

## Ocular motor disorders

### Update on diagnosis and treatment

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#### Abstract

It is often quite demanding for clinicians to diagnose the different forms of central ocular motor disorders and the nystagmus associated with them. There are three reasons for this: first, the anatomy and the physiology of the ocular motor, vestibular, and cerebellar systems are complex; second, the detailed neurological and neuro-ophthalmological as well as neuro-otological examinations require a systematic approach, precise skills, and experience; third, it is often difficult to interpret the findings, and clinical experience is required to do so. Therefore, a standardized approach with careful taking of the patient's medical history and a neurological, neuro-ophthalmological and neuro-otological examination are crucial for the diagnosis. For common central ocular motor disorders like downbeat nystagmus the new treatment option with aminopyridines improves gait and gaze stability in these patients.

#### Clinical examination

Clinical examination of patients with suspected ocular motor disorders should begin with the **examination of the eyes in nine different positions** (*i.e.*, looking straight ahead, to the right, left, up, down as well as diagonally right up, right down, left up, and left down) to determine ocular alignment, fixation deficits, spontaneous or fixation nystagmus, range of movement, and disorders of gaze-holding abilities. The examination can be performed with an object for fixation or a small rod-shaped flashlight. In **primary position** one should look for periodic eye movements, such as **nystagmus** (*e.g.*, horizontal-rotatory, suppressed by fixation as in peripheral vestibular dysfunction), vertically upward (**upbeat nystagmus**) or downward (**downbeat nystagmus**), or horizontal or torsional movements with only slight suppression of intensity during fixation as in a central vestibular dysfunction. A **congenital nystagmus** beats, as a rule, horizontally at various frequencies and amplitudes and increases during fixation. **Ocular flutter** (intermittent rapid bursts of horizontal oscillations without an intersaccadic interval) or **opsoclonus** (combined horizontal, vertical, and torsional oscillations) occur in various disorders such as encephalitis, tumors of the brainstem or cerebellum, intoxication, or in paraneoplastic syndromes.

The examination of the eyes with **Frenzel's glasses** is a sensitive method for detecting spontaneous nystagmus. This can also be achieved by examining one eye with an **ophthalmoscope** (while the other eye is covered) and simultaneously checking for movements of the optic papilla or retinal vessels even with low, slow-phase velocities/frequencies.

After checking for possible eye movements in primary position and the misalignment of the axes of the eyes, the examiner should then establish the **range of eye movements** monocularly and binocularly in the eight end-positions; deficits found here can indicate, *e.g.*, extraocular muscle or nerve palsy. **Gaze-holding deficits** can also be determined by examining eccentric gaze position. Use of a small rod-shaped flashlight has the advantage that the corneal reflex images can be observed and thus ocular misalignments can be easily detected. The flashlight also allows one to determine whether the patient can fixate with one or both eyes in the end-positions. This is important for detecting a defect of gaze holding. **Gaze-evoked nystagmus** can only be clearly identified when the patient fixates with both eyes. It is most often a side effect of medication (*e.g.*, anti-convulsants, benzodiazepines) or toxins (*e.g.*, alcohol). **Horizontal gaze-evoked nystagmus** can indicate a structural lesion in the area of the brainstem or cerebellum, *i.e.*, the neural eye velocity to position integrator). **Vertical gaze-evoked nystagmus** is observed in midbrain lesions involving the interstitial nucleus of Cajal. A **dissociated horizontal gaze-evoked nystagmus** (greater in the abducting than the adducting eye) in combination with an adduction deficit points to internuclear ophthalmoplegia (INO) due to a defect of the medial longitudinal fascicle (MLF), ipsilateral to the adduction deficit. **Downbeat nystagmus** usually increases in eccentric gaze position and when looking down. To examine for a so-called **rebound nystagmus** the patient should gaze at least 15 seconds to one side and then return the eyes to the primary position; this can cause a transient nystagmus to appear with slow phases in the direction of the previous eye position. Rebound nystagmus generally indicates cerebellar dysfunction or damage to the cerebellar pathways.

To examine **smooth pursuit** the patient is asked to visually track an object moving slowly in horizontal and vertical directions (10 to 20°/s) while keeping his head stationary. Corrective (catch-up or back-up) saccades are looked for; they indicate a smooth pursuit gain that is too low or too high. Many anatomical structures (visual cortex, motion sensitive areas MT, V5, frontal eye fields, dorsolateral pontine nuclei, cerebellum, vestibular and ocular motor nuclei) are involved in smooth pursuit eye movements, which keep the image of a moving object stable on the fovea. These eye movements are also influenced by alertness, various drugs, and age. Even healthy persons exhibit a slightly saccadic smooth pursuit during vertical downward gaze. For these reasons a saccadic smooth pursuit as a rule does not allow either an exact topographical or etiological classification. Marked **asymmetries** of smooth pursuit, however, indicate a structural lesion; strongly impaired smooth pursuit is observed in intoxication (anticonvulsives, benzodiazepines, or alcohol) as well as degenerative disorders involving the cerebellum or extrapyramidal system. A **reversal of slow smooth pursuit** eye movements during optokinetic stimulation is typical for congenital nystagmus (*see above*).

To **examine saccades** it is first necessary to observe spontaneous saccades triggered by visual or auditory stimuli. Then the patient is asked to glance back and forth

between two horizontal and two vertical targets. The velocity, accuracy, and the conjugacy of the saccades should be noted. Normal individuals can immediately reach the target with a fast single movement or one small corrective saccade. **Slowing of saccades** — often accompanied by **hypometric saccades** — occurs for example with intoxication (medication, especially anticonvulsives or benzodiazepines) or in neurodegenerative disorders. **Slowing of horizontal saccades** is generally observed in brainstem lesions; there is often a dysfunction of the ipsilateral paramedian pontine reticular formation (PPRF). **Slowing of vertical saccades** indicates a midbrain lesion in which the rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) is involved, not only in ischemic inflammatory diseases but also in neurodegenerative diseases, especially progressive supranuclear palsy. **Hypermetric saccades**, which can be identified by a corrective saccade back to the object, indicate lesions of the cerebellum or the cerebellar pathways. Patients with Wallenberg's syndrome make hypermetric saccades toward the side of the lesion due to a dysfunction of the inferior cerebellar peduncle; defects of the superior cerebellar peduncle, conversely, lead to contralateral hypermetric saccades. A slowing of the **adducting saccade ipsilateral to a defective MLF** is pathognomonic for INO. **Delayed onset saccades** are mostly caused by supratentorial cortical dysfunction.

#### Treatment of downbeat and upbeat nystagmus with aminopyridines

Two types of vertically beating central nystagmus are of special importance: downbeat nystagmus (DBN) and upbeat nystagmus (UBN), each named after the direction of the rapid, beating phase. Downbeat nystagmus is the most common type of acquired, persistent nystagmus. Both types manifest themselves above all with swaying nystagmus and unsteadiness of gait and only secondarily with oscillopsia, *i.e.*, apparent movement of the environment due to oscillation of the retinal image. In distinction to spontaneous nystagmus such as in vestibular neuritis, DBN and UBN are types of fixation nystagmus, *i.e.*, their intensity increases with visual fixation. Both DBN and UBN always indicate the presence of a central disturbance and possess special localizing significance. Downbeat nystagmus is usually due to bilateral dysfunction of the cerebellar

lar flocculus; its three common causes are cerebellar atrophy, ischemia, and Arnold-Chiari malformation. Upbeat nystagmus — which, unlike DBN, generally persists for no more than a few weeks — can be caused by paramedian medullary or pontomesencephalic lesions, *e.g.*, brainstem infarct or hemorrhage. A randomized, placebo-controlled study of DBN has shown that the potassium-channel blockers 3,4-diaminopyridine and 4-aminopyridine can significantly improve this type of nystagmus. The dosage is 5–10 mg t.i.d.; follow-up ECG is necessary. The effectiveness of this treatment has since been confirmed by multiple studies. 4-aminopyridine seems to be effective against UBN as well, but this has been documented to date only in a single case study. The familial episodic ataxias are rare genetic diseases of autosomal dominant transmission. There are at least two well-defined varieties. Type 2 (EA 2) is characterized by recurrent attacks of dizziness and ataxia that are precipitated by physical activity, stress, or alcohol and usually last for hours. In between attacks, more than 90% of patients have marked central ocular motor disturbances, often DBN. EA 2 is caused by mutations in the CACNA1A gene (PQ calcium channel gene). Most patients can be treated successfully with acetazolamide. If this treatment is ineffective, or if adverse effects such as kidney stones develop, patients with EA 2 can also be treated with 4-aminopyridine (5 mg t.i.d.). Aminopyridines are thus an effective treatment for DBN, UBN, and EA 2 which is well tolerated at the low dose that is generally used. These studies have also led to the development of a new principle of treatment; activation of cerebellar Purkinje cells through potassium-channel blockade enhances the cerebellar inhibitory influence on the vestibular and cerebellar nuclei.

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