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SPECIAL ARTICLE/CME ARTICLE

EFNS task force – therapy of nystagmus and oscillopsia

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An overview of possible treatment options for oculomotor disorders that prevent clear vision is given. Downbeat nystagmus, upbeat nystagmus, seesaw nystagmus, periodic alternating nystagmus, acquired pendular nystagmus, and saccadic oscillations such as opsoclonus/ocular flutter are discussed. In addition, superior oblique myokymia and vestibular paroxysmia are reviewed. All treatment recommendations available in the literature are classified as *class C* only. In general, only some of the patients benefit from the treatment.

Introduction

The ocular motor system serves to hold images steady on the retina (especially the central fovea). Abnormal eye movements may cause excessive motion of images on the retina, leading to blurred vision and to the illusion that the seen world is moving (oscillopsia). Abnormal eye movements may also interfere with spatial localization and the ability to make accurate limb movements. In clinical practice, the identification of specific abnormalities of eye movements is often useful in the topological diagnosis of a broad range of disorders that affect the brain. Although we now know quite a lot about the anatomy, physiology, and pharmacology of the ocular motor system, our treatment options for abnormal eye movements remain fairly limited. Most drug treatments are based on case reports. Only a few controlled trials have been published in recent years, and they were all based on a small number of subjects, and not all patients respond positively to the treatment. Thus, all treatment recommendations have to be classified as *class C* (Hilgers, 2001). The goal of the paper is to summarize all published treatment options for nystagmus and oscillopsia as well as to provide a short overview of the definition and pathophysiology of certain distinct ocular motor syndromes.

A large part of this review concerns nystagmus, which is defined as repetitive, to-and-fro involuntary eye movements that are initiated by slow drifts of the eye. Physiological nystagmus that occurs during rotation of the body in space acts to *preserve* clear vision. In contrast, pathological nystagmus causes the eyes to drift away from the target, thus degrading vision. One form, pendular nystagmus, consists of to-and-fro quasi-sinusoidal oscillations. More commonly, nystagmus consists of an alternation of unidirectional drifts away from the target and their correction by fast movements (saccades), which temporarily bring the visual target back to the fovea; this is jerk nystagmus. Nystagmus should be distinguished from inappropriate saccades that prevent steady fixation. Saccades are fast movements, and the smeared retinal signal due to these movements is largely ignored. However, patients in whom abnormal saccades repeatedly misdirect the fovea often complain of difficulty reading.

Methods

One member of the Task Force Panel (AS) searched through all available published information using the database Med-Line (last search March 2003). The search was restricted to papers published in English, French, or German. The key words used for the search included the following sequences: 'nystagmus and therapy', 'treatment of ocular motor disorders', and 'treatment of double vision'. All published papers were included, as only a limited number of

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controlled studies are available. The other members of the task force read the first draft of the recommendation and discussed changes (informative consensus approach).

Supranuclear ocular motor disorders

Central vestibular disorders

The vestibulo-ocular reflex (VOR) normally generates eye rotations, after a short latency, in the same plane as the head rotation that elicits them. Disorders of the vestibular *periphery* cause nystagmus in a direction that is determined by the pattern of involved labyrinthine semicircular canals. The complete, unilateral loss of one labyrinth causes a mixed horizontal-torsional nystagmus that is suppressed by visual fixation. *Central* vestibular disorders may also cause an imbalance of these reflexes, leading to upbeat, downbeat, or torsional nystagmus (see below). Another consequence of vestibular disease is a change in the size (gain) of the overall dynamic VOR response. As a result of this change, patients complain of oscillopsia during rapid head movements. A VOR gain larger than 1 (eye speed exceeds head speed) results from a disinhibition of the brainstem circuits responsible for the VOR and is caused by vestibulo-cerebellar dysfunction. Loss of peripheral vestibular function causes impaired vision and oscillopsia during locomotion, due to the inability to compensate for the high-frequency head perturbations that occur with each footfall.

Downbeat nystagmus

Downbeat nystagmus is a central form of vestibular nystagmus that is often present when the eyes are close to the central position; it usually increases on downgaze and especially on lateral gaze. It also often becomes evident or is increased by placing the patient in a head-hanging position, or by tipping the head forward. In patients with cerebellar atrophy, some authors found that downbeat nystagmus is more prominent in prone than in supine body position (Marti *et al.*, 2002), but this could not be confirmed by others (Bronstein *et al.*, 1987). Visual fixation has little effect on its slow-phase speed; convergence may suppress or enhance it in some patients. In general the nystagmus is accompanied by a vestibulocerebellar ataxia with a tendency to fall backward (Büchele *et al.*, 1983). Lesions that cause downbeat nystagmus occur in the vestibulocerebellum bilaterally and in the underlying medulla (Leigh and Zee, 1999). The pathophysiological mechanism of downbeat nystagmus appears to be due to a central imbalance of the vertical VOR (Baloh and Spooner, 1981) or due to an abnormality of the vertical-torsional gaze-holding mechanism – the 'neural integrator for eye movements' (Glasauer *et al.*, 2003).

Etiology

The most common cause of downbeat nystagmus is cerebellar degeneration (hereditary, sporadic, or paraneoplastic). Other important causes are Chiari malformation and drug intoxication (especially the anticonvulsants and lithium). Multiple sclerosis (MS) is an uncommon cause, and a congenital form is rare (Halmagyi *et al.*, 1983). In practice cerebellar atrophy, Arnold–Chiari malformation, various cerebellar lesions (MS, vascular, tumors), and idiopathic causes account for approximately one-fourth of the cases each (Bronstein *et al.*, 1987). Downbeat nystagmus occurs in the channelopathy episodic ataxia type 2, for which a new treatment option has recently been developed (Strupp and Schüler, 2002).

Upbeat nystagmus

Upbeat nystagmus is present with the eyes close to the central position and usually increases on upgaze. Vertical smooth pursuit is usually disrupted by the nystagmus. In some patients the upbeat nystagmus changes to downbeat nystagmus during convergence.

Etiology Probable causes of upbeat nystagmus are lesions in the ascending pathways from the anterior canals (and/or the otoliths) at the pontomesencephalic or pontomedullary junction, near the perihypoglossal nuclei (Fisher *et al.*, 1983). Upbeat nystagmus is most often seen after medullary lesions (Stahl *et al.*, 2000). The main causes are MS, tumors of the brainstem, Wernicke's encephalopathy, cerebellar degeneration, and intoxication (e.g. nicotine).

Therapeutic recommendations

Downbeat nystagmus No studies on the natural course of downbeat nystagmus are available. In non-placebo-controlled studies with a limited number of patients, administration of the GABA-A agonist clonazepam (0.5 mg p.o. three times daily; Currie and Matsuo, 1986), the GABA-B agonist baclofen (10 mg p.o. three times daily) (Dieterich *et al.*, 1991), and gabapentin (probably calcium channel blocker) (Averbuch-Heller *et al.*, 1997) had positive effects and reduced downbeat nystagmus. Intravenous injection of the cholinergic drug physostigmine (Ach-esterase inhibitor) worsened downbeat nystagmus in five patients. This effect was partially reversed in one patient by the anticholinergic drug biperiden, suggesting that anticholinergic drugs might be beneficial, as was shown in a double-blind study on intravenous scopolamine (Barton *et al.*, 1994). In isolated patients with a craniocervical anomaly, a surgical decompression by removal of part of the occipital bone in the region of the foramen magnum was beneficial (Pedersen *et al.*,

1980; Spooner and Baloh, 1981; personal observation). Recent placebo-controlled studies (Strupp *et al*., 2003) have suggested that the potassium channel blocker 3,4-diaminopyridine may be effective in downbeat nystagmus. As downbeat nystagmus is generally less pronounced in upward gaze, base-down prisms sometimes help to reduce oscillopsia during reading.

Upbeat nystagmus

Treatment with baclofen (5–10 mg p.o. three times daily) resulted in an improvement in several patients (Dieterich *et al*., 1991).

Seesaw nystagmus

Seesaw nystagmus is a rare pendular or jerk oscillation. One half cycle consists of elevation and intorsion of one eye with synchronous depression and extorsion of the other eye. During the next half cycle there is a reversal of the vertical and torsional movements. The frequency is lower in the pendular (2–4 Hz) than in the jerk variety.

Etiology

Jerk hemi-seesaw nystagmus has been attributed to unilateral meso-diencephalic lesions (Halmagyi *et al*., 1994), affecting the interstitial nucleus of Cajal and its vestibular afferents from the vertical semicircular canals (Endres *et al*., 1996; Rambold *et al*., 1999). The pendular form is associated with lesions affecting the optic chiasm. Loss of crossed visual input seems to be the crucial element in the pathophysiology of pendular seesaw nystagmus (Stahl *et al*., 2000).

Therapeutic recommendations

Alcohol had a beneficial effect (1.2 g/kg body weight) in two patients (Frisèn and Wikkelso, 1986; Lepore, 1987), as was clonazepam (Carlow, 1986). Recently, Averbruch-Heller *et al*. (1997) reported on three patients with a seesaw component to their pendular nystagmus, who improved on gabapentin.

Periodic alternating nystagmus

Periodic alternating nystagmus is a spontaneous horizontal beating nystagmus, the direction of which changes periodically. Periods of oscillation range from 1 s to 4 min, typically 1–2 min. When the nystagmus amplitude gradually decreases, the nystagmus reverses its direction, and then the amplitude increases again. During the nystagmus patients often complain of increasing/decreasing oscillopsia.

Etiology

Patients with periodic alternating nystagmus commonly have vestibulocerebellar lesions. Their nystagmus also disrupts visual fixation, being present also during normal viewing. These observations and animal experiments support the idea that this type if nystagmus is caused by lesions of the inferior cerebellar vermis (nodulus and uvula), leading to a disinhibition of the GABA-ergic velocity-storage mechanism, which is mediated in the vestibular nuclei (Waespe *et al*., 1985; Furman *et al*., 1990). The underlying etiologies are craniocervical anomalies, MS, cerebellar degenerations or tumors, brainstem infarction, anticonvulsant therapy, and bilateral visual loss.

Therapeutic recommendations

In general, periodic alternating nystagmus does not improve spontaneously. Several case reports describe a positive effect of baclofen, a GABA-B agonist, in a dose of 5–10 mg p.o. three times daily (Halmagyi *et al*., 1980; Larmande and Larmande, 1983; Isago *et al*., 1985; Carlow, 1986; Nuti *et al*., 1986). Furthermore, phenothiazine and barbiturates have been found to be effective in single cases (Nathanson *et al*., 1953; Isago *et al*., 1985). Periodic alternating nystagmus due to bilateral visual loss resolves if vision is restored (Cross *et al*., 1982; Jay *et al*., 1985).

Non-vestibular supranuclear oculomotor disorders

Acquired pendular nystagmus

Acquired pendular nystagmus (APN) is a quasi-sinusoidal oscillation that may have a predominantly horizontal, vertical, or mixed trajectory (i.e. circular, elliptical, or diagonal); it can predominantly be either monocular or binocular (Gresty *et al*., 1982; Traccis *et al*., 1990; Leigh *et al*., 1992; Lopez *et al*., 1996). The frequency of this type of nystagmus is 2–7 Hz (Zee, 1985), and often the nystagmus is associated with head titubation (not synchronized with the nystagmus), trunk and limb ataxia, or visual impairment.

Etiology

Acquired pendular nystagmus occurs with several disorders of myelin (MS, toluene abuse, Pelizaeus–Merzbacher disease), as a component of the syndrome of oculopalatal tremor (myoclonus), in Whipple's disease (Leigh and Zee, 1999); the two more common etiologies in the adult are MS and brainstem stroke (Lopez *et al*., 1996). On the basis of observations that the nystagmus is often dissociated and that eye movements other than optokinetic nystagmus and voluntary saccades are also disturbed, a lesion in the brainstem near the oculomotor nuclei has been suggested (Gresty *et al*., 1982). Alternatively, an inhibition of the inferior olive due to lesions of the 'Mollaret triangle' (Lopez *et al*., 1996) or an instability of the gaze-holding

network (neural integrator) has been proposed; this suggestion has received experimental modeling support (Das *et al.*, 2000) and has led to the proposal of potential therapies (Stahl *et al.*, 2000).

Therapeutic recommendations

Most reports (case reports or case series) state that anticholinergic treatment with trihexyphenidyl (20–40 mg p.o. daily) is effective (Herishanu and Louzoun, 1986; Jabbari *et al.*, 1987), but in a double-blind study by Leigh *et al.* (1991a) only one of six patients showed improvement from this oral treatment, whereas three patients showed a decrease in nystagmus and improvement of visual acuity during treatment with tridihexethyl chloride (a quaternary anticholinergic that does not cross the blood–brain barrier). In contrast, Barton *et al.* (1994) found in a double-blind trial that scopolamine (0.4 mg i.v.) decreased the nystagmus in all five tested patients with acquired pendular nystagmus. However, there are even observations that scopolamine may make the pendular nystagmus worse in some patients (Kim *et al.*, 2001). In three other patients the combination with lidocaine (100 mg i.v.) decreased nystagmus (Ell *et al.*, 1982; Gresty *et al.*, 1982). Recently, Starck *et al.* (1997) reported an improvement in three of 10 patients who received a scopolamine patch (containing 1.5 mg scopolamine, released at a rate of 0.5 mg per day). The same authors failed to observe further improvement when scopolamine and mexiletine (400–600 mg p.o. daily) were given in combination. The most effective substance in their study was memantine, a glutamate antagonist, which significantly improved the nystagmus in all nine tested patients (15–60 mg p.o. daily). Two patients responded to clonazepam (3×0.5–1.0 mg p.o. daily), a GABA-A agonist (Starck *et al.*, 1997). Two other groups have reported benefit with GABA-ergic drugs. Traccis *et al.* (1990) showed improvement in one of three patients with APN and cerebellar ataxia due to MS when treated with isoniazid (800–1000 mg p.o. daily) and glasses with prisms that induced convergence. This observation was not confirmed by other investigators (Leigh *et al.*, 1994). Gabapentin substantially improved the nystagmus (and visual acuity) in 10 of 15 patients (Averbruch-Heller *et al.*, 1997). Gabapentin was superior to vigabatrin in a small series of patients (Bandini *et al.*, 2001). Interestingly Mossman *et al.* (1993) described two patients who benefited from intake of alcohol but not from other substances. The necessary blood levels were 20–35 mmol/l. Recently, a beneficial effect of cannabis was also reported (Schon *et al.*, 1999; Dell'Osso, 2000).

Practically, treatment should start with memantine in a dosage of 15–60 mg p.o. or alternatively 300–400 mg gabapentin three times daily. If there is no or only a small effect, benzodiazepines like clonazepam (0.5–1.0 mg p.o. three times daily) can be tried. Further possibilities are scopolamine patches or trihexyphenidyl. However, side effects are a major limitation of anticholinergic therapy.

Opsoclonus and ocular flutter

Opsoclonus consists of repetitive bursts of conjugate saccadic oscillations, which have horizontal, vertical, and torsional components. During each burst of these high-frequency oscillations, the movement is continuous, without any intersaccadic interval. These oscillations are often triggered by eye closure, convergence, pursuit, and saccades; amplitudes range up to 2–15°; (overview in Leigh and Zee, 1999). In ocular flutter the same pattern is restricted to the horizontal plane. The ocular symptoms are often accompanied by cerebellar signs, such as gait and limb myoclonus (the 'dancing feet, dancing eyes syndrome').

Etiology

A functional disturbance of active saccadic suppression by the pontine omnipause neurons is the most probable pathophysiological mechanism. As histological abnormalities of these neurons have not been shown (Ridley *et al.*, 1987), a functional lesion of the glutaminergic cerebellar projections from the fastigial nuclei to the omnipause cells is a likely cause for their disinhibition. Opsoclonus can be observed in benign cerebellar encephalitis (post-viral, e.g. coxsackie B37; post-vaccinal), or as a paraneoplastic symptom (infants, neuroblastoma; adults, carcinoma of the lung, breast, ovary, or uterus).

Therapeutic recommendations

In addition to therapy for any underlying process such as tumor or encephalitis, treatment with immunoglobulins or prednisolone may be occasionally effective (Pless and Ronthal, 1996). Four of five patients with square-wave oscillations, probably a related fixation disturbance, showed an improvement on therapy with valproic acid (Traccis *et al.*, 1997). In single cases an improvement has been observed during treatment with propranolol (40–80 mg p.o. three times daily), nitrazepam (15–30 mg p.o. daily), and clonazepam (0.5–2.0 mg p.o. three times daily) (overview in Leopold, 1985; Carlow, 1986). Nausieda *et al.* (1981) reported a dramatic improvement in one patient after the administration of 200 mg thiamine i.v.; no further descriptions of the patient are given in the paper.

Nuclear and infranuclear ocular disorders

Superior oblique myokymia

Superior oblique myokymia consists of paroxysmal monocular high-frequency oscillations. In the primary

gaze position and in abduction these oscillations are mainly torsional, but when the eyes are in adduction the oscillations have a vertical component. Voluntary eye movements, as when looking down, can provoke the oscillations. The patients usually complain of oscillopsia during these paroxysmal attacks.

Etiology

The pathophysiology of this condition is not totally clear. Analogous to hemifacial spasm and trigeminal neuralgia, vascular compression of the IVth nerve (Lee, 1984; Hashimoto *et al*., 2001; Yousry *et al*., 2002), or alternatively spontaneous discharges in the IVth nerve nucleus (Hoyt and Keane, 1962) or of the superior oblique muscle may be responsible (Leigh *et al*., 1991b).

Therapeutic recommendations

Spontaneous remissions, which can last for days up to years, are typical of superior oblique myokymia but there are several reports that anticonvulsants, especially carbamazepine, have a therapeutic effect. Carbamazepine (200–400 mg p.o. three or four times daily) or, less often, phenytoin (250–400 mg p.o. daily) are recommended (Susac *et al*., 1973; Rosenberg and Glaser, 1983). Gabapentin has also been reported to be effective (Tomsak *et al*., 2002). Long-term studies on the continued effectiveness of these drugs are not available. Rosenberg and Glaser (1983) described a decrease in the efficacy of the treatment after a month in some patients. Beta-blockers, even topically, have been reported to be effective (Tyler and Ruiz, 1990; Bibby *et al*., 1994).

In chronic cases that did not improve with anticonvulsants, tenotomy of the superior oblique muscle has been performed, but usually it necessitates inferior oblique surgery as well (Palmer and Shults, 1984; Brazis *et al*., 1994). Surgical decompression of the IVth nerve has also been reported to be beneficial but may result in superior oblique palsy (Samii *et al*., 1998; Scharwey *et al*., 2000).

Practically, treatment should be started with carbamazepine (200–400 mg p.o. three to four times daily) or phenytoin (250–400 mg p.o. daily). The side effects and the risk of such therapy are the same as when used to treat trigeminal neuralgia.

Paroxysmal vestibular episodes

Clinically, the patients describe short, repeated, paroxysmal attacks of to-and-fro vertigo lasting for seconds to maximally minutes, which can sometimes be provoked by particular head positions. Other symptoms can be tinnitus, hyperacusis, or facial contractions during the attacks. Clinical examination between the attacks may reveal signs of permanent vestibular deficit, hypoacusis, or facial paresis on the affected side (Brandt and Dieterich, 1994; Straube *et al*., 1994).

Etiology

High-resolution magnetic resonance imaging may show the compression of the VIIth nerve by an artery (most often AICA) or seldom a vein in the region of the root entry zone of the vestibular nerve in some patients, but this can also be seen in subjects without symptoms. The neuropathological mechanism may be peripheral ephaptic transmission that takes place in the part of the cranial nerve still containing central myelin (derived from oligodendroglia), if the nerve has direct contact with a blood vessel. This hypothesis is supported by the analysis of epidemiological data which show a correlation of the incidence of the syndrome with the anatomical length of the central myelin (De Ridder *et al*., 2002). Another theory is that the pulsation of the blood vessel causes an afferent sensory inflow that then causes a false central response.

Therapeutic recommendations

As initial therapy, an anticonvulsant [carbamazepine (slow release formulation) 2×200–800 mg p.o. daily; phenytoin 250–400 mg p.o. daily, lamotrigine 100–400 mg p.o. daily] should be given (Brandt, 1999). In general, a positive response to antiepileptic drugs can be achieved with low dosages. If the symptoms do not cease, a surgical approach may be considered (Jannetta *et al*., 1984). There are no satisfactory follow-up studies, and the diagnostic criteria have not yet been fully established.

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