including the fixational eye

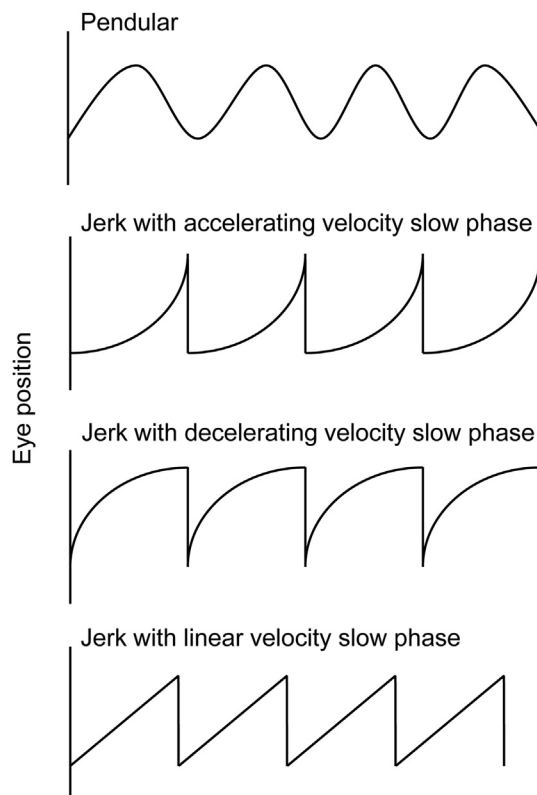


Figure 4 Eye movement recordings showing different nystagmus waveforms. Pendular nystagmus is a sinusoidal like oscillation without any obvious quick phase, whereas jerk nystagmus exhibits a quick and slow phase. The slow phase can have accelerating and decelerating velocities.

movement system, the pursuit system, and the saccadic system.³⁰ Recently, it has also been suggested that IIN is a developmental response to poor high-contrast foveal vision, where contrast sensitivity to low spatial frequencies is enhanced by moving images across the retina.⁶

Recently the gene *FRMD7* has been identified as the major cause of hereditary X-linked nystagmus, which is the most frequent familial type. Although the exact function of this gene is still unknown, it is expressed in the retina, cerebellum, and lateral ventricles during development.³¹ *FRMD7* has been shown to be involved in neurite outgrowth and development and interaction with CASC (plasma membrane scaffolding protein) has been shown.^{32–34} Individuals with mutations in the *FRMD7* gene have relatively good visual acuity (better than 6/12), often possess stereopsis and show less pronounced anomalous head posture compared to individuals with IIN not caused by *FRMD7* mutations. Periodic alternating nystagmus occurs in approximately 25% of patients with *FRMD7* related nystagmus.²¹

2.2. Manifest latent nystagmus

Manifest latent nystagmus (MLN) is a predominantly horizontal, jerk nystagmus that becomes more apparent when one eye is covered. The fast phase beats towards the direction of the fixing/open eye. In almost all patients, nystagmus is present with both eyes open: it is smaller in intensity and may be subclinical in size.³⁵ The manifest component of the nystagmus is evident when both eyes are open. The latent component (increase in nystagmus amplitude) is revealed when one eye is occluded.

MLN is almost always associated with congenital squint syndrome, which leads to disrupted binocular vision. In patients with alternating esotropia, the nystagmus fast phases can change spontaneously depending on which eye is fixing. Additionally, it is often associated with conditions that cause unilateral loss of vision during visual development such as cataract and optic nerve hypoplasia, and it is also found in conjunction with IIN, in which case a complex nystagmus wave form is seen.³⁶ MLN is often associated with Down syndrome, as children with Down syndrome often have strabismus.³⁷

MLN dampens in adduction; hence patients with strabismus and MLN will place the fixing eye in adduction to improve vision, and this will lead to a face turn to the side of the fixing eye (Figure 5A). Patients may also show a head tilt which could be part of the congenital squint syndrome unrelated to MLN or may be to compensate for the cyclovertical (i.e., torsional and vertical) component often seen in MLN.³⁸

The underlying mechanism behind MLN is the disruption of binocular vision during visual development, through strabismus and amblyopia. MLN can be treated by correcting the squint: this can be combined with correction of the head posture using eye muscle surgery, in which case the fixing eye needs to be operated.³⁹ Treating the underlying amblyopia using patching therapy can also reduce the nystagmus caused by MLN.⁴⁰

2.3. Albinism

Oculocutaneous albinism (OCA) is characterized by a lack of pigmentation in the eyes, skin, and hair and is caused by

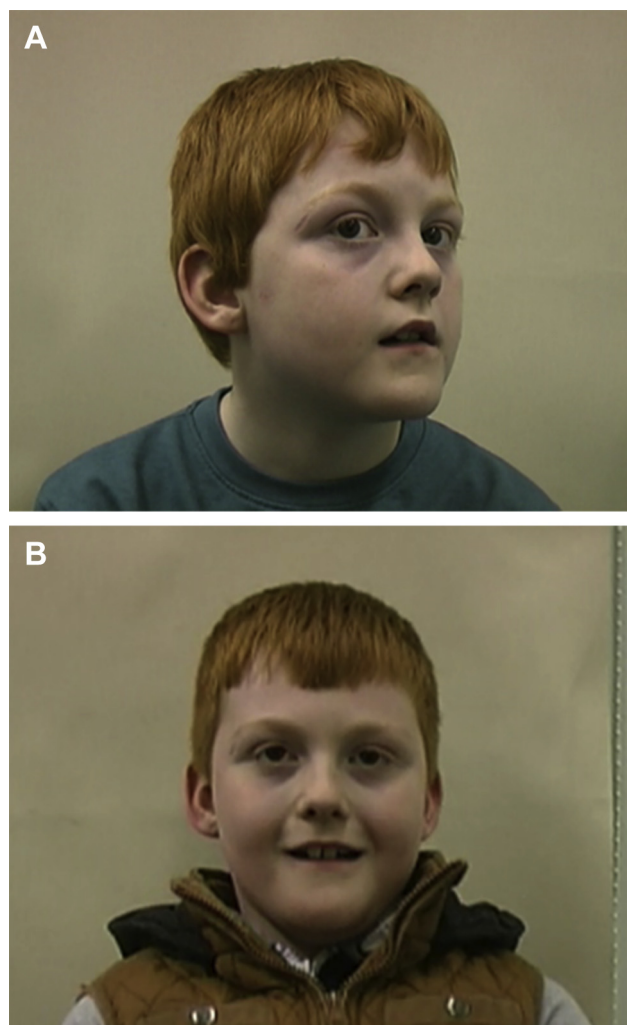


Figure 5 This child with albinism-associated nystagmus and a left head turn (A) underwent a Kestenbaum procedure for correction of his head posture. (B) No head turn is present after the operation.

disruption in the production of melanin due to a number of genetic mutations.⁴¹ In certain forms of albinism there is no apparent lack of pigmentation in hair or skin and only the visual system is affected. This is described as ocular albinism (OA).

OCA is associated with several changes in the eye and visual pathway, including iris transillumination (Figure 6), foveal hypoplasia, retinal hypopigmentation (Figure 7), abnormal crossing of the optic nerves at the chiasm, reorganization of the striate cortex, and nystagmus. Optical coherence tomography shows a spectrum of foveal development in albinism, sometimes with complete absence of development or with a central depression with thickened fovea (Figure 8).^{42,43} The abnormal foveal development frequently leads to reduced visual acuity. The optic discs can be small and dysplastic (small cupless disks or oblique cup with situs inversus).⁴⁴ One of the most distinguishable features of albinism is abnormal crossing of axons at the chiasm.⁴⁵ This can be detected diagnostically as an asymmetry in the visual evoked potential. Albinism is often

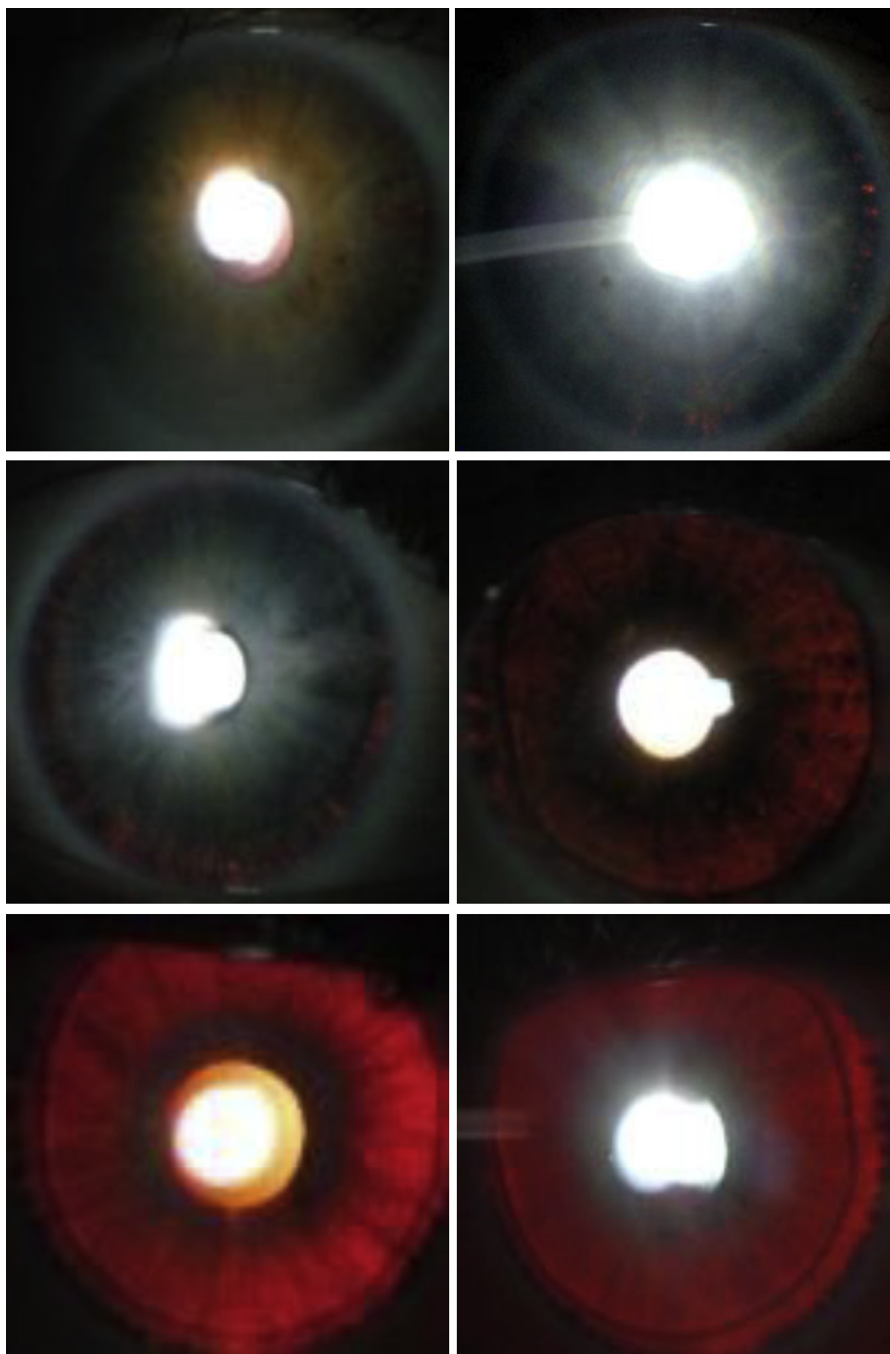


Figure 6 Anterior segment photos in albinism show various degrees of iris transillumination.



Figure 7 Fundus photographs in albinism demonstrate Grades 1, 2 and 3 macular transparency according to a previously described grading scheme.⁴²

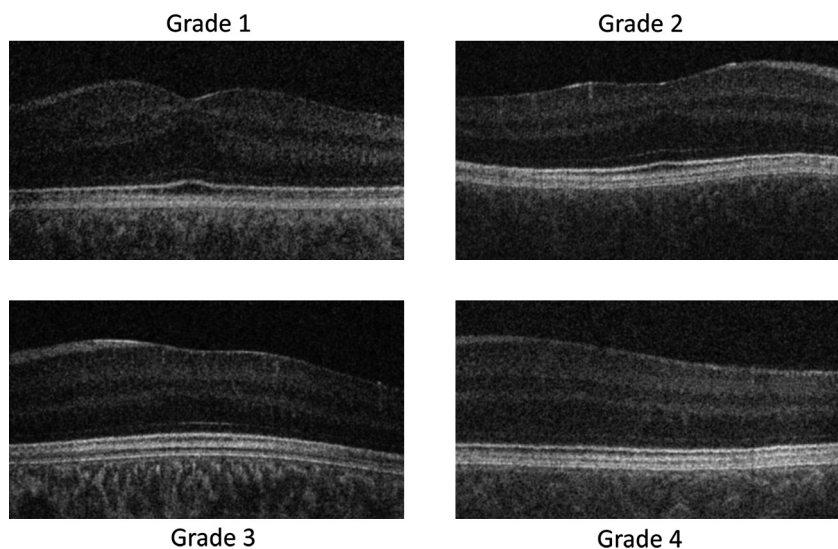


Figure 8 Classification of foveal hypoplasia according to Thomas et al. In Grade 1 foveal hypoplasia extrusion of plexiform retinal layers is absent, but a shallow foveal pit, outer nuclear layer (ONL) widening and lengthening of the cone outer segment (OS) are seen. Grade 2 foveal hypoplasia consists of all features of Grade 1 except the presence of a foveal pit. Grade 3 foveal hypoplasia involves all features of Grade 2 foveal hypoplasia except the widening of the cone outer segment. In Grade 4 foveal hypoplasia, all the features of Grade 3 are seen except the widening of the ONL at the fovea. *Note.* From “Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity?”, M.G. Thomas, A. Kumar, S. Mohammad, F.A. Proudlock, EC Engle, C. Andrews, et al, 2011, *Ophthalmology*, 118, p. 1653–60. Copyright 2011. *American Academy of Ophthalmology*. Adapted with permission.

associated with a loss of cortical stereoscopic vision due to misrouting of axons through to the cortex and also strabismus.

The nystagmus shows many similarities to that observed in IIN patients. It is usually horizontal, conjugate, with increasing slow-phase velocities and the nystagmus intensity and waveform changing with gaze direction. These patients also typically show a null zone and often have an anomalous head posture. However, in cases of IIN associated with *FRMD7* mutations, there were slight differences in nystagmus characteristics. The *FRMD7*-IIN patients showed a higher proportion of pendular waveform types compared with the albinos.⁴⁶ Additionally, the nystagmus frequency was significantly lower in albinos compared with the *FRMD7*-IIN group. Strabismus and anomalous head posture were seen in higher proportions in the albinism group, and stereopsis was worse compared with the *FRMD7*-IIN group.⁴⁶

OCA is linked to mutations in four known genes and OA in one known gene. All these mutations lead to dysfunctional melanin synthesis and storage. *OCA1* is present in most populations except African-Americans and can present with either a complete lack of melanin production (*OCA1A*) or partial melanin production (*OCA1B*). It is caused by mutations in the tyrosinase gene (*TYR*). *OCA2* and *OCA3* are more common in African populations and are milder forms of albinism. *OCA4* is another mild form of albinism that has recently been found in Turkish, Japanese, German, and Korean patients. There are two known causes of OA: (1) due to mutations in the *OA1* gene which follows an X-linked recessive inheritance; or (2) autosomal-recessive ocular albinism (AROA).⁴⁷

2.4. Spasmus nutans

Spasmus nutans is a rare form of infantile nystagmus that is characterized by a triad of nystagmus, head nodding, and head torticollis. It is an intermittent, fine, high-frequency, pendular dissociated nystagmus. It appears at ~ 1–3 years of age but abates to subclinical levels at ~ 5–12 years of age.⁴⁸ Spasmus nutans is not inherited and is more common in low socioeconomic classes.⁴⁹ Interestingly, head nodding evokes the vestibular ocular reflex that may dampen the spasmus nutans and thus improve vision.²⁰ In other nystagmus forms head nodding has not been found to benefit the patient and might be an associated pathological phenomenon.⁵⁰ Spasmus nutans can be differentiated from infantile nystagmus by the high frequency of eye movements. Additionally, although congenital idiopathic nystagmus and sensory deficit nystagmus usually have an onset before 6 months of age, it is generally agreed that the onset of spasmus nutans is always after 6 months of age and usually before 2–3 years of age.^{50,51} However, because the eye movements are often dissociated, spasmus nutans cannot be separated from nystagmus associated with retinal disease (such as achromatopsia and congenital stationary night blindness) or nystagmus caused by lesions to the anterior visual pathway caused by tumors, for example, optic nerve and chiasmal gliomas.^{51,52} Therefore, thorough neuroophthalmological (including electrophysiology), neuropaediatric, and possibly neuroradiological workup of the patient is necessary.

2.5. Nystagmus associated with retinal diseases and low vision

In infancy >90% of all cases of nystagmus seen will be due to abnormalities at numerous locations along the sensory visual pathway.⁵³ In nystagmus associated to afferent diseases, it is not entirely clear whether the afferent deficits cause the nystagmus or whether the nystagmus is intrinsic to the disease.³ Nystagmus associated to retinal diseases and low vision is more common than the infantile idiopathic nystagmus.^{2,54} However, it does show similar oculomotor features.⁵⁵ Nystagmus associated with retinal diseases and low vision can be horizontal or vertical or a combination of both, or it can also be dissociated.⁵⁶ The visual acuity in patients with nystagmus associated to afferent diseases is often lower than in idiopathic nystagmus due to the anatomical pathology of the eye. In the vast majority of cases, nystagmus associated to afferent diseases is associated with bilateral anterior visual pathway pathology, although occasionally binocular nystagmus is associated with monocular visual loss (especially in untreated persistent hyperplastic primary vitreous).⁵⁷ Congenital cataracts can lead to nystagmus if not operated on early enough.³⁶ Corneal opacities, *PAX6* mutations, developmental disorders of the optic disc and retina such as bilateral optic nerve hypoplasia and chorioretinal or optic nerve coloboma, and retinopathy of prematurity are also associated with nystagmus. Deficits of rod and cone systems, such as congenital stationary night blindness, achromatopsia (complete or partial, e.g., blue-cone monochromatism), Leber's amaurosis, Bardet–Biedl syndrome, Joubert's syndrome, and Alström's syndrome are all associated with nystagmus.⁵⁸ Careful history-taking is important, as for example photophobia with poor color discrimination may indicate achromatopsia or blue-cone monochromatism, and night blindness with high myopia may suggest congenital stationary night-blindness. Achiasmatic individuals have been described to have congenital seesaw nystagmus.⁵⁹ These congenital disorders require differentiation by clinical findings, family history, laboratory tests, radiology, and detailed electrophysiological findings under photopic and scotopic conditions.⁵⁷

2.6. Nystagmus associated with neurologic diseases and syndromes

A variety of developmental and neurological syndromes are associated with nystagmus, such as Down's syndrome, Noonan's syndrome, Pelizaeus–Merzbacher syndrome, fetal alcohol syndrome, Sotos syndrome, Cockayne's syndrome, and microcephaly. These are usually related to abnormalities in the brainstem and cerebellum. Space-occupying lesions, cerebral palsy, periventricular leukomalacia, leukodystrophy, Chiari malformation, as well as metabolic and mitochondrial diseases are also associated with nystagmus.^{18,60} Neurological disease should be suspected when the nystagmus is asymmetrical (dissociated) or unilateral. Acquired nystagmus is less frequent in children (17% of nystagmus patients) than in adults (40%).² Visual pathway disease giving rise to nystagmus includes chiasmal and optic nerve glioma (i.e., in neurofibromatosis

type 1), craniopharyngioma, and optic nerve compression by other tumors or bone anomalies. Many patients with neurological nystagmus also have associated neurological symptoms or present with vertigo, nausea, and headaches due to elevated intracranial hypertension. Ocular signs, such as relative afferent pupillary defect, papilloedema, optic atrophy, and visual loss may also be present. Additionally, children with arrested or compensated hydrocephalus can present with IN of the sensory deficit nystagmus type. There is usually associated optic atrophy. Therefore, optic atrophy and nystagmus in infancy indicate a strong possibility of either raised intracranial pressure and/or intracranial tumor in infancy.⁵⁷ Therefore, an MRI examination should be performed in the presence of atypical nystagmus, accompanying neurological signs, developmental delay, or optic atrophy.

2.7. Optical coherence tomography (OCT) in nystagmus

Optical coherence tomography (OCT) allows high-resolution *in vivo* imaging of the retina. In particular, the recent introduction of hand-held spectral domain OCT (HH SD-OCT) provides reliable measurements in children and allows detailed assessment of foveal structure in several pediatric eye conditions associated with nystagmus (Figure 3C).⁶¹ Characteristic foveal abnormalities have been described in patients with albinism, ranging from complete absence of development to a central depression corresponding to a rudimentary annular reflex detected with ophthalmoscopy.^{43,62,63} The degree of foveal hypoplasia has been correlated to visual acuity.^{64–66} Furthermore, in achromatopsia a characteristic lesion has been described, which is associated with cone photoreceptor degeneration. The signs of photoreceptor degeneration were progressive, which suggests that gene therapy is likely to be most beneficial if given within the first few years of life.⁶⁷ Abnormal foveal morphology was also present in cases of retinal dystrophy and *PAX6* mutations.⁴³ Most importantly, the classification of foveal abnormalities by means of HH SD-OCT can be used to determine the underlying cause of infantile nystagmus.⁴³ Therefore, the combination of OCT and genetic methods along with other clinical diagnostic tools permit the discrimination of infantile nystagmus subtypes with a precision that has not previously been possible.⁶⁸

3. Treatment in infantile nystagmus

3.1. Surgical

In cases of obvious head turn, eye muscle surgery can be performed to shift the null zone of nystagmus into primary position. The procedure is performed not only for cosmetic reasons, but also to alleviate neck problems that can arise due to an abnormal head posture. There may also be improvement in visual acuity in some patients. For example, surgically correcting the head position in patients who wear glasses can enable them to view through their glasses centrally and achieve better optical correction (Figure 5A and B).⁴ Several attempts have also been made to improve visual acuity. Recession of all four horizontal

muscles and, more recently, tenotomy (disinsertion and reattachment on the original insertion) of the four horizontal muscles have been reported to improve visual function and eye movements in IIN.^{39,69} However, there are no randomized controlled studies to confirm these results. Surgeries used to treat nystagmus and anomalous head postures associated with IIN have also been used to treat albinism and other nystagmus forms.^{69,70} Although improvements in intensity of nystagmus have been shown to be effective by means of surgical intervention, improvements in visual acuity are limited by the underdeveloped fovea and other afferent deficits in these patients.⁷⁰

3.2. Pharmacological

Although drugs have been administered for some time in AN, pharmacological treatment for IN had not been explored until recently. Gabapentin and memantine, drugs which may have an antiglutamnergic action, both showed a positive effect in patients with IIN (i.e., unassociated with other visual deficits) and in patients with IN associated with other visual deficits (albinism, achromatopsia, optic atrophy, optic nerve hypoplasia, and congenital cataracts). The tolerability of the drugs was good and only mild side effects were noted, such as, dizziness and tiredness.⁷⁰ Treatment for IN was trialed in a dosage of either up to 2400 mg gabapentin per day in three divided doses or 20–40 mg of memantine. The mechanism behind how these interventions improve nystagmus is unclear. No trials have been done on children.⁴

3.3. Refractive correction

Refractive error in nystagmus is often high and it is therefore important that refractive error is examined for and appropriately prescribed for if required.⁷¹ As many of these children have strabismus, occlusion, and other strabismus management is important. There has been some controversy with regard to the use of contact lenses in nystagmus; there are reports that contact lenses improve visual acuity and reduce nystagmus, particularly in IN.⁷² 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.⁷³ A recent randomized trial assessing the use of hard and soft contact lenses in infantile nystagmus showed that neither hard nor soft lenses dampen nystagmus as compared to wearing glasses. Visual acuity with soft contact lens wear in this study was worse than with both hard lenses and glasses (oral communication with Dr. R. McLean).

3.4. Prisms

Prisms can also be used to dampen nystagmus. In some occurrences of IN, where the amplitude of nystagmus is smaller in convergence, prisms can be introduced if the patient has binocular vision. The prisms create an artificial divergence that the patient is required to overcome by converging the eyes even when looking at distance.⁷⁴

3.5. Botulinum toxin injections

Weakening muscles by retrobulbar injections of botulinum toxin is another approach used in the treatment of nystagmus. Studies of AN have shown that nystagmus reduces after botulinum injections, although the effects only last for approximately 6 months.⁷⁵ There are drawbacks to this type of management, as ptosis and diplopia can occur, which limits the therapeutic value and effectiveness of the treatment.⁷⁶

4. Conclusion

Nystagmus can result from a variety of conditions leading to diverse but characteristic eye oscillations. Detailed eye movement recordings may not be always be available to clinicians. However, certain clinical features can be identified and provide clues concerning the underlying pathogenesis. Manifest latent nystagmus, idiopathic infantile nystagmus, and albinism can be diagnosed clinically and neurological investigations are unnecessary. It is important that both pediatricians and ophthalmologists exclude any underlying ocular or systemic pathology in a child with nystagmus. This may require electrophysiology, neurological, and imaging work-up. OCT has been proven to be very helpful to investigate whether patients have foveal hypoplasia or other retinal disorders. Clinically proven pharmacological treatments for nystagmus are now beginning to emerge, although their role in children is still limited. Additionally, surgical procedures to correct a head turn in nystagmus are effective, and surgeries to dampen nystagmus such as tenotomy of four muscles are also being performed. However, randomized controlled studies are necessary to prove their effectiveness.

Conflicts of interest

The authors report no conflicts of interest.

References

1. Stahl JS, Plant GT, Leigh RJ. Medical treatment of nystagmus and its visual consequences. *J R Soc Med* 2002;**95**:235–7.
2. Sarvanathan N, Surendran M, Roberts EO, Jain S, Thomas S, Shah N, et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. *Invest Ophthalmol Vis Sci* 2009;**50**:5201–6.
3. Gottlob I. Nystagmus. *Curr Opin Ophthalmol* 2001;**12**:378–83.
4. McLean RJ, Gottlob I. The pharmacological treatment of nystagmus: a review. *Expert Opin Pharmacother* 2009;**10**:1805–16.
5. Abadi RV. Mechanisms underlying nystagmus. *J R Soc Med* 2002;**95**:231–4.
6. Harris C, Berry D. A developmental model of infantile nystagmus. *Semin Ophthalmol* 2006;**21**:63–9.
7. Choudhuri I, Sarvanathan N, Gottlob I. Survey of management of acquired nystagmus in the United Kingdom. *Eye (Lond)* 2007;**21**:1194–7.
8. Leigh RJ, Das VE, Seidman SH. A neurobiological approach to acquired nystagmus. *Ann N Y Acad Sci* 2002;**956**:380–90.

9. Chung ST, Bedell HE. Velocity criteria for "foveation periods" determined from image motions simulating congenital nystagmus. *Optom Vis Sci* 1996;**73**:92–103.
10. Pilling RF, Thompson JR, Gottlob I. Social and visual function in nystagmus. *Br J Ophthalmol* 2005;**89**:1278–81.
11. Straube A, Leigh RJ, Bronstein A, Heide W, Riordan-Eva P, Tijssen CC, et al. EFNS task force—therapy of nystagmus and oscillopsia. *Eur J Neurol* 2004;**11**:83–9.
12. Abadi RV, Worfolk R. Retinal slip velocities in congenital nystagmus. *Vision Res* 1989;**29**:195–205.
13. Goldstein HP, Gottlob I, Fendick MG. Visual remapping in infantile nystagmus. *Vision Res* 1992;**32**:1115–24.
14. Schlindwein P, Schreckenberger M, Dieterich M. Visual motion suppression in congenital pendular nystagmus. *Ann N Y Acad Sci* 2009;**1164**:458–60.
15. van der Geest JN, Frens MA. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neurosci Methods* 2002;**114**:185–95.
16. Leigh RJ, Zee DS, editors. *The neurology of eye movements*. 4th ed. Oxford: Oxford University Press; 2006.
17. Khanna S, Dell'Osso LF. The diagnosis and treatment of infantile nystagmus syndrome (INS). *Scientific World Journal* 2006;**6**:1385–97.
18. Proudlock FA, Gottlob I. In: Taylor D, Hoyt CS, editors. *Nystagmus Paediatric Ophthalmology and Strabismus*. 4th ed. Kidlington, UK: Elsevier B.V.; 2011.
19. Roberti G, Russo P, Segrè G. Spectral analysis of electro-oculograms in the quantitative evaluation of nystagmus surgery. *Med Biol Eng Comput* 1987;**25**:573–6.
20. Ehrh O. Infantile and acquired nystagmus in childhood. *Eur J Paediatr Neurol* 2012;**16**:567–72.
21. Thomas S, Proudlock FA, Sarvananthan N, Roberts EO, Awan M, McLean R, et al. Phenotypical characteristics of idiopathic infantile nystagmus with and without mutations in FRMD7. *Brain* 2008;**131**:1259–67.
22. Gottlob I. Infantile nystagmus. Development documented by eye movement recordings. *Invest Ophthalmol Vis Sci* 1997;**38**:767–73.
23. Abadi RV, Dickinson CM. Waveform characteristics in congenital nystagmus. *Doc Ophthalmol* 1986;**64**:153–67.
24. Dell'Osso LF, Daroff RB. Congenital nystagmus waveforms and foveation strategy. *Doc Ophthalmol* 1975;**39**:155–82.
25. Fu VL, Bilonick RA, Felius J, Hertle RW, Birch EE. Visual acuity development of children with infantile nystagmus syndrome. *Invest Ophthalmol Vis Sci* 2011;**52**:1404–11.
26. Abadi RV, Whittle J. The nature of head postures in congenital nystagmus. *Arch Ophthalmol* 1991;**109**:216–20.
27. Gresty MA, Barratt HJ, Page NG, Ell JJ. Assessment of vestibulo-ocular reflexes in congenital nystagmus. *Ann Neurol* 1985;**17**:129–36.
28. Kerrison JB, Giorda R, Lenart TD, Drack AV, Maumenee IH. Clinical and genetic analysis of a family with X-linked congenital nystagmus (NYS1). *Ophthalmic Genet* 2001;**22**:241–8.
29. Danek A. The challenge of axonal path-finding. *Strabismus* 2006;**14**:95–9.
30. Akman OE, Broomhead DS, Abadi RV, Clement RA. Eye movement instabilities and nystagmus can be predicted by a nonlinear dynamics model of the saccadic system. *J Math Biol* 2005;**51**:661–94.
31. Tarpey P, Thomas S, Sarvananthan N, Mallya U, Lisgo S, Talbot CJ, et al. Mutations in FRMD7, a newly identified member of the FERM family, cause X-linked idiopathic congenital nystagmus. *Nat Genet* 2006;**38**:1242–4.
32. Betts-Henderson J, Bartesaghi S, Crosier M, Lindsay S, Chen HL, Salomoni P, et al. The nystagmus-associated FRMD7 gene regulates neuronal outgrowth and development. *Hum Mol Genet* 2010;**19**:342–51.
33. Toyofuku T, Yoshida J, Sugimoto T, Zhang H, Kumanogoh A, Hori M, et al. FARP2 triggers signals for Sema3A-mediated axonal repulsion. *Nat Neurosci* 2005;**8**:1712–9.
34. Watkins RJ, Patil R, Goult BT, Thomas MG, Gottlob I, Shackleton S. A novel interaction between FRMD7 and CASK: evidence for a causal role in idiopathic infantile nystagmus. *Hum Mol Genet* 2013;**22**:2105–18.
35. Dell'Osso LF, Schmidt D, Daroff RB. Latent, manifest latent, and congenital nystagmus. *Arch Ophthalmol* 1979;**97**:1877–85.
36. Abadi RV, Forster JE, Lloyd IC. Ocular motor outcomes after bilateral and unilateral infantile cataracts. *Vision Res* 2006;**46**:940–52.
37. Averbuch-Heller L, Dell'Osso LF, Jacobs JB, Remler BF. Latent and congenital nystagmus in Down syndrome. *J Neuro-ophthalmol* 1999;**19**:166–72.
38. Guyton DL, Cheeseman Jr EW, Ellis FJ, Straumann D, Zee DS. Dissociated vertical deviation: an exaggerated normal eye movement used to damp cyclovertical latent nystagmus. *Trans Am Ophthalmol Soc* 1998;**96**:389–424.
39. Zubcov AA, Stärk N, Weber A, Wizov SS, Reinecke RD. Improvement of visual acuity after surgery for nystagmus. *Ophthalmology* 1993;**100**:1488–97.
40. Simonsz HJ. The effect of prolonged monocular occlusion on latent nystagmus in the treatment of amblyopia. *Doc Ophthalmol* 1989;**72**:375–84.
41. Grønskov K, Ek J, Brøndum-Nielsen K. Oculocutaneous albinism. *Orphanet J Rare Dis* 2007;**2**:43.
42. Summers CG, Knobloch WH, Witkop Jr CJ, King RA. Herman-sky-Pudlak syndrome. Ophthalmic findings. *Ophthalmology* 1988;**95**:545–54.
43. Lee H, Sheth V, Bibi M, Maconachie G, Patel A, McLean RJ, et al. Potential of handheld optical coherence tomography to determine cause of infantile nystagmus in children by using foveal morphology. *Ophthalmology* 2013;**120**:2714–24.
44. Charles SJ, Green JS, Grant JW, Yates JR, Moore AT. Clinical features of affected males with X linked ocular albinism. *Br J Ophthalmol* 1993;**77**:222–7.
45. Jeffery G. Architecture of the optic chiasm and the mechanisms that sculpt its development. *Physiol Rev* 2001;**81**:1393–414.
46. Kumar A, Gottlob I, McLean RJ, Thomas S, Thomas MG, Proudlock FA. Clinical and oculomotor characteristics of albinism compared to FRMD7 associated infantile nystagmus. *Invest Ophthalmol Vis Sci* 2011;**52**:2306–13.
47. Oetting WS. New insights into ocular albinism type 1 (OA1): mutations and polymorphisms of the OA1 gene. *Hum Mutat* 2002;**19**:85–92.
48. Gottlob I, Wizov SS, Reinecke RD. Spasmus nutans. A long-term follow-up. *Invest Ophthalmol Vis Sci* 1995;**36**:2768–71.
49. Wizov SS, Reinecke RD, Bocarnea M, Gottlob I. A comparative demographic and socioeconomic study of spasmus nutans and infantile nystagmus. *Am J Ophthalmol* 2002;**133**:256–62.
50. Gottlob I, Zubcov AA, Wizov SS, Reinecke RD. Head nodding is compensatory in spasmus nutans. *Ophthalmology* 1992;**99**:1024–31.
51. Gottlob I, Wizov SS, Reinecke RD. Quantitative eye and head movement recordings of retinal disease mimicking spasmus nutans. *Am J Ophthalmol* 1995;**119**:374–6.
52. King RA, Nelson LB, Wagner RS. Spasmus nutans. A benign clinical entity? *Arch Ophthalmol* 1986;**104**:1501–4.
53. Casteels I, Harris CM, Shawkat F, Taylor D. Nystagmus in infancy. *Br J Ophthalmol* 1992;**76**:434–7.
54. Lorenz B, Gampe E. Analysis of 180 patients with sensory defect nystagmus (SDN) and congenital idiopathic nystagmus

- (CIN). *Klin Monbl Augenheilkd* 2001;218:3–12. [Article in German]
55. Hertle RW, Dell'Osso LF. Clinical and ocular motor analysis of congenital nystagmus in infancy. *J AAPOS* 1999;3:70–9.
 56. Gottlob I, Wizov SS, Reinecke RD. Head and eye movements in children with low vision. *Graefes Arch Clin Exp Ophthalmol* 1996;234:369–77.
 57. Hoyt CS. Nystagmus and other abnormal ocular movements in children. *Pediatr Clin North Am* 1987;34:1415–23.
 58. Gottlob I. Eye movement abnormalities in carriers of blue-cone monochromatism. *Invest Ophthalmol Vis Sci* 1994;35:3556–60.
 59. Apkarian P, Bour LJ. See-saw nystagmus and congenital nystagmus identified in the non-decussating retinal-fugal fiber syndrome. *Strabismus* 2001;9:143–63.
 60. Salati R, Borgatti R, Giammari G, Jacobson L. Oculomotor dysfunction in cerebral visual impairment following perinatal hypoxia. *Dev Med Child Neurol* 2002;44:542–50.
 61. Lee H, Proudlock F, Gottlob I. Is handheld optical coherence tomography reliable in infants and young children with and without nystagmus? *Invest Ophthalmol Vis Sci* 2013;54:8152–9.
 62. Harvey PS, King RA, Summers CG. Spectrum of foveal development in albinism detected with optical coherence tomography. *J AAPOS* 2006;10:237–42.
 63. Chong GT, Farsiu S, Freedman SF, Sarin N, Koreishi AF, Izatt JA, et al. Abnormal foveal morphology in ocular albinism imaged with spectral-domain optical coherence tomography. *Arch Ophthalmol* 2009;127:37–44.
 64. Healey N, McLoone E, Mahon G, Jackson AJ, Saunders KJ, McClelland JF. Investigating the relationship between foveal morphology and refractive error in a population with infantile nystagmus syndrome. *Invest Ophthalmol Vis Sci* 2013;54:2934–9.
 65. Thomas MG, Kumar A, Mohammad S, Proudlock FA, Engle EC, Andrews C, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? *Ophthalmology* 2011;118:1653–60.
 66. Seo JH, Yu YS, Kim JH, Choung HK, Heo JW, Kim SJ. Correlation of visual acuity with foveal hypoplasia grading by optical coherence tomography in albinism. *Ophthalmology* 2007;114:1547–51.
 67. Thomas MG, Kumar A, Kohl S, Proudlock FA, Gottlob I. High-resolution *in vivo* imaging in achromatopsia. *Ophthalmology* 2011;118:882–7.
 68. Proudlock F, Gottlob I. Foveal development and nystagmus. *Ann N Y Acad Sci* 2011;1233:292–7.
 69. Hertle RW, Yang D. Clinical and electrophysiological effects of extraocular muscle surgery on patients with Infantile Nystagmus Syndrome (INS). *Semin Ophthalmol* 2006;21:103–10.
 70. McLean R, Proudlock F, Thomas S, Degg C, Gottlob I. Congenital nystagmus: randomized, controlled, double-masked trial of memantine/gabapentin. *Ann Neurol* 2007;61:130–8.
 71. Hertle RW. Examination and refractive management of patients with nystagmus. *Surv Ophthalmol* 2000;45:215–22.
 72. Allen ED, Davies PD. Role of contact lenses in the management of congenital nystagmus. *Br J Ophthalmol* 1983;67:834–6.
 73. Rutner D, Ciuffreda K. Soft contact lenses to improve motor and sensory function in congenital nystagmus. *J Behav Optom* 2005;16:17–20.
 74. Spielmann A. Nystagmus. *Curr Opin Ophthalmol* 1994;5:20–4.
 75. Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994;112:1320–4.
 76. Tomsak RL, Remler BF, Averbuch-Heller L, Chandran M, Leigh RJ. Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. *Am J Ophthalmol* 1995;119:489–96.