CHAPTER 32
Nystagmus and oscillopsia

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Introduction

One function of the ocular motor system is to stabilize images during eye and head movements on the retina (especially the central fovea). Involuntary or abnormal eye movements cause excessive motion of images on the retina without a corresponding efference copy (or corollary discharge) [1], leading to blurred vision and to the illusion that the seen world is moving (oscillopsia). This leads to spatial disorientation, impaired postural balance and vertigo. In clinical practice, the identification of specific eye movement abnormalities 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 recently several small controlled trials have been published, and they were all based on a small number of subjects, and not all patients always respond positively to the treatment. Thus, all treatment recommendations have to be classified as Class C [2]. The goal of the paper is to summarize all published treatment options for nystagmus and oscillopsia as well as to provide a short overview on definitions and pathomechanisms 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 occurs during rotation of the body in space or during ocular following of moving scenes and acts to preserve clear vision (vestibular and optokinetic nystagmus respectively). In contrast, pathological nystagmus causes the eyes to drift away from the visual target, thus degrading vision. Most commonly, nystagmus consists of an alternation of unidirectional drifts away from the target, e.g. due to a vestibular imbalance, and their correction by fast movements (saccades), which temporarily bring the visual target back to the fovea; this is jerk nystagmus. Another rarer form, pendular nystagmus, consists of to-and-fro quasi-sinusoidal eye oscillations. Nystagmus should be distinguished from inappropriate saccades that prevent steady fixation (e.g. ocular flutter). Saccades are fast movements, and the smeared retinal signal due to these movements remains largely unperceived. However, patients in whom abnormal saccades repeatedly misdirect the fovea often complain of difficulty in reading. In general most of the later in life acquired nystagmus syndromes as well as saccadic oscillations cause oscillopsia and vertigo; in contrast, most of the congenital or in early youth acquired nystagmus syndromes are not accompanied by oscillopsia. The recommendations are a revised and extended version of the 2004 guidelines [3].

Methods

One member of the task force panel (AS) searched through all available published information using the database MEDLINE (last search September 2009). 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
Neurological Problems 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 many patients with vestibulo-cerebellar atrophy, the drift velocity increases in prone position and is minimal in supine position [5]. As a result, many cerebellar patients report better reading capability when lying on their back. In other patients, the gravity-dependence of DBN is opposite or missing [6]. 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 (vermal) ataxia with a tendency to fall backwards [7]. The pathomechanism of downbeat nystagmus remains unclear. Hypotheses conjectured various deficits such as an imbalance of central vertical vestibular [8], asymmetric impairment of vertical SP pathways [9] or dissociation between internal coordinate systems for vertical saccade generation and gaze holding [10]. DBN and associated ocular motor signs (impaired vertical smooth pursuit, gaze-evoked nystagmus, and gravity dependence of the upward drift) can be explained by damage of the inhibitory vertical gaze-velocity-sensitive Purkinje cells in the cerebellar flocculus [11]. These cells show spontaneous activity and a physiological asymmetry in that most of them exhibit downward on-directions. A loss of floccular Purkinje cells therefore leads to disinhibition of their brainstem target neurons and, consequently, to spontaneous upward drift.

Aetiology
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 [12]. In practice, cerebellar atrophy, Arnold-Chiari malformation, various cerebellar lesions (MS, vascular, tumours), and idiopathic causes account for approximately 25% of the cases each [6]. In a recent study about one-third were classified as idiopathic and about a half of these patients showed a combination of bilateral vestibulopathy, peripheral polyneuropathy, and/or cerebellar signs [13]. There seems to be no change over long time of the DBN [14]. Downbeat nystagmus occurs in the channelopathy episodic ataxia type 2, for which a new treatment option has recently been developed [15].

Supranuclear ocular motor disorders
Central vestibular disorders
The vestibulo-ocular reflex (VOR) normally generates compensatory eye rotations of short latency and in the same plane but opposite direction to the head rotation that elicits them. Disorders of the vestibular periphery cause nystagmus in a direction that is determined by the pattern of the 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); typically a straight horizontal beating nystagmus (e.g. no rotational component) or nystagmus beats not in the direction of the stimulated semicircular canal (e.g. crosscoupling) is due to a central vestibular lesion. Another consequence of vestibular disease is a change in the size (gain = eye velocity divided by head velocity) 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 (i.e. eye velocity exceeds head velocity) results from a disinhibition of the brainstem circuits responsible for the VOR and is caused by central, 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 footstep, i.e. the gain of the VOR remains too low for gaze stabilization after peripheral vestibular lesions. The treatment of oscillopsia due to bilateral vestibular failure (e.g. idiopathic, gentamycin intoxication, postmeningitic, due to autoimmune diseases, and idiopathic [4]) is vestibular rehabilitation including head-eye coordination exercises.

Downbeat nystagmus
Downbeat nystagmus (DBN) is a central vestibular nystagmus, present when the eyes are close or in the primary gaze position; it usually increases on down gaze 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 many patients with vestibulo-cerebellar atrophy, the drift velocity increases in prone position and is minimal in supine position [5]. As a result, many cerebellar patients report better reading capability when lying on their back. In other patients, the gravity-dependence of DBN is opposite or missing [6]. 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 (vermal) ataxia with a tendency to fall backwards [7]. The pathomechanism of downbeat nystagmus remains unclear. Hypotheses conjectured various deficits such as an imbalance of central vertical vestibular [8], asymmetric impairment of vertical SP pathways [9] or dissociation between internal coordinate systems for vertical saccade generation and gaze holding [10]. DBN and associated ocular motor signs (impaired vertical smooth pursuit, gaze-evoked nystagmus, and gravity dependence of the upward drift) can be explained by damage of the inhibitory vertical gaze-velocity-sensitive Purkinje cells in the cerebellar flocculus [11]. These cells show spontaneous activity and a physiological asymmetry in that most of them exhibit downward on-directions. A loss of floccular Purkinje cells therefore leads to disinhibition of their brainstem target neurons and, consequently, to spontaneous upward drift.
**Upbeat nystagmus**

Upbeat nystagmus (UBN) is present with the eyes close to the central position and usually increases on up gaze. Vertical smooth pursuit is usually disrupted by the nystagmus. In some patients the upbeat nystagmus changes to downbeat nystagmus during convergence. UBN can appear as a result of a pontine lesion along the ventral tegmental tract, which originates in the superior vestibular nucleus. The associated relative hypoactivity of the drive to the motoneurons of the elevator muscles results in a downward drift.

**Aetiology**

The main causes are MS, tumours of the brainstem, Wernicke’s encephalopathy, cerebellar degeneration, and intoxication (e.g. nicotine), which may be the causes for lesions in the ascending pathways from the anterior canals (and/or the otoliths) at the pontomesencephalic or pontomedullary junction, near the perihypoglossal nuclei [16]. Upbeat nystagmus is most often seen after medullary lesions [17], but can also be seen after pontine lesion along the ventral tegmental tract, which originates in the superior vestibular nucleus [18].

**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 per os (p.o.) three times daily [19], the GABA-B agonist baclofen (10 mg p.o. three times daily) [20], and gabapentin (probably calcium channel blocker) [21] 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 [22]. 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 [23–25]; personal observation. Recent placebo-controlled studies have suggested that the potassium channel blockers 3,4-diaminopyridine (3x20mg/day) and 4-aminopyridine (3 × 10mg/day) may be effective in reducing downbeat nystagmus [26] and in improving the VOR and smooth pursuit [27]. A further study in 11 patients with DBN due to cerebellar degeneration confirmed this effect and showed that 3,4-diaminopyridine especially reduce the gravity-independent velocity bias [28]. As downbeat nystagmus is generally less pronounced in upward gaze, base-down prisms sometimes help to reduce oscillopsia during reading in some patients.

Upbeat nystagmus. Treatment with baclofen (5–10 mg p.o. three times daily) resulted in an improvement in several patients [20]. There are some observations that 10 mg 4-aminopyridine three times a day reduces upbeat nystagmus [29].

**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.

**Aetiology**

Jerk hemi-seesaw nystagmus has been attributed to unilateral meso-diencephalic lesions [30], affecting the interstitial nucleus of Cajal and its vestibular afferents from the vertical semicircular canals [31, 32]. 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 [17].

**Recommendations**

Alcohol had a beneficial effect (1.2 g/kg body weight) in two patients [33, 34], but this cannot be recommended as treatment, as did clonazepam [35]. Recently, Averbruch-Heller et al. [21] 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.
Neurological Problems

Aetiology
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 of 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 [36, 37]. The underlying aetiologies are craniovertebral anomalies, MS, cerebellar degenerations or tumours, brainstem infarction, anticonvulsant therapy, and bilateral visual loss.

Recommendations
In general, periodic alternating nystagmus (PAN) does not improve spontaneously. Several case reports of acquired as well as congenital PAN describe a positive effect of baclofen, a GABA-B agonist, in a dose of 5–10 mg p.o. three times daily [35, 38–42]. Furthermore, phenothiazine and barbiturates have been found to be effective in single cases [40, 43]. Recently, also memantine was described as effective [44]. Periodic alternating nystagmus due to bilateral visual loss resolves if vision is restored [45, 46]. In a case of PAN associated to a Chiari-malformation a surgical decompression resolved the PAN [47].

Non-vestibular supranuclear ocular motor 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 be predominantly monocular or binocular [48–51]. The frequency of this type of nystagmus is 2–7 Hz [52], and often the nystagmus is associated with head titubation (not synchronized with the nystagmus), trunk and limb ataxia, palatal myoclonus, or visual impairment.

Aetiology
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), and in Whipple’s disease [53]; the two more common aetiologies in the adult are MS and brainstem stroke [51]. 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 [48]. Alternatively, an inhibition of the inferior olive due to lesions of the ‘Mollaret triangle’ [51] or an instability of the gaze-holding network (neural integrator) has been proposed; this suggestion has received experimental modelling support [54] and has led to the proposal of potential therapies [17].

Recommendations
Most reports (case reports or case series) state that anticholinergic treatment with trihexyphenidyl (20–40 mg p.o. daily) is effective [55, 56], but in a double-blind study by Leigh et al. [57] 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. [22] found in a double-blind trial that scopolamine (0.4 mg intravenous (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 [58]. In three other patients the combination with lidocaine (100 mg i.v.) decreased nystagmus [48, 59]. Recently, Starck et al. [60] 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 [60]. In a further crossover study Starck and co-workers [61] showed that memantine as well as gabapentin was able not only to reduce the nystagmus but also to improve visual acuity. Two other groups have reported benefit with GABA-ergic drugs. Traccis et al. [49] 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).
Nystagmus and oscillopsia

Congenital nystagmus

Congenital nystagmus is a fixational nystagmus and is characterized by gaze-dependent involuntary to and fro eye movements, which can be pendular, jerky, or elliptic. Typically the patients report little or no oscillopsia or visual blurring, compared to the fast nystagmus velocities seen. The prevalence of congenital nystagmus is estimated to be 1/1000.

Aetiology

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 [67], a functional lesion of the glutaminergic cerebellar projections from the fastigial nuclei to the omnipause cells is a likely cause for their disinhibition. In a functional magnetic resonance imaging (fMRI) study, an increased activation of the fastigial region during opsoclonus was shown [68]. Ramat and colleagues suggested that the lesion of the fastigial nucleus interrupts the local feedback loop through the cerebellum but not the brainstem interconnections [69]. 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).

Recommendations

In most cases therapy not necessary. Besides surgical inventions [77] only a few reports on medical treatment trials are reported. Baclofen [78], cannabis [79], and especially memantine and gabapentin are described. In a study with 47 patients, memantine (up to 40mg) as well as gabapentin (up to 2400mg) were shown to be superior to placebo and both also improved visual acuity [76]. A similar result was in a retrospective study of 23 patients with acquired as well as congenital nystagmus reported [80, 81].

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 [53]). 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’).

Aetiology

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Recommendations

In addition to therapy for any underlying process such as tumour or encephalitis, treatment with immunoglobulins or prednisolone may be occasionally effective [70]. Four of five patients with square-wave oscillations, probably a related fixation disturbance, showed an improvement on therapy with valproic acid [71] or in patients with hereditary spinocerebellar ataxia on therapy with memantine 20mg daily [72]. 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) can be tried. Further possibilities are scopolamine patches or trihexyphenidyl.

and glasses with prisms that induced convergence. This observation was not confirmed by other investigators [62]. Gabapentin substantially improved the nystagmus (and visual acuity) in 10 of 15 patients [21]. Gabapentin was superior to vigabatrin in a small series of patients [63]. Interestingly, Mossman et al. [64] described two patients who benefited from intake of alcohol but not from other substances. Recently, a beneficial effect of cannabis was also reported [65, 66]. 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.
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.

Aetiology
The pathophysiology of this condition is not entirely clear. In analogy to hemifacial spasm and trigeminal neuralgia, vascular compression of the IV nerve [82–84], or alternatively spontaneous discharges in the IV nerve nucleus [85] or of the superior oblique muscle may be responsible [86].

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 [87, 88]. Gabapentin has also been reported to be effective [89]. Rosenberg and Glaser [88] 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 [90, 91]. In chronic cases that did not improve with anticonvulsants, tenotomy of the superior oblique muscle was performed, but usually it necessitates inferior oblique surgery as well [92, 93]. Surgical decompression of the IV nerve has also been reported to be beneficial but may result in superior oblique palsy [94, 95]. 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).

Paroxysmal vestibular episodes
Clinically, the patients describe short, repeated, paroxysmal attacks of to-and-fro vertigo and unsteadiness of stance or gait lasting usually 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. In some patients, such attacks can be triggered by head turning [96]. Clinical examination between the attacks may reveal signs of permanent vestibular deficit, hyperacusis, or facial paresis on the affected side [97, 98]. Mild vestibular deficits can be found with caloric testing in about 70% of the patients [96].

Aetiology
High-resolution magnetic resonance imaging may show the compression of the VIII 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 that show a correlation of the incidence of the syndrome with the anatomical length of the central myelin [99]. Another theory is that the pulsation of the blood vessel causes an afferent sensory inflow that then causes a false central response.

Recommendations
As initial therapy, an anticonvulsant should be given [100]. Mean dosages of carbamazepine of about 600 mg daily and of oxcarbazepine of about 900 mg daily led to a reduction of the attack frequency of about 90% [95]. 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 [101]. There are no satisfactory follow-up studies, and the diagnostic criteria have not yet been fully established.

Conflicts of interest
The present guidelines were developed without external financial support. None of the authors reports conflicting interests.

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