Infantile (congenital) nystagmus

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Infantile nystagmus is a type of developmental nystagmus often associated with an underlying bilateral congenital afferent defect. It is the most studied of all types of pathological of nystagmus, with a large literature spanning many decades, yet it remains poorly understood, with no cure in sight, and easily misdiagnosed. This article provides an overview of this elusive condition.

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Learning objectives
Be able to identify and manage children with a binocular vision anomaly, with specific reference to infantile (congenital) nystagmus (Group 8.1.5)

About the author
After studying physics and optics at Imperial College London, Professor Chris Harris obtained his PhD from City University of New York, where he studied the development of human eye movements. In 1989 he set up an eye movement laboratory in Great Ormond Street Hospital carrying out research into abnormal oculomotor development. In 2000, he was appointed professor of neuroscience at Plymouth University. He has published over 100 papers in the area and continues research into visual and motor development. He is honorary visiting professor at the School of Optometry and Vision Sciences in Cardiff University, where he collaborates on studies of nystagmus. He is scientific adviser to the Nystagmus Network and co-edited its recent book on nystagmus. He teaches many aspects of vision and eye movements, including visual perception on the new Plymouth University optometry programme.
Background

Infantile nystagmus (IN), formerly known as ‘congenital nystagmus’ is a specific type of nystagmus with an onset at birth or in early infancy (less than six months) which cannot be acquired later in life. It is not a generic term for nystagmus occurring in infancy – it is distinct from latent nystagmus and other types of rare ‘neurological’ nystagmus which start in infancy. Even when the underlying afferent defect can be corrected (such as cataract removal), the nystagmus continues. Thus, IN is a ‘developmental’ nystagmus, alongside latent nystagmus. The prevalence of IN has been difficult to establish reliably but the most recent epidemiological survey reports about one in 800.2

Typically, IN is a horizontal conjugate nystagmus, although, rarely, it can be vertical or asymmetric (more pronounced in one eye).3 Eye movement recording has demonstrated waveforms which are mostly specific to IN. They usually have the common theme of accelerating slow phases (Figure 1), which, when present, is diagnostically useful in positively identifying IN. However, for some patients, the waveform is pendular (quasi-sinusoidal), which can also occur in neurological conditions. Infants may show a progression from large amplitude pendular to more typical jerk waveforms with age. The completely blind infant may have random multi-directional ‘roving eyes’, which should not be confused with the more rhythmical horizontal nystagmus.

The intensity of IN usually depends on eye position relative to the head, with a ‘null region’ where the nystagmus is least. This region may be straight ahead, but in about 25% of patients, it is eccentric (Figure 1) and the patient may adopt an abnormal head posture (AHP) to align the null region with the object of interest. Typically, the nystagmus beats away from the null region, with increasing intensity the further from the null. In the null region the nystagmus may be jerk or pendular. In perhaps as many as half of patients, the nystagmus dampens with convergence. In some, head-shaking (horizontal) or head-nodding (vertical) may occur.

Foveation periods

Because of the waveform, there has been much enthusiasm for measuring the so-called ‘foveation period’. This is the part of the waveform cycle where the target is supposed to be fixated.
to be on, or near, the fovea, and where the eye velocity is also low (Figure 2 page 49). The concept is based on the idea that in normal fixation, contrast sensitivity is largely unaffected as long as image speed (retinal slip) remains below about 4 deg/s. The duration of foveation periods has been thought of as a surrogate ‘visual’ measure of a waveform (discussed later).

**Stress**

Most patients will report that their nystagmus worsens and vision deteriorates when they are stressed. Recent studies have distinguished the visual demand of a task from the autonomic arousal/stress associated with the task. When there is no stress attached to a task (for example no time constraint on performance), increasing visual demand does not increase nystagmus, but may actually increase foveation periods. The effect of stress per se (for example electric shock, reward manipulation) is to increase the nystagmus intensity (reduce foveation periods), but has surprisingly little effect on VA. However, stress does increase response time, and it is possible that VA worsens because of time pressure (discussed later).

**Periodic alternating nystagmus (PAN)**

There is a strong association between IN and periodic alternating nystagmus (PAN). In PAN, the nystagmus spontaneously reverses after tens of seconds. PAN is often undiagnosed because of the lengthy observation time required. It is generally accepted as part of IN without any sinister implications, and is distinct from acquired PAN. However, PAN is a contra-indication for head posture surgery.

**Sensory versus idiopathic**

Approximately 80% of patients have an underlying sensory defect, which usually affects both eyes, and where the eye velocity is also low (Figure 2 page 49). The concept is based on the idea that in normal fixation, contrast sensitivity is largely unaffected as long as image speed (retinal slip) remains below about 4 deg/s. The duration of foveation periods has been thought of as a surrogate ‘visual’ measure of a waveform (discussed later).

*Figure 3 Some associations of infantile nystagmus, from Lorenz and Gampe.*

- **Idiopathic** 21%
- **Albinism** 30%
- **CSNB** 3%
- **Familial isolated** 5%
- **Aniridia** 6%
- **Colobomata** 6%
- **Optic nerve hypoplasia** 8%
- **Stationary cone dysfunction** 10%
- **Progressive cone/rod dystrophy** 11%
- **Idiopathic** 21%

Approximately 80% of patients have an underlying sensory defect, which usually affects both eyes (Figure 3). However, in 20% of cases, none can be detected, and they are then labelled as ‘idiopathic’ (formerly called congenital idiopathic or congenital motor nystagmus).

In sensory defect IN, the associations are numerous and include achromatopsia, albinism (ocular and oculocutaneous), aniridia, neonatal cataracts, congenital stationary night blindness, colobomata, optic nerve hypoplasia, early optic atrophy, cone dysfunction, isolated foveal hypoplasia, retinopathy of prematurity, and Leber’s congenital amaurosis. This list is not exhaustive, and probably any congenital bilateral visual deficit can precipitate INS.

Indeed, nystagmus following corneal infections acquired during birth has been reported.

The term ‘idiopath’ is a diagnosis by exclusion, and depends on the tests used. Subtle disorders, such as congenital stationary night-blindness, cone dysfunction and ocular albinism, can be difficult to detect with ophthalmoscopy alone. The electroretinogram (ERG) and cortical pattern visual evoked potentials (VEPs) have long been recommended investigations, but electrophysiology is still not routine in many centres. In the author’s experience, many
patients today have not been diagnosed correctly and mislabelled as idiopathic (especially ocular albinos). ‘Idiopathic’ does not mean ‘otherwise’ normal. Some infants with Down syndrome, and others with developmental delay secondary to in utero exposure to opiates or benzodiazepines may also appear to have idiopathic IN.

Genetics

IN is often familial, but there is no single gene or single genetic cause. Some mutations are associated with underlying sensory defects (‘syndromic genes’) with Mendelian inheritance. Mutations of these genes should not be considered causes of IN. They cause early-onset visual defects, which if they lead to visual deprivation, can lead to nystagmus. For example, congenital cataract may not lead to nystagmus if the visual axis remains clear. Some sensory defects have heterogeneous aetiology – optic nerve hypoplasia can be caused by in utero exposure to drugs, but also by PAX6 or HESX1 mutations. PAX6 mutations can lead to a variety of structural abnormalities which can each, in turn, lead to nystagmus. Leber’s congenital amaurosis is progressive, but quite heterogeneous with 15 known genes.

At least five idiopathic genes are known, two X-linked and probably three autosomal dominant (see Table 1). The discovery of the FRMD7 and CASK genes has opened up the exciting possibility of understanding the molecular development of idiopathic IN. These genes are part of the network which appears to control synapse development in the oculomotor areas of the brain and retina.

Understanding infantile nystagmus

The medical model

There are two fundamentally different ways to understand IN: 1) the medical model; and 2) the adaptationist approach.

In the medical model, it is assumed that an oculomotor abnormality gives rise to nystagmus, which then causes visual impairment due to poor foveation. The developmental reason(s) for this abnormality is not clear, but typically not asked. It is assumed that eliminating or reducing the nystagmus should improve vision. Over the years, many interventions have been claimed to improve VA including flashing lights (intermittent photic stimulation), after-image feedback, tactile feedback via contact lenses, auditory biofeedback, acupuncture, muscle surgery, drug therapy and others. One of the difficulties has been the subjective nature of VA and the sensitivity of IN to mental state. In a pioneering randomised placebo controlled trial, Evans et al. demonstrated that VA can improve through practice or reduced anxiety by simply revisiting the clinic, and a target therapy may not be significantly different from placebo. Despite the enthusiasm of their protagonists, most therapeutic claims have not undergone rigorous testing.

To circumvent the subjective nature of VA, Sheth et al. developed an objective performance measure based on an

Table 1 A few examples of genes known to be associated with infantile nystagmus. Note that other genes also exist for these conditions, and many other conditions and genes can also be associated with infantile nystagmus.
individual’s foveation periods called a nystagmus acuity function (NAF). Subsequently, a number of variants have emerged – NAF,29 NAFX,30 NOFF,31 and ANAF.32 The idea is that ‘potential’ VA can be predicted by objective measurement of the waveform. The implicit assumption is that, if the nystagmus could be eliminated, underlying vision would be normal (which is implying the existence of the ‘ideal’ idiopath), and hence not applicable to sensory defect IN.

In the only randomised control trial since Evans and co-workers, McLean et al.33 investigated the effects of the neuroactive drugs, memantine and gabapentin, on idiopathic and sensory IN. They measured subjective VA and NAFX and found that the drugs, but not the placebo, improved on NAFX measures for both patient groups equivalent to 0.1-0.15 logMAR over an eight-week period. That is, the nystagmus waveform was susceptible to the drugs for both groups. The improvement in subjective VA was similar for the idiopathic group, but negligible for the sensory group. Presumably, the underlying sensory defect, rather than the nystagmus, was the limiting factor.

In the author’s view, nystagmus acuity functions are not a substitute for subjective outcome measures. They should be considered only as ‘figures of merit’ of nystagmus waveforms, and not VA per se. They assume the ideal idiopath without any amblyopia. Nystagmus acuity functions have only been calibrated against subjective VA across individuals, not within an individual. Thus, it is possible to select idiopaths with different subjective VAs and waveforms and correlate them, but this may not necessarily apply within an individual (see later).

Even in idiopaths, the effect of waveform manipulation on subjective VA has been disappointing. In biofeedback studies, waveforms can be changed but again VA improvement is still of the order of one line of acuity.44 One possible reason is that mechanisation of waveform are inherently limited, but the adaptationist approach provides an alternative view.

**Adaptationist approach**

In the adaptationist approach, the nystagmus is postulated to emerge as a developmental response to visual deprivation. There is no ‘lesion’; instead the oculomotor system adapts to oscillate the eyes to generate image motion because it improves contrast sensitivity in infancy.35 Waning of the critical period and/or amblyopia perpetuates the nystagmus. The underlying idea is that eye movements maximise visual contrast, which is determined by the spatio-temporal contrast sensitivity function (CSF) – not just the spatial CSF. Even in normal adult vision, small eye drifts and microsaccades prevent Troxler fading of high spatial frequencies.36 At low spatial frequencies, contrast is maximised by more rapid image movement.37 During early infancy when the fovea is differentiating and smooth pursuit movement.37 During early infancy when the fovea is differentiating and smooth pursuit movements maximise visual contrast, possibly in different ways.35 The nystagmus becomes permanent because of reduced plasticity with time (waning sensitive period) and amblyopia in the meridian of the nystagmus.35 This could prevent future development of high spatial frequency sensitivity, and hence lock-in the nystagmus permanently.

The prolonged post-natal development of smooth pursuit may be a developmental strategy to prevent nystagmus from developing in normal infants phenotype but, if for any reason, afferent development is delayed relative to oculomotor development, then nystagmus could develop and become permanent. Thus, sensory developmental delay may be the ultimate cause of IN, which is supported empirically, even in infant idiopaths.42

The implication of this adaptationist approach is that the nystagmus is tuned to the visual deficit starting in infancy. Wiggins et al.43 have shown that increasing visual demand (without stress) actually prolongs foveation periods in adults, implying at least some degree of plasticity. It follows that the nystagmus waveform might adapt to each individual’s visual ability. Thus, an idiopath with near normal VA would generate a waveform with foveation periods which are longer than for an individual with lower VA. Thus, a correlation between foveation periods and VA would emerge across, but not necessarily within an individual because VA may be limited by amblyopia or other undetected sensory defect; this may explain why manipulating the waveform has only minor or temporary effects on VA. It is the underlying visual defects which need to be addressed. For idiopaths, this may mean early intervention to prevent amblyopia.

**Clinical testing**

The investigation of nystagmus is challenging for any clinician. There is no substitute for clinical acumen and experience, and onward referral pathways (ophthalmic and neurological) should exist. There are two stages which require rather different skillsets. The first is to identify the type of nystagmus; the second is to find any underlying visual or neurological explanation.
**Nystagmus**

Without eye movement recording, it is not possible to identify IN with absolute certainty. With recording, however, a horizontal waveform with accelerating slow phases is definitive of IN (exceptions are extraordinarily rare). It is important to record the nystagmus in lateral gaze as this usually induces clear IN waveform, and also in vertical gaze as nystagmus usually remains horizontal. Oscillopsia is usually absent, but may be reported in far lateral gaze or under stress, when the nystagmus is more intense than usual (for the patient). The nystagmus may be memorably intense or remarkably quiescent, but this should not influence further investigations. Nystagmus that remains fine pendular, vertical, or asymmetric should be considered suspicious of a neurological type of nystagmus, but IN cannot be excluded. A history of abnormal vision does not preclude a neurological cause for nystagmus.

The horizontal optokinetic response is usually chaotic, with no recognisable optokinetic nystagmus (OKN). Some have argued that OKN reverses, but in the author’s experience, this is the patient’s own IN, in which the null has shifted. Typically, vertical OKN is normal and an important sign as it indicates the presence of some degree of underlying vision. A definitive identification of IN does not distinguish between sensory defect and idiopathic IN.

Strabismus is common, and monocular recording is important to detect any additional latent component.

**Precipitating factors**

Medical history of nystagmus onset is invaluable, but can be vague, especially for first-borns or older patients. If family members are affected, a family tree should be physically drawn. Patterns of inheritance can narrow down possibilities, but they do not distinguish between sensory and idiopathic IN. In X-linked pedigrees, notably FRMD7, females can be affected. Genetic counselling should be offered only after a complete investigation has been made.

 Structural abnormalities including transilluminating irides, cataracts, corneal opacities and foveal hypoplasia should be investigated. Pale pigmentation incongruent with genetic family members should be noted. Other signs such as photophobia, poor night vision, high myopia, paradoxical pupils, and eye poking/rubbing are suggestive of an underlying retinal problem.

 Electrophysiological investigations are essential when no sensory defect can be otherwise identified. The electoretinogram (ERG) can reveal subtle retinal disorders such as conerod dystrophies and congenital stationary night-blindness. Cortical VEPs are useful for detecting abnormal cortical projections due to chiasmic misrouting including albinism (ocular and ocurolcutaneous) and achiasma. Without VEPs, it is quite remarkable how frequently ocular albinism is misdiagnosed as idiopathic.

**Management**

Treatment options are limited, but the main goals are to:

- Improve vision (usually as measured by VA)
- Reduce an abnormal head posture by shifting the null
- Correct for any strabismus.

It is often claimed that reducing the intensity of nystagmus is a goal in itself. However, this is only useful if it has tangible benefits to the patient.

 Refractive errors are common in IN, and all patients require cycloplegic refraction and precise correction. Contact lenses are preferable where feasible, as they move with the nystagmus. Prisms can be used to shift the null, but tend to be large and unwieldy.

 Surgical goals include correction for strabismus, surgery for abnormal head posture, broadening the null region (tenotomy), artificial divergence surgery, reducing nystagmus intensity, and cosmesis. More than one objective can often be achieved simultaneously.

 Surgery for a head posture is contraindicated if PAN is present, but thorough work-up, including nystagmus recording, is needed. It is important to explain the realistic benefits to the patient (and parents), as well as risks.

 Parents should be told explicitly that their infant will have nystagmus for life, with lifelong social consequences – prevarication is not helpful. The author recommends that parents should consult a local support group, such as the Nystagmus Network in the UK, which has a wealth of experience in the social, educational and occupational aspects of living with IN.

**Conclusion**

IN is specific type of nystagmus usually due to an afferent developmental anomaly and is irreversible. It is important to correctly identify the nystagmus and any underlying visual defect, and to offer genetic counselling, when appropriate. Treatment options are limited with a gain of one or two lines in some, but often with no improvement. Supporting children and families for life-long nystagmus is crucial, but rarely considered by professionals. Each year in the UK, 1,000 infants develop infantile nystagmus for life.