An Update on Nystagmus

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. 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 24/10,000 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). 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. 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. 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-DAP (Figure 1). An alternative target 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 oculopatatal 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 oculopatatal myoclonus the oculopatatal 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. The oculopatatal 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. For APN related to oculopatatal 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 oculopatatal tremor, have recently been reported. 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...
forms that are associated with IN; several of these have been produced that are able to generate waveforms occurring in the horizontal plane that is linked idiopathic familial nystagmus.10 Further studies have shown that FRMD7 is expressed within the first few months after birth and individuals can be singly affected or have a strong genetic source.11 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 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 strabismus surgery and, most recently the tenotomy of the horizontal rectus muscles.15 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 imaging methods. The genetic sources for forms of IN are being recognised, including the discovery of the FRMD7 gene for idiopathic IN.18 This, coupled to advances in imaging, such as OCT, allows for greater discrimination of sensory deficits in IN. As these techniques advance further, this may lead to a greater understanding and a more informed classification, of nystagmus.

REFERENCES