

An Update on Nystagmus



Rebecca McLean

is conducting her PhD on nystagmus at the Ophthalmology Group, University of Leicester. Her particular research interests are the treatment of nystagmus and measuring quality of life for those who have nystagmus.



Irene Gottlob

Irene Gottlob graduated and completed her ophthalmology training in Vienna, Austria. She was Head of Department of Strabismus and Neuro-Ophthalmology in St Gall, Switzerland and subsequently appointed as Chair in Ophthalmology at the University of Leicester, UK, with a particular interest in nystagmus. Email: ig15@le.ac.uk

Correspondence to:

Rebecca McLean,
Ophthalmology Group,
University of Leicester,
Faculty of Medicine & Biological
Sciences,
Robert Kilpatrick Clinical Sciences
Building,
Leicester Royal Infirmary,
PO Box 65, Leicester LE2 7LX, UK.
Tel: +44 (0)116 258 6291.
Email: rjmi19@le.ac.uk

Nystagmus is an involuntary to and fro movement of the eyes. Pathological nystagmus can be classified into infantile nystagmus (IN), which emerges in the first six months of life, and acquired nystagmus (AN), which develops later.¹ AN can be due to peripheral and central vestibular disorders or caused by neurological disease. IN can be of an idiopathic nature or associated with other visual disorders such as albinism, retinal disease, low vision and neurological childhood diseases. Nystagmus causes decreased visual acuity due to movement of images away from the foveal area of the retina. The prevalence of nystagmus is reported to be 24/10,000² and the impact of nystagmus is significant, with nystagmus scoring worse than in other visual disease, such as age related macular degeneration, on visual function questionnaires. In general, mechanisms underlying AN are better understood than those behind IN. We give a summary of the recent literature in the field of nystagmus.

Acquired nystagmus

The more common forms of acquired nystagmus are downbeat nystagmus (DBN), upbeat nystagmus (UBN), acquired pendular nystagmus (APN), periodic alternating nystagmus (PAN) and gaze evoked nystagmus (usually causes very few problems in primary position).¹ Animal experiments have provided evidence as to the underlying mechanisms for AN and these experiments have also helped to identify useful therapeutic interventions. Each form of AN has distinguishing characteristics that can be influenced by the aetiology.

PAN consists of a horizontal jerk nystagmus that periodically switches direction and is probably the best understood form of nystagmus. Results from animal studies have suggested that PAN may arise from the disinhibition of the optokinetic vestibular system.³ The treatment reported to reduce PAN is baclofen. However these results are based upon case reports and it is important to note that to date no large randomised controlled trials that assess the efficacy of baclofen use in PAN have yet been performed.

Animal studies have suggested that DBN (a vertical nystagmus with a slow drift upward and fast downward phase) is related to vertical gaze-velocity cerebellar Purkinje cells in the flocculus and paraflocculus. This has been more recently confirmed with functional magnetic resonance imaging in humans with DBN, who showed reduced activity of both floccular lobes during downward pursuit.⁴ Furthermore, computational model simulation of the effect of extensive loss of floccular Purkinje cells resulted in ocular motor features that are typically associated with DBN.

The most effective pharmacological treatments for DBN have been reported in studies administering the potassium channel blockers 3,4-diaminopyridine (3,4-DAP) and, more recently, 4-aminopyridine (4-AP). As cerebellar Purkinje cells are potassium channel-rich it has been thought that enhancing Purkinje cell activity would restore the inhibitory influence of the cerebellum upon vertical eye movements to a normal level. A recent randomised controlled trial has compared the use of 10mg doses of 3,4-DAP and 4-AP and concluded that although both 3,4-DAP and 4-AP significantly reduced DBN, 10mg doses of 4-AP led to a more pronounced decrease in the slow phase velocity of DBN than equivalent doses of 3,4-DAP⁵ (Figure 1). An alternative hypothesis for the mechanism behind 4-AP is that it restores the diminished precision of the Purkinje cells pacemaking ability by prolonging the action potential. 4-AP may also be useful for upbeat nystagmus (UBN) by increasing the excitability of the cerebellar Purkinje cells.

APN is a sinusoidal movement that can occur in the horizontal or vertical plane but often has both horizontal and vertical components and most commonly occurs in disorders of central myelin (often multiple sclerosis [MS]) and vascular disease (syndrome of oculopalatal myoclonus). These two conditions result in APN that differs in clinical features. In a direct comparison of the clinical features of APN associated with MS and APN associated with syndrome of oculopalatal myoclonus the oculopalatal group showed a nystagmus of a significantly higher mean amplitude and mean peak velocity with a lower mean frequency than that of the MS group.⁶ The oculopalatal group also presented with more disconjugacy and irregularity of APN. These distinct features have led to separate models for their pathogenesis. For APN in demyelinating disease it is suggested that the oscillations arise in the eye movement neural integrator which ensures steady gaze.¹ For APN related to oculopalatal tremor the main pathologic finding is hypertrophic olivary degeneration. It is hypothesised that deafferentation of the inferior olive gives rise to modification of connexion junctions between adjacent neurons leading to abnormal oscillatory neural activity. Successful pharmaceutical therapy for APN has been reported with gabapentin and memantine. Two randomised crossover trials, administering memantine (40-60mg) and gabapentin (1200mg) for APN due to multiple sclerosis and oculopalatal tremor, have recently been reported.^{7,8} These trials similarly recommend the use of both gabapentin and memantine as safe and effective methods of improving APN, oscillopsia and visual acuity. Furthermore it is

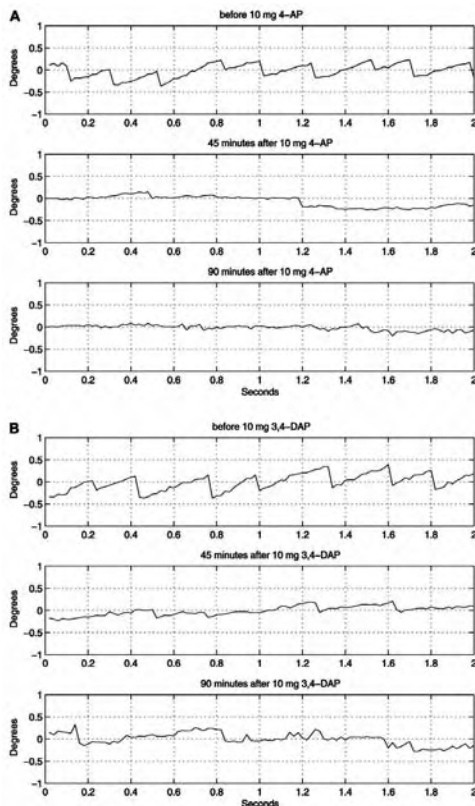


Figure 1: Eye movement recordings in one patient with downbeat nystagmus prior to administration and 45 minutes and 90 minutes following administration of 4-Aminopyridine and 3,4-Diaminopyridine (B). Reproduced from: Comparison of 10-mg Doses of 4-Aminopyridine and 3,4-Diaminopyridine for the Treatment of Downbeat Nystagmus. *Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society* 2011.

possible to analyse the effects drugs have to test models of nystagmus; analysis of the effects gabapentin and memantine have on APN is reported to support the hypothesis of APN pathogenesis models.⁹

Infantile nystagmus

Infantile nystagmus (IN) can be idiopathic or associated with other visual disease such as albinism, retinal disease and low vision, for example congenital cataracts. IN develops within the first few months after birth and individuals can be singly affected or have a strong family history. A gene (FRMD7) has recently been discovered to be the cause of most X-linked idiopathic familial nystagmus.¹⁰ Further studies have shown that FRMD7 is expressed in the ventricular layer of the forebrain, midbrain, cerebellum primordium, spinal cord, and also the developing neural retina. Although the function of the gene is not yet known FRMD7 has been shown to be involved in neurite outgrowth and development.¹¹

IN is usually of either a pendular waveform or a jerk waveform with an accelerating slow phase occurring in the horizontal plane that is bilateral and conjugate.¹² Many models have been produced that are able to generate waveforms that are associated with IN; several of which include unstable circuitry of the slow

eye movement and gaze holding systems. Contrary to this it has also been suggested that IN may be attributed to early visual deprivation, perhaps due to delayed visual maturation. Currently there is no consensus as to which of these theories are correct. Recently a classification for eye movement abnormalities and strabismus (CEMAS) has collectively termed all IN as 'infantile nystagmus syndrome' (INS), suggesting that IN has one underlying primary cause. However, in terms of classifying IN, eye movement recordings have shown subtle but significant difference between IN subtypes such as albinism and retinal disease.¹³ In addition to eye movement recordings, the use of optical coherence tomography is able to document the progression of retinal diseases with age and also predict visual acuity based upon the foveal development in albinism. These findings suggest that the classification of all IN into one form (INS) is inappropriate at this time until further evidence is available.

The pharmacological treatment of IN has been largely based upon the success of medication for AN. Following on from reports that gabapentin and memantine were successful in the treatment of APN, these drugs were trialled for use in IN.¹⁴ The first randomised controlled trial for IN included participants who had both idiopathic IN and IN associated with other visual disease and concluded that both gabapentin and memantine reduced eye movement and improved vision in idiopathic IN. Although vision did not significantly improve for the group that had other visual deficits, eye movement was significantly less for this group.

Surgical options that have been reported for IN include large recessions of the horizontal rectus muscles, Kestenbaum procedures for the correction of head postures, artificial divergence surgery and, most recently the tenotomy procedure.¹⁵ The tenotomy procedure is the removal and replacement of the horizontal eye muscles into the original position. The suggested mechanism by which tenotomy reduces nystagmus is by an interruption of the afferent proprioceptive loop which in turn produces a dampened peripheral ocular motor response to the nystagmus signal. Tenotomy procedures can be combined with strabismus surgery and Kestenbaum operations. Other treatment options include refractive correction, prisms, botulinum toxin injections and biofeedback.

Future considerations

The lack of understanding of the underlying mechanisms behind nystagmus has led to a delay in ascertaining effective treatment for nystagmus, although, of late, more treatment options have emerged. A limited amount of these reports are randomised controlled trials. Further high quality evidence is required in order to validate potential pharmacological treatments for all forms of nystagmus. Most recently pharmacological therapies are being reported as a method for testing models for

APN and in the future this technique may be applied to test hypotheses for other eye movement disorders.

The characterisation and classification of nystagmus types has been helped with recent developments in genetic and imaging methods. The genetic sources for forms of IN are being recognised, including the discovery of the FRMD7 gene for idiopathic IN.¹⁰ This, coupled to advances in imaging, such as OCT, allows for greater discrimination of sensory deficits in IN.¹³ As these techniques advance further this may lead to a greater understanding and a more informed classification, of nystagmus. ♦

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