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Visual perception in infantile nystagmus

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Abstract

Infantile nystagmus (IN) is often found in conjunction with afferent visual system pathology, but even in isolated cases, visual acuity (VA) is usually reduced. Most individuals with IN do not experience oscillopsia (illusory motion of the world). The presence of visual stability, despite constant eye motion, provides a uniquely dynamic perceptual scenario. Recent advances have demonstrated that VA alone is insufficient to fully explain the subjective perceptual experience of IN. The purpose of this review is to provide a clinical perspective on recent developments in the field, and summarise the novel techniques being used to gain a better understanding of the impact of treatment on visual function in IN.

Introduction

Infantile nystagmus (IN; also known as infantile nystagmus syndrome or [formerly] congenital nystagmus) is a regular, repetitive movement of the eyes, predominantly in the horizontal axis. It usually develops within the first six months of life, causing ocular oscillations that are constant and persist throughout life (Gottlob et al. 1990).

IN often occurs in conjunction with pathology of the visual system such as albinism, achromatopsia or infantile cataracts. See Leigh and Zee [2006] for a complete list of associated conditions. IN can also occur apparently in isolation, in which case it is termed idiopathic infantile nystagmus (IIN). Although frequently associated with some form of visual deprivation, the extent of a causal relationship is still unknown. Indeed, it is unclear whether or not rectifying visual problems promptly can prevent the condition developing. For example, over 40% of children receiving operations for infantile cataracts have been shown to develop IN postoperatively, regardless of when the surgery is performed (Young, Heidary and VanderVeen 2011; Young, Heidary and Vanderveen 2012). IN is significantly

more common in white Europeans than in Asian populations, and, based on a large scale study of the population of Leicestershire, the prevalence of IN has been estimated at 14 in 10,000 (Sarvananthan et al. 2009).

It is possible, although rare, for IN to appear only transiently in infancy, usually beginning and regressing in the first year of life (Good, Hou and Carden 2003). The authors of this study point out that not all forms of regressing nystagmus should be diagnosed as spasmus nutans syndrome (a condition causing high frequency, low amplitude nystagmoid oscillations that ceases spontaneously, usually by the second year of life [Gottlob, Wizov and Reinecke 1995]). The mechanism for regression in these cases is unknown, but may ultimately provide valuable clues as to whether and how early intervention might impact on IN.

Visual acuity (VA) is usually reduced in individuals with IN, with the magnitude of the reduction being related to the underlying pathology (typically an average of 0.67 logMAR in individuals with albinism and 0.55 logMAR in patients with a comorbid ocular pathology). However, even in cases of IIN, VA is moderately reduced, typically to around 0.35 logMAR (Abadi and Bjerre 2002). The reduction of VA in cases of IN with no associated visual pathology begs the question as to whether nystagmus is responsible for poor VA, or whether an underlying diagnosis has not been ascertained in these patients. It is worth noting that, whilst there is usually a moderate reduction in visual function with IIN, cases have been reported with VA better than -0.10 logMAR (Abadi and Bjerre 2002).

Waveforms

IN can be characterised by its waveform, representing eye position over time, which depicts the frequency, amplitude and pattern of the oscillations. Nystagmus intensity describes the

amplitude multiplied by the frequency, and is often used as a quantitative metric. Figure 1 shows the clinically significant characteristics of a typical nystagmus waveform. Note that, in horizontal eye movement traces, an upward displacement conventionally indicates a rightward movement of the eye.

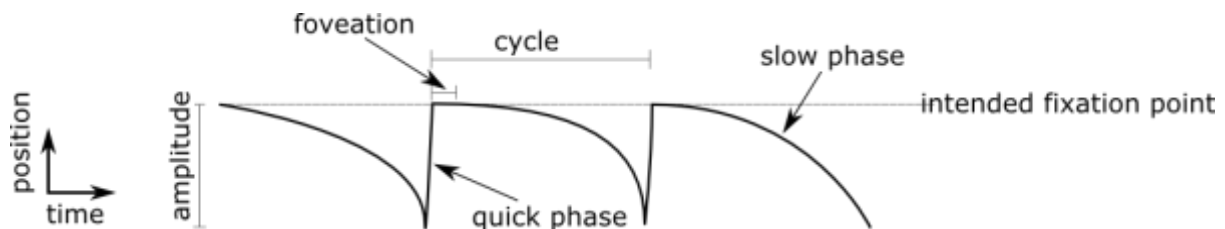


Figure 1: The components of a nystagmus waveform (type JRE_F). Frequency is inferred from cycles per time unit.

By definition, foveations in a nystagmus waveform are regular reductions in velocity during which the fovea is directed towards the point of regard. The actual parameters that define the start and end of a foveation period are somewhat ambiguous; the exact definition remains a subject of debate. Typically, it is defined as those portions of the waveform during which the eyes are moving at 4°/s or less (Dell’Osso et al. 1992; Cesarelli et al. 2000; Bifulco et al. 2003).

The three major types of IN waveform are *pendular* (three subtypes), *jerk* (eight subtypes), and *dual jerk* (Dell’Osso and Daroff 1975). The waveform in Figure 1 shows both quick phases and slow phases. This indicates a jerk type movement. A nystagmus quick phase is generally assumed to be equivalent to, and generated by the same neural circuitry as, a saccade (Ron, Robinson and Skavenski 1972; Garbutt, Harwood and Harris 2001; Harrison et al. 2015), while a slow phase is a drift from fixation. Note that IN slow phases always accelerate; the presence of accelerating slow phases is considered diagnostic of the condition (Abadi and Bjerre 2002). Pendular waveforms have no quick phases, but may be

asymmetrical or contain foveating saccades superposed on the pendular waveform (Dell'Osso and Daroff 1975).

Figure 2 shows the 12 'classical' waveforms of IN as described by Dell'Osso and Daroff (1975). Many individuals with nystagmus will exhibit multiple waveforms, with different types being elicited at different times, or by varying gaze angle (Davis and Smith 1971; Dell'Osso and Daroff 1975).

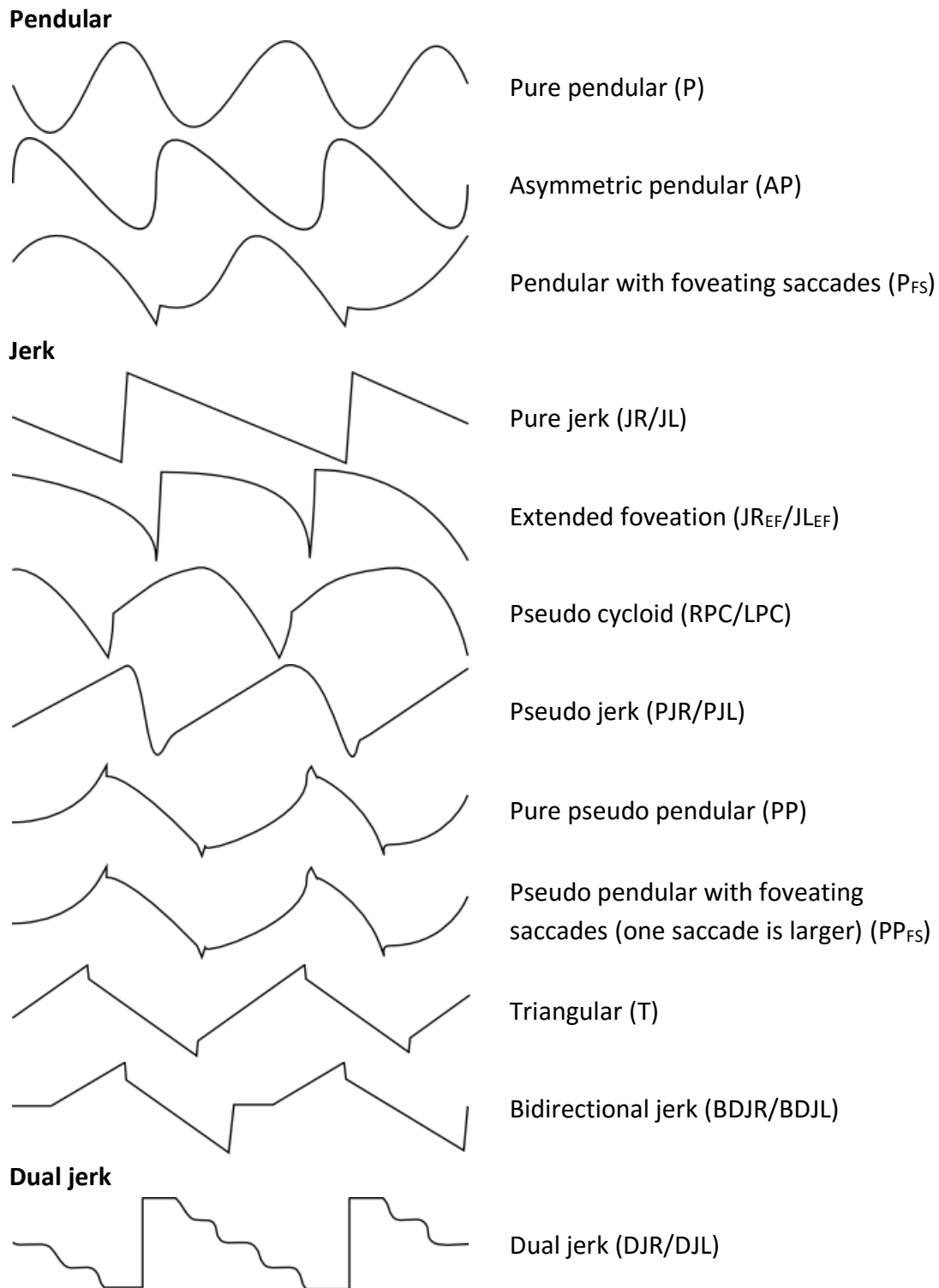


Figure 2: The 12 waveforms found in IN according to Dell'Osso and Daroff (1975). Commonly used acronyms are given in parentheses (R = right; L = left).

The parameters of IN waveforms vary enormously between individuals; frequencies have been recorded ranging from 0.5-8 Hz (most are 2-3 Hz), whilst amplitudes can vary from 0.3-15.7° (typically 6-8°) (Abadi and Bjerre 2002). The average eye velocity throughout a

nystagmus waveform is $14^{\circ}/s$ (Bedell 2000), and the peak velocity of the slow phase has been shown to vary from $20-180^{\circ}/s$ (Abadi and Worfolk 1989).

Visual and oculomotor development in infantile nystagmus

The term infantile nystagmus was first proposed in 1988 (Reinecke, Guo and Goldstein) due to the observed inaccuracy of the term congenital nystagmus. Of the 35 cases studied in their report, only three were noted to have had nystagmus in the first two weeks of life. Gottlob et al. (1990) estimate the average age of onset of IN to be 1.9 months. Nystagmus typically begins with a large-amplitude triangular waveform (without foveation periods), and the waveform typically shifts to a pendular type before $1\frac{1}{2}$ years of age (Reinecke, Guo and Goldstein 1988). One case study has reported longitudinal eye movement recordings during the development of IN, in an infant considered highly likely to develop IN. Square wave jerks were observed at seven weeks of age, followed by pendular nystagmus at eight weeks, and jerk at 10 weeks. The waveform returned to a pendular type at 14 weeks (Gottlob 1997). Foveation periods usually first develop at around 35 months of age, and individuals whose waveform evolves more rapidly are more likely to have better VA later in life (Felius and Muhanna 2013). However, the 56 children documented in this study came from a total of 105 with IN; only these 53% exhibited a distinct waveform evolution from pendular to jerk type (Joost Felius, personal communication 2013). As yet, it is not known whether this correlation indicates that delayed waveform evolution leads to poor VA, or if poor underlying VA leads to delayed waveform evolution.

The rate of development of VA in IN has been shown to be similar to that of normally sighted infants; i.e. despite an infant with IN having a relatively reduced VA both at the time

of diagnosis and visual maturity, the rate of visual development progresses as normal (Weiss and Kelly 2007; Fu et al. 2011).

Pathogenesis

There is currently no consensus on the exact cause of IN (Gottlob and Proudlock 2014), although the strong association between congenital visual pathology and IN suggests that visual deprivation plays a role in its development. However, the types of pathologies observed are hugely variable, and further to this, in IIN there is no appreciable pathology evident (at least with current diagnostic techniques) other than nystagmus oscillations.

Discussion of the various pathogenic theories for IN are beyond the scope of this article. For more information, the reader is directed to works published by Optican and Zee (1984), Broomhead et al. (2000), Jacobs and Dell'Osso (2004), Harris and Berry (2006), Chen et al. (2014) and Brodsky and Dell'Osso (2014).

Idiopathic infantile nystagmus

IIN can only be diagnosed by exclusion, i.e. after all other possible causes and associated conditions are ruled out¹. Detailed electrophysiological testing is essential to rule out many of the conditions known to be associated with nystagmus (Casteels et al. 1992). Thirty per cent of people with IN are idiopathic (Lorenz and Gampe 2001). Although it is possible that nystagmus is the primary defect in IIN, it remains a possibility that some other pathology of the visual pathway remains undiagnosed in these individuals. Significant refractive error is more common in individuals with IIN, perhaps indicating poor emmetropisation (Sampath

¹ Since the term *idiopathic* refers to a condition with an unknown cause, one might consider that *idiopathic infantile nystagmus* ought to refer to *all* forms of IN. Despite the fact that sensory defects have not been proven to *cause* IN, only IIN is referred to as being 'idiopathic'. Brodsky and Dell'Osso (2014) have recently proposed the phrase *isolated IN* as a more appropriate term for this group of patients.

and Bedell 2002). High ametropia and/or strabismus associated with nystagmus in the absence of other ocular pathology is still classified as IIN.

Visual acuity in idiopathic infantile nystagmus

In a sample of 139 individuals with IIN, the average clinical VA was 0.35 logMAR (Abadi and Bjerre 2002), which is clearly much lower than the VA of normally sighted individuals (usually -0.14 – 0.00 logMAR [Elliot 2003]). Since there is no detectable visual pathology aside from the nystagmus itself in IIN, there are three possible explanations for the reduced VA:

1. An undetected pathology of the visual system exists
2. Motion blur from the eye movements actively degrades visual performance
3. Amblyopia develops as a result of visual deprivation during the critical period of visual development

Each of these possibilities are discussed in turn below.

Undetected pathology?

Since, by definition, IIN describes the absence of any other known pathology, if a common cause were to be discovered for this group of patients, IIN would no longer exist as a classification. In a recent study, 15 patients with an existing diagnosis of IIN underwent extensive medical testing to identify comorbid pathologies. The study resulted in 13 of these participants being re-diagnosed, thus removing their idiopathic label (Holmström et al. 2013). The new diagnoses included albinism, foveal hypoplasia, achromatopsia, rod-cone dystrophy and pathological myopia. However, participants in this study were recruited from a low vision centre. Since this would involve individuals with particularly poor VA (a feature that is less common in IIN), this study may not represent the true incidence of detectable

visual system pathology in cases of IN. Opinions differ as to whether or not truly isolated IIN exists; whilst improvements in medical diagnostics are leading to a decrease in cases, some argue that IN may be caused by abnormalities in the smooth pursuit system, without necessarily requiring an associated visual system pathology to be present (Jacobs and Dell'Osso 2004).

Recent genetic work has identified a restriction in expression of the four point one ezrin, radixin, moesin domain containing 7 (FRMD7) gene in many individuals with X-linked IIN (Tarpey et al. 2006). These mutations account for approximately 40-50% of X-linked cases of IIN, and 3-5% of isolated cases (Jay Self, personal communication 2014). Individuals with the mutation have been shown to express different phenotypical characteristics to those without it; for example, nystagmus amplitude tends to vary more with gaze angle in FRMD7-related IIN, whereas anomalous head postures are more prevalent without FRMD7 mutations (Thomas et al. 2008). In addition, individuals with FRMD7-related IIN are more likely to express pendular waveforms with higher frequencies than individuals with comorbid albinism (Kumar et al. 2011). All of these variations suggest that FRMD7 mutations represent a unique subclass of nystagmus, or a subtle afferent visual pathology.

If one assumes that there are undiagnosed pathologies underlying IIN, then hope lies in the possibility that emerging clinical technologies will elucidate the exact causal nature of IIN.

Motion blur?

One previous study examining the effects of nystagmoid image motion on the vision of visually normal subjects found a decline in VA at velocities above 3°/s (Chung and Bedell 1995). The average eye velocity in IN is 14°/s (Bedell 2000); it has therefore been suggested that the presence of motion smear during nystagmus slow phases might contribute to the

poor VA observed in these patients (Chung 2012). Indeed, individuals with high intensity nystagmus typically have poorer VA (Theodorou 2006). Chung, LaFrance and Bedell (2011) found that normally-sighted individuals presented with an image moving in a nystagmoid fashion have poorer VA if the image is shown continuously, due to motion blur during the non-foveating periods of the simulated waveform. One might therefore expect VA to be similarly degraded by motion blur during the entire slow phase in individuals with IN. However, a recent study by Dunn et al. (2014) has revealed, by measuring VA under tachistoscopic conditions (i.e. flashed illumination), that motion blur does not contribute significantly to the poor VA in IIN. The results of this study indicate that there is a fundamental, unresolvable impairment to VA in adults with IIN. The implications of this finding for treatments are discussed later in this article.

Amblyopia?

It is possible that visual deprivation during the critical period of visual development (i.e. amblyopia) could be responsible for reduced visual function in adults with IIN. Felius and Muhanna (2013) found that slow evolution of the nystagmus waveform in infancy (from a pendular to jerk type) increases the likelihood of poor VA later in life, presumably due to deprivation amblyopia. However, the authors admit that the inverse might also be true; that poor VA could lead to slow evolution of the nystagmus waveform.

VA has been shown to be further reduced in IN in the presence of visual crowding, an effect that is usually suggestive of amblyopia (Chung and Bedell 1995; Huurneman and Boonstra 2013). In addition, normally sighted individuals, presented with an image moving in a similar fashion to horizontal jerk nystagmus (through the use of a galvanometer-mounted mirror), have been shown to have higher contrast sensitivity than most individuals with IIN (Bedell

2006). This provides further evidence that there is a true visual impairment in IIN, beyond motion blur from the eye movements.

Meridional amblyopia

Individuals with horizontal IN typically have worse VA for vertically oriented gratings than horizontal gratings (Abadi and Sandikcioglu 1975; Jones 2011; Loshin and Browning 1983; Bedell and Loshin 1991). It has been suggested that the nearly constant image motion in nystagmus causes meridional amblyopia to develop (Bedell and Loshin 1991). Meridional amblyopia can also develop in response to uncorrected astigmatism (Harvey 2009). The incidence of corneal with-the-rule astigmatism is much higher than normal in IN (Dickinson and Abadi 1984). In Abadi and Bjerre's study (2002), 57% of individuals with nystagmus had astigmatism exceeding 2.00 DC. The level of astigmatism in IIN, and IN associated with albinism, is inversely correlated with corrected VA (Bedell and Loshin 1991). A recent retrospective study found a high prevalence of astigmatism (mainly with-the-rule) in 488 patients with IIN, with a tendency for this to increase with age (Fresina et al. 2013).

Oscillopsia

Oscillopsia describes the perceptual experience of the visual scene oscillating back and forth (Brickner 1936). Acquired nystagmus often causes oscillopsia (Lee and Brazis 2006).

However, despite experiencing similar retinal image motion, individuals with IN very rarely describe such symptoms. It is believed that perceptual stability is achieved by efference copy of the eye movements effectively cancelling out the perception of motion (Bedell and Bollenbacher 1996; Bedell 2000). This is currently the most widely accepted theory, and is corroborated by the fact that stabilising an image on the retina of an individual with IN causes oscillopsia (Leigh et al. 1988).

Can visual function be improved?

There is a direct relationship between the parameters of nystagmus waveforms and VA; i.e. those with higher intensity nystagmus and shorter foveation periods tend to have poorer VA (Dell’Osso and Jacobs 2002). As a result, it has long been assumed that improving the parameters of the nystagmus waveform ought to lead to improvements in VA.

This relationship has led to the development of a number of metrics (known as NAF, NAFX, NOFF, NAEF and ANAF), designed as tangible ways of tracking changes in visual function when normal measures of VA fail to find a difference (Sheth et al. 1995; Dell’Osso and Jacobs 2002; Feliuss et al. 2011; Cesarelli et al. 2000; Yao, Tai and Yin 2014). They require the use of an eye tracker to record the eye movements, and provide an objective outcome measure by collapsing various waveform characteristics into a single number. These metrics (especially NAFX) are often used to demonstrate changes in nystagmus, for example, before and after surgical or medical intervention (Hertle et al. 2004; McLean et al. 2007).

Nystagmus quantification functions are designed to act as predictors of VA, and are based on the fact that their values correlate with the VAs of patients with IN. However, these correlations are only evident when examining between-subject data – improvement in a nystagmus function within any single individual has been shown not to correlate with VA (Wiggins 2007; Erichsen et al. 2013). This suggests that the relationship between VA and motor characteristics may have been misinterpreted: perhaps it is not a poor waveform that leads to poor VA, but poor VA that leads to adoption of a poorly formed waveform.

IN is a lifelong condition: no ‘cure’ has yet been discovered. However, there are a large number of therapies that have been shown to be effective at modifying waveforms or correcting abnormal head postures. Some of these treatments have demonstrated modest

improvements in visual function. However, these changes are rarely significant in large studies. Treatment options include prism therapy, botox injections, surgery, contact lenses, and medications. For a complete summary of the options available, the reader is directed to a review article by Thurtell and Leigh (2010).

Of the many treatments that have been shown to reduce nystagmus intensity, very few have ever shown significant improvements in VA, and of those that have, none measured VA using a strict psychophysical protocol (i.e. forced choice staircase procedure or similar). It is worth noting that all previous studies of IN that have involved the use of such techniques have failed to detect a significant change in VA following waveform modification, whether through altering the gaze angle (i.e. using the nystagmus null zone [Ericksen et al. 2013; Yang et al. 2005]), or by inducing stress, (which has an adverse effect on the waveform [Cham, Anderson and Abel 2008; Jones et al. 2013]). Despite this, many individuals with nystagmus prefer to turn their head to use their null zone for viewing (Abadi and Bjerre 2002), and it is not uncommon following treatment for individuals with IN to report subjective improvements in their perceived vision where VA measurement fails to detect a change (Hertle et al. 2003).

Individuals with nystagmus often complain of worsened vision in stressful situations and improved vision during near work (Wiggins 2008), despite evidence that VA does not improve in these circumstances (Dickinson 1986; Jones et al. 2013). Clearly, VA is neither a complete nor a consistent measure of visual performance in IN.

While the increase in intensity brought on by stress does not have an adverse effect on VA, it does significantly increase the time taken by participants with IN to respond to a visual stimulus (Jones et al. 2013). In addition, children with IN have been shown to take longer to

fixate on cartoon and high contrast stimuli as compared to controls (Pel et al. 2011; Pel et al. 2013). It seems that visual function in IN is somehow slowed. A recent study has confirmed that this 'slow to see' phenomenon is due to an increase in the time taken to move the eyes towards objects of interest (of around 60 ms), and that cognitive visual processing speed is not impaired (Dunn et al. 2015). Therefore, when considering the visual abilities of a patient with nystagmus, temporal aspects of vision should be taken into consideration as well.

New methods for visual assessment

Recognising the inadequacy of VA, alternative tests of visual function have been proposed, which assess the temporal aspects of the condition. These methods are outlined below.

Restricted viewing time

Yang et al. (2005) proposed the use of optotypes with a restricted viewing time to quantify visual function in IN. This takes the format of single surrounded optotype letters that are displayed for 550 ms on a computer screen. They found that time-restricted VA is significantly reduced when viewing out of the null zone as compared to non-time-restricted VA. Restricted viewing tests may therefore prove to be useful when assessing patients with IN.

A 2012 study of surgical interventions in IN (ElKamshoushy et al. 2012) used a similar VA measure to Yang et al.'s 2005 study. To validate surgical methods, they presented three tumbling Es for 100 ms each. If participants could correctly identify the orientation of at least two of the optotypes, the test ended. If not, new tumbling E optotypes were presented for 200 ms each. This process continued, with presentation time increasing by 100 ms each time, until at least two optotypes were correctly identified. Following surgical intervention, the authors of this study found a mean improvement in recognition time of 0.3 seconds.

Moving optotypes

Recognising that people with IN are slow to redirect their gaze toward moving targets, Hertle et al. (2002) designed a test which involves measuring the time taken to respond to the orientation of single moving tumbling E optotypes at various spatial frequencies (0.60 – 1.04 logMAR) and speeds of movement (10 – 30°/s). The study concluded that this might be a useful test of visual function in IN.

Conclusions

Nystagmus is in a unique class of visual pathology, due to the fact that visual input to the retina changes from moment to moment. When an individual with nystagmus views an object, the image alternates between the fovea and extrafoveal retina. Despite this, the majority of patients with IN are unaware of their involuntary eye movements (i.e. they do not suffer from oscillopsia). Vision simply cannot be optimal at any given moment if the object of regard is not imaged on the photoreceptor-rich fovea. As such, proper assessment of a patient with nystagmus has to take into account the temporal aspects of the visual experience.

While many patients with IN are labelled as 'idiopathic', as medical technology and diagnostic techniques continue to improve, we are seeing fewer cases of IN without a known associated condition. Although there are still individuals for whom this term can justifiably be applied, as a diagnosis by exclusion, the 'idiopathic' label should only be given after a patient has undergone an exhaustive clinical workup, including eye movement recording, electrophysiology, optical coherence tomography, and genetic testing. There is a growing consensus within the literature that nystagmus is a response of the visual system to moderately poor binocular VA, rather than poor VA being a direct result of nystagmus.

Measurement of VA in the clinic is typically undertaken with a letter chart, and, despite the best efforts of clinicians to give patients plenty of time to read the chart, there is an implicit 'need to move on' to the next test. Recent studies have demonstrated that, under controlled conditions and without the pressure of time, VA is unlikely to improve significantly (if at all) following treatment. Despite this, patients will often report 'improved vision' following treatments, and also prefer to use their null zone.

VA is not a complete measure of visual ability; other measures of visual function may be required to provide a complete understanding of how an individual with IN sees the world. The use of restricted-duration optotype testing or other measures of visual 'timing' may prove to be a more accurate monitoring tool in the future – research into this area is ongoing.

Summary

Infantile nystagmus (IN) is a complex and variable condition, which is still very poorly understood. Although the condition often occurs in conjunction with another pathology of the visual system, visual acuity is usually reduced, even in those without comorbid pathology. In adults with IN, visual acuity may be fundamentally limited, and relatively insensitive to treatment. Other aspects of visual function, such as the time taken to interpret dynamic visual information, appear to be more modifiable. Clinical tests incorporating measures of 'time to see' may provide a better means for understanding the visual experience of IN.

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