

REVIEW ARTICLE

Central Oculomotor Disturbances and Nystagmus

A Window Into the Brainstem and Cerebellum

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SUMMARY

Background: Oculomotor disturbances and nystagmus are seen in many diseases of the nervous system, the vestibular apparatus, and the eyes, as well as in toxic and metabolic disorders. They often indicate a specific underlying cause. The key to diagnosis is systematic clinical examination of the patient's eye movements. This review deals mainly with central oculomotor disturbances, i.e., those involving smooth pursuit, saccades, gaze-holding, and central types of nystagmus.

Methods: We searched the current literature for relevant publications on the diagnosis and treatment of oculomotor disturbances and nystagmus, and discuss them selectively in this review along with the German Neurological Society's guidelines on the topic.

Results: A detailed knowledge of the anatomy and physiology of eye movements usually enables the physician to localize the disturbance to a specific area in the brainstem or cerebellum. The examination of eye movements is an even more sensitive method than magnetic resonance imaging for the diagnosis of acute vestibular syndromes and for the differentiation of peripheral from central lesions. For example, isolated dysfunction of horizontal saccades is due to a pontine lesion, while isolated dysfunction of vertical saccades is due to a midbrain lesion. Generalized gaze-evoked nystagmus (GEN) has multiple causes; purely vertical GEN is due to a midbrain lesion, while purely horizontal GEN is due to a pontomedullary lesion. Internuclear ophthalmoplegia involves a constellation of findings, the most prominent of which is impaired adduction to the side of the causative lesion in the ipsilateral medial longitudinal fasciculus. The most common pathological types of central nystagmus are downbeat and upbeat nystagmus (DBN, UBN). DBN is generally due to cerebellar dysfunction, e.g., because of a neurodegenerative disease.

Conclusion: This short review focuses on the clinical characteristics, pathophysiology and current treatment of oculomotor disorders and nystagmus.

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Many patients present to hospitals and doctor's surgeries with symptoms of blurred vision, "bouncing images" (oscillopsias), double vision, staggering or vestibular vertigo, tendency to fall, or gait disturbances. These symptoms are often accompanied by oculomotor disturbances. In acute onset of symptoms, the most important differential diagnosis is ischemia of the brainstem or cerebellum. If the symptoms become chronic, then the possible causes range from neurodegenerative or inflammatory disorders to tumors. In order to classify the symptoms topographically-anatomically, a precise clinical examination of the different eye movements is required, particularly in order to distinguish between central and peripheral oculomotor and vestibular disorders (1). A recent publication showed that the examination of eye movements is more sensitive for the diagnosis of acute vestibular syndromes and the differentiation between peripheral and central lesions than magnetic resonance imaging (MRI) (including diffusion weighted sequences) (2). The diagnosis of an acute central disorder requires rapid admission to the hospital, since this may be caused by brainstem ischemia, for example.

Examining patients with oculomotor disturbances presents a particular challenge for many clinicians, for three reasons:

- The anatomy and physiology of the affected oculomotor, vestibular, and cerebellar systems are complex.
- The neurological and neuro-ophthalmological examination requires a systematic approach and an "experienced diagnostic perspective."
- The interpretation requires an evaluation of all neuro-otological and neuro-ophthalmological findings.

Because of the clinical importance of this topic for several disciplines (especially neurology; otorhinolaryngology; ophthalmology; internal medicine, pediatrics), it seems useful to summarize the current state of knowledge.

This review article will present the examination procedure and the different eye movements with their topographical-anatomical relevance. The second part will present the most common forms of nystagmus.

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TABLE 1

Examination of oculomotor and vestibular systems

Type of examination	Look for
Inspection	
– Body and head posture	Head tilt
– Position of the eyelids	Ptosis
Eye position / motility:	
– Position of the eyes when looking straight ahead – cover-test – examination of the eyes in the eight final positions (binocular and monocular) – that is, right, left, upwards, downwards, and in the 4 diagonals	Primary misalignment, spontaneous nystagmus, fixation nystagmus, horizontal or vertical misalignment, latent nystagmus, determining the extent of movement of extreme end-point nystagmus
Gaze function	
– Gaze to about 10° to 40° horizontal or 10° to 40° vertical and back to 0°	Gaze-evoked nystagmus horizontal and vertical rebound nystagmus
Smooth pursuit	
– horizontal and vertical	Saccadic
Saccades	
– horizontal and vertical when looking around and when precisely instructed to look in a direction	Latency, velocity, precision of aim, and non-conjugated movements
Optokinetic nystagmus (OKN)	
– horizontal and vertical with OKN drum or OKN tape	Trigger, vertical or horizontal direction, and phase (reversed?)
Peripheral vestibular function	
– clinical testing of the vestibulo-ocular reflex (VOR), rapid head rotation and fixation of a stationary point	Unilateral or bilateral peripheral vestibular lesion
Visual fixation suppression of the VOR	
– Fixation of a target while rotating the head and moving the target at the same angular velocity	No suppression of the VOR; this is a sign of a central, mostly cerebellar, impairment
Examination with Frenzel's spectacles	
– Looking straight ahead, right, left, up, down - head-shaking test - positioning maneuver for vertigo	Spontaneous nystagmus (typically suppressed by fixation) head-shaking nystagmus postural vertigo in benign paroxysmal positional vertigo or central positioning nystagmus (rare)

Any repetitions are intentional, owing to two different perspectives: from the clinical symptom to functional anatomy, and vice versa.

Clinical importance

Oculomotor disturbances or nystagmus—periodic, mostly involuntary, eye movements—are of topodiagnostic importance especially in patients with lesions in the brainstem region (which often means additional brainstem symptoms) or cerebellum. This also applies to patients with rotatory or postural vertigo, caused, for example, by acute unilateral failure of the labyrinth, a brainstem infarction, or cerebellar disorders. Provided a systematic approach is taken, it is possible in most cases—even without equipment-based additional investigations—to make a correct topographical-anatomical diagnosis, since precise anatomical and neurophysiological information is available (3–6) and relevant functional impairments will be identified during the physical examination.

Before we focus on pathological eye movements, here is a list of the 6 physiological forms:

- Gaze pursuit, the eye follows a moving target
- Saccadic pursuit—that is, the gaze rapidly jumps from one fixation point to another
- Fixation
- Vergence eye movements—that is, movements during which the eyes do not move in parallel but relative to one another
- Vestibulo-ocular reflex (VOR, the signal triggering eye movements comes from the labyrinth), and
- Optokinetic reflex (consists of smooth pursuit and saccades).

All these eye movements serve to keep the visual target on the macula stable and thus avoid illusory movements and blurred vision.

Medical history and clinical examination

Depending on the underlying cause, patients with oculomotor disturbances usually report the following symptoms, in isolation or in combination:

- Blurred vision
- Double vision
- Jumping images, so called oscillopsias
- Rotatory vertigo
- Postural vertigo
- Tendency to fall and/or
- Brainstem-related symptoms (for example, swallowing or speaking difficulties) or cerebellar symptoms (for example, coordination problems of the extremities) or the inner ear (for example, hearing loss or tinnitus).

Table 1 shows the most important aspects of the clinical examination.

When examining the patient, attention should be paid to the position of the eyes, when the patient looks straight ahead or when one eye is covered or when either eye is covered in alternation—that is, parallel position or horizontal/vertical misalignment. The



Figure 1: Clinical examination of eye position and eye movements with an examination flashlight. The advantage of this examination is that the images reflected on the retina can be observed and ocular misalignments therefore identified. It is important that the examiner looks at the retinal images from the direction of the light and that the patient is instructed to fixate his/her gaze on the target object. Gaze-evoked nystagmus to all sides is usually caused by medication (such as antiepileptic drugs, benzodiazepines) or intoxication (for example, alcohol). Downbeat nystagmus increases when looking sideways and when looking downwards.

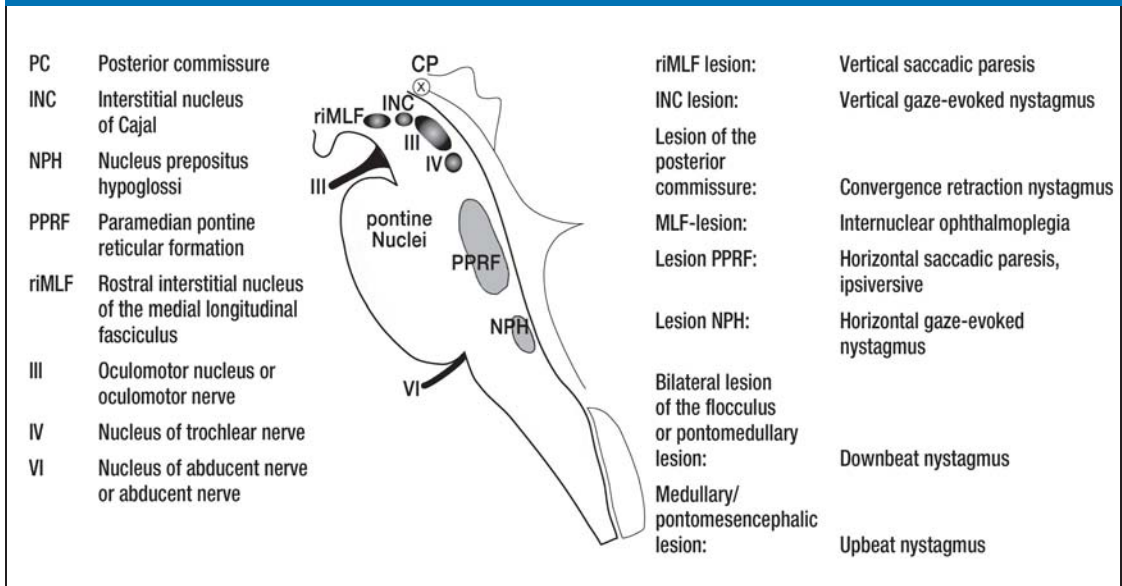


Figure 2: Clinical examination of saccades. Spontaneous saccades that are triggered by visual or acoustic stimuli should be studied first. Then the patient should be asked to switch his/her gaze between two horizontal and two vertical targets. The velocity and accuracy of the saccades should be observed, and whether they are conjugate. In healthy subjects, the target will be reached immediately or will be made by one correctional saccade. Generally slower saccades, which are usually accompanied by hypometric saccades, occur in neurodegenerative disorders, for example. Slowed horizontal saccades are usually observed in pontine brainstem lesions and slowed vertical saccades in midbrain lesions. Hypermetric saccades, which are recognized by a corrective saccade back to the target, are found in cerebellar lesions. The pathognomonic sign of internuclear ophthalmoplegia is a slowed adducting saccade ipsilaterally to the defect of the medial longitudinal fasciculus.



Figure 3: Clinical examination using Frenzel's spectacles. The lenses, which are illuminated from within and contain enlargement lenses (+16 diopters) prevent gaze fixation, which may suppress peripheral vestibular spontaneous nystagmus, for example. On the other hand, they make it easier to study the patient's eye movements. When Frenzel's spectacles are used to examine a patient, attention should be paid to possible spontaneous nystagmus, gaze-evoked nystagmus, head-shaking nystagmus (to this end, the patient should be asked to turn his/her head quickly from right to left and back, about 20 times; subsequently the eye movements should be studied), positional nystagmus and hyperventilation induced nystagmus. Pay attention to positioning nystagmus which indicates a muscle tonus imbalance of the vestibulo-ocular reflex; if this originates from a peripheral vestibular lesion—such as occurs, for example, in vestibular neuritis—then the nystagmus can be typically suppressed by visual fixation. Head-shaking nystagmus indicates a latent asymmetry of the so-called velocity storage; this may be due to peripheral or central vestibular functional disorders.

FIGURE 4



The supranuclear centers for controlling eye movements. These allow exact topographical determination: lesions in the region of the interstitial nucleus of Cajal (INC) lead to a vertical gaze-holding defect, lesions in the region of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) leads to impairments of vertical saccades, lesions of the paramedian pontine reticular formation (PPRF) result in impairments of the horizontal saccades, lesions of the nucleus prepositus hypoglossi (NPH) are characterized by a horizontal gaze-holding defect (adapted from [5, 6]).

question to ask is whether latent heterophoria or manifest heterotropia is present.

Afterwards the position of the eyes should be examined in the eight final positions, looking for positional deficits of one eye (for example, in cases of paresis of the ocular muscle) or both eyes (for example, in supranuclear gaze palsy). While doing this it is possible to identify a so-called saccadic dysmetria in the form of a gaze deviation nystagmus (the rapid phase of the nystagmus beats in the direction of the line of vision) (Figure 1). The examination for so-called end-point nystagmus is a widespread clinical problem. End-point nystagmus is pathological if it lasts for longer than 20 seconds (sustained end-point nystagmus), is notably asymmetrical, and/or is accompanied by other oculomotor disturbances.

For smooth pursuit one should test whether the movement is smooth or saccadic; the latter would indicate a central oculomotor disturbance. A vertically slightly downwards saccadic pursuit is also found in healthy subjects. The physiological visual suppression of fixation of the VOR is an important test for the pursuit system. It is impaired in people with central lesions in the cerebellar region. In order to test the visual fixation suppression of the VOR, the patient fixates a target that moves at the same angle speed as the patient's head.

In case of saccades, attention should be paid to their velocity and accuracy (Figure 2) and to whether both eyes move in parallel (see internuclear ophthalmoplegia). Hypermetric saccades are present in cerebellar

impairments, hypometric saccades mostly in brainstem lesions and neurodegenerative disorders. In progressive supranuclear gaze palsy—an important differential diagnosis for idiopathic Parkinson's syndrome—the vertical saccades slow down first and then, during disease progression, the horizontal saccades also, with bilateral gaze palsy as the ultimate outcome. This oculomotor disturbance can be overcome by the VOR (testing by means of Halmagyi's head-impulse test [1]) because it does not pass through the supranuclear gaze centers.

Finally, the optokinetic drum can be used to examine slow and rapid eye movements by triggering optokinetic nystagmus (OKN). This examination method is particularly helpful in patients with impaired vigilance or unsatisfactory compliance, and in children. A horizontally and vertically intact OKN indicates intact brainstem functioning.

Clinical examination of nystagmus

The term nystagmus comes from the Greek word "nystázein," which means "to drop off to sleep." This usually means involuntary eye movements, mostly consisting of slow eye drift (of pathological cause) and a rapid reversal (3–6). The direction of the nystagmus is indicated by the rapid phase as it is more easily detectable. Readers can view most forms of nystagmus in video sequences by following this link (www.Schwin.delambulanzMuenchen.de).

Patients with suspected nystagmus should be examined as follows:

- In the so-called primary position—meaning: gazing straight ahead—the question is whether they are affected by fixation nystagmus or spontaneous nystagmus. Fixation nystagmus is not substantially suppressed by fixation but rather increases and is caused by a central disorder, mostly in the brainstem/cerebellar regions (*Case Illustration*). Horizontal-torsional spontaneous nystagmus in peripheral vestibular disorders is suppressed by fixation, and the suppression requires intact functioning of brainstem and cerebellum. Nystagmus that is purely horizontal, vertical, or torsional usually has a central cause.
- Frenzel’s spectacles reduce visual fixation suppression, so that spontaneous nystagmus becomes obvious. All patients should therefore be examined using Frenzel’s spectacles (*Figure 3*) or the ophthalmoscope. The typical direction in which peripheral vestibular spontaneous nystagmus beats is horizontal-rotating to the non-affected side in acute vestibular neuritis, for example.
- In the sideways, upwards, and downwards gaze, the question is whether gaze deviation nystagmus or an increase/decrease in the intensity of a fixation or spontaneous nystagmus is present (*Figure 1*). Typically, an increase is noted when the patient looks in the direction of the rapid phase of nystagmus.
- While the patient lies on his/her side, it should be determined whether peripheral positioning nystagmus (as in the most common form of vertigo: benign, peripheral, positioning vertigo [BPPV]) or a rare central positional or positioning nystagmus is present. Positioning nystagmus occurs during or shortly after change of position; central positional nystagmus is sustained after changing position. How can the common BPPV be distinguished from the rare central positioning or positional nystagmus? In BPPV the direction of the nystagmus corresponds to the level of the semicircular canal that is stimulated or inhibited by the otoconias that move freely within it—which is mostly the posterior semicircular canal. In central spontaneous or positioning nystagmus, the assumption of different positions of the head will trigger a very similar nystagmus.
- Finally, use the “head-shaking” test: the patient is asked to rapidly turn his/her head from side to side about 20 times while keeping the eyes closed. Subsequently, the eye movements are studied with Frenzel’s spectacles. In case of unilateral vestibular functional impairment, horizontal-torsional head-shaking nystagmus will develop towards the side of the non-affected labyrinth. In central impairments, horizontal shaking of the head can trigger vertical nystagmus (so-called cross-coupling).

Oculomotor disturbances

Topographically and anatomically, oculomotor disturbances can be classified as follows:

TABLE 2

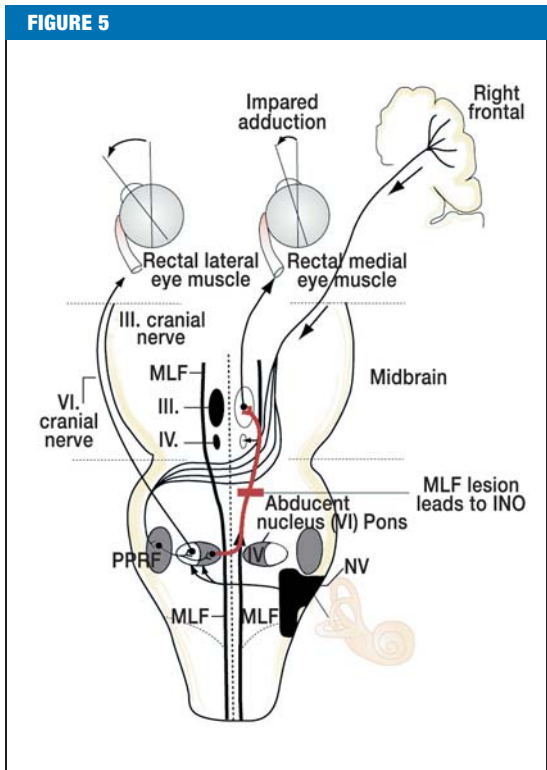
a) Anatomical origin of oculomotor disturbances and nystagmus

Clinical finding: oculomotor disturbances and nystagmus	Suspected location of damage in the brainstem/cerebellum
Isolated vertical saccadic paresis	Midbrain (rostral interstitial nucleus of the medial longitudinal fasciculus, riMLF)
Isolated horizontal saccadic paresis isolated unilateral horizontal saccadic paresis	Pons (paramedian pontine reticular formation, PPRF) lesion ipsilateral to PPRF
Hypermetric saccades	Cerebellum
Isolated vertical gaze-evoked nystagmus - that is, upwards and downwards	Midbrain (interstitial nucleus of Cajal, INC, - that is, of the neuronal integrator of vertical [and torsional] eye movements)
Isolated gaze-paretic nystagmus, right and left	Ponto-medullary/cerebellar (nucleus prepositus hypoglossi, vestibular nuclei, vestibulocerebellum - that is, of the neuronal integrator of horizontal eye movements)
Internuclear ophthalmoplegia	Ipsilateral MLF-lesion on the side of impaired eye adduction
Downbeat nystagmus	Mostly cerebellum with bilateral flocculus impairment
Upbeat nystagmus	Medulla oblongata or midbrain
Convergence-retraction nystagmus	Midbrain (posterior commissure)

b) Functional anatomy of the cerebellum with regard to oculomotor disturbances and nystagmus

Location of damage	Typical findings
Flocculus/Paraflocculus	Saccadic pursuit, downbeat nystagmus, rebound nystagmus, impaired visual fixation of the vestibulo-ocular reflex (VOR)
Nodulus/uvula	Central positional nystagmus, periodic alternating nystagmus
Vermis/fastigial nucleus	Hypermetric or hypometric saccades

- Peripheral forms affect the 6 outer and/or 2 inner ocular muscles or the oculomotor nerve, trochlear nerve, or abducent nerve. Patients with peripheral oculomotor disturbances often complain of diplopia, which intensifies in the direction of the paretic muscle/nerve. Peripheral oculomotor disturbances usually affect one eye only (important exceptions: myasthenia gravis, chronic progressive, external ophthalmoplegia).
- Central forms usually affect both eyes. These are manifestations of functional impairments of the brainstem (*Figure 4*), cerebellum, or (rarely) other higher-level centers. Patients with central oculomotor disturbances may report unclear or blurred vision. If the oculomotor disturbance is slowly progressive, such as in progressive supranuclear gaze palsy, it may remain undetected for a long time. Mostly, the extent of the subjective impairments also depend on how acutely the impairments develop.



Defects of the medial longitudinal fasciculus (MLF) with the result of an impairment of the VI to III projection (between abducent nucleus and oculomotor nerve via abducent interneurons) (pathway shown in red) as the cause of internuclear ophthalmoplegia (INO). This leads to a lack of or defective signal transmission to the oculomotor nucleus, resulting in impaired adduction (this, not the dissociated nystagmus, is pathognomonic for INO). The side of the impaired adduction corresponds to the side of the INO and the defective MLF. The direct projection from the abducent nucleus via motoneurons to the rectal lateral eye muscle is not impaired.

Central oculomotor disturbances can be classified as:

- Fascicular lesions, i.e., defects of the (short) part of the individual ocular muscle nerves within the brainstem. These are very rare; at first glance they look like unilateral peripheral lesions, but are accompanied by central oculomotor disturbances.
- Nuclear lesions: defects of the oculomotor nucleus (because of the anatomical proximity, almost always both nuclei are affected), the trochlear nucleus or the abducent nucleus.
- Supranuclear lesions due to defects of oculomotor pathway systems or supranuclear nuclei (Table 2a). Supranuclear oculomotor disturbances usually impair the movement of both eyes, for example, in the form of gaze palsy, slowed saccades, saccadic pursuit, or a gaze-holding defect, because the structures that are higher-level to the cerebral nerve nuclei are affected. Often, such oculomotor disturbances are associated with other

neurological deficits, so that the “overlap” of the neurological findings allows us to locate the level of the lesion in the brainstem region as well as the side.

- Cerebellar impairments lead to impaired smooth pursuit, gaze-holding function, or saccades (Table 2b).

Topographical anatomy

For triggering and controlling eye movements, only a few brainstem centers are important, which have clearly allocated functions (Figure 4, Table 2a). This makes their pathological anatomy easy to understand. The following simple clinical rule applies: horizontal eye movements are generated and controlled in the pontine region, whereas vertical (and torsional) eye movements originate in the midbrain.

- Midbrain centers: the center for vertical saccades is the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), the center for vertical gaze-holding function is the interstitial nucleus of Cajal (INC). Clinically this means that an isolated vertical saccadic paresis or isolated vertical gaze deviation nystagmus would suggest a midbrain lesion.
- Pontine and pontomedullary centers: the center for horizontal saccades is the paramedian pontine reticular formation (PPRF); the center for the horizontal gaze-holding function the nucleus prepositus hypoglossi together with the vestibular nuclei and the vestibulocerebellum; these form the “neuronal integrator.” Clinically this means that isolated horizontal saccadic palsy indicates a pontine lesion, and a unilateral PPRF lesion will result in saccadic disturbances on the side of the lesion. A purely horizontal gaze-evoked nystagmus originates from a pontine lesion.
- Cerebellar centers: cerebellar lesions are often accompanied by clinically easily identifiable oculomotor disturbances. For example, defects of the flocculus/paraflocculus are characterized by saccadic pursuit, downbeat nystagmus, and impairments of the visual fixation suppression of the VOR (Table 2b). Paraneoplastic cerebellar disorders often lead to opsoclonus, in addition to the oculomotor disturbances mentioned above. This term describes rapid, irregular saccades in all directions.

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) originates from a lesion of the internuclear pathway between the nuclei of the abducent and oculomotor nerves. The pathways from the interneurons of the abducent nucleus cross at the same level and then extend right into the medial longitudinal fasciculus (MLF) and innervate the motoneurons of the rectus medialis muscle (Figure 5). Clinically, internuclear ophthalmoplegia is characterized by an impairment of the conjugated sideways gaze, with adduction inhibition of the eye on the side of the MLF lesion. This is the pathognomonic sign.

Additionally, dissociated nystagmus is present. The proof of internuclear ophthalmoplegia is the fact that the adduction paresis is overcome by convergence at close range, since this is not connected with the medial longitudinal fasciculus. In mild forms of this disturbance, the only symptom will be slowing of the adduction saccades. Examination of the saccades is therefore the most sensitive clinical test. With regard to the etiology, a simple rule applies: the cause of INO in a patient younger than 60 is likely to be multiple sclerosis, in a patient older than 60, a vascular lesion.

Wallenberg's syndrome

The cause of Wallenberg's (lateral medullary) syndrome is an infarction in the region of the dorsolateral medulla oblongata. Typical vestibular and oculomotor disturbances are

- "Ocular tilt reaction": this is characterized by tilting of the subjective visual vertical (SVV), ocular torsion, vertical misalignment (skew deviation or vertical divergence), which means that one eye is lower than the other, and/or the head is inclined to the affected side. Determining the SVV is a sensitive test for acute impairments of the peripheral or central vestibular system and can easily be conducted using the "bucket" test.
- Nystagmus to the non-affected side
- Hypermetric saccades to the side of the lesion, hypometric to the other side
- Horizontal gaze-evoked nystagmus. Often, central Horner syndrome is present (ptosis, miosis, and enophthalmos) on the affected side.

Central forms of nystagmus

Finally, we describe the two most common forms of nystagmus and the current therapeutic approaches: downbeat nystagmus and upbeat nystagmus, and their treatment with aminopyridines. Both are types of fixation nystagmus, which, in contrast to other types of peripheral vestibular spontaneous nystagmus can hardly or not at all be suppressed by gaze fixation—which rather increases them, leading to blurred vision and oscillopsia.

Downbeat nystagmus (DBN)

DBN is the most common form of persistent nystagmus. It is a type of fixation nystagmus with the fast phase beating in a downward direction. It generally increases when looking to the side and down and when lying prone. This type of nystagmus manifests in 80% of patients with uncertain posture and gait and in 40% with vertical oscillopsia (8).

DBN is mostly due to a bilateral defect of the cerebellar flocculus (3). The causes are degenerative disorders of the cerebellum, cerebellar ischemias or Arnold-Chiari malformation, and in individual cases paramedian lesions of the medulla oblongata (8, 9).

The defect of the flocculus will result in reduced release of gamma-aminobutyric acid (GABA) and thus disinhibition of the vestibular nuclei. On the basis of

KEY MESSAGES

- The clinical examination of the different eye movements (pursuit, rapidly jumping gaze, gaze function) and nystagmus (for example, spontaneous nystagmus or fixation nystagmus) in most cases allows topographic-anatomic diagnosis in the brainstem or cerebellum and differentiation between peripheral and central oculomotor and vestibular lesions.
- The diagnosis of peripheral vestibular impairments is a diagnosis of exclusion, which can only be made if no central oculomotor disturbances are found. Peripheral ophthalmological impairments—such as paresis of an eye muscle or a nerve thereof—usually affect one eye only, and no central oculomotor disturbances are found.
- Isolated impairments of vertical eye movements (for example, vertical gaze paresis, vertically saccadic pursuit, vertical gaze deviation nystagmus) indicate a lesion in the midbrain region; isolated impairments of horizontal eye movements indicate a lesion in the pontine region.
- Cerebellar impairments can result in a multitude of oculomotor disturbances, such as saccadic pursuit, gaze-evoked nystagmus, impaired visual fixation suppression of the vestibulo-ocular reflex (VOR), or downbeat nystagmus.
- Downbeat nystagmus is the most common form of persistent nystagmus. The cause is usually a bilateral impairment in the flocculus region. The treatment of choice is administration of 4-aminopyridine.

this pathomechanism, a study investigated the effects of aminopyridines in a prospective, randomized, placebo-controlled study that showed a significant improvement (10); the results were confirmed by other studies (11, 12). The strongest effect was observed in patients with cerebellar atrophy (13). The current therapeutic recommendation is for 4-aminopyridine $2 \times 5-2 \times 10$ mg/d (nonstandard treatment); one hour before and after the first ingestion a control ECG should be performed (the QTc interval should not be prolonged). Since the drug only has a symptomatic effect, continuous treatment is required. The stipulated mechanism of action is an increase in the resting activity and excitability of Purkinje cells; this was confirmed by in-vitro studies (14). Recent animal studies have shown that aminopyridines synchronize the irregular spontaneity of Purkinje cells (15). By means of an increased release of GABA this is assumed to strengthen the inhibitory influence of Purkinje cells on vestibular/cerebellar nuclei.

Upbeat nystagmus (UBN)

UBN is rarer than DBN and is also a fixation nystagmus. In primary position the UBN beats upward. Oscillopsias are often very irritating, but the symptoms are usually transient. In most cases, paramedian lesions in the medulla oblongata or the midbrain are found, for example, in patients with multiple sclerosis, brainstem ischemia or tumors, or Wernicke's encephalopathy (4). Observational studies have shown a positive effect of baclofen (15–30 mg/d) (16) and 4-aminopyridine (5–10 mg/d) (17).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

1. Strupp M, Brandt T: Diagnosis and treatment of vertigo and dizziness [Leitsymptom Schwindel: Diagnose und Therapie]. *Dtsch Arzteblatt Int* 2008; 105: 173–80.
2. Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE: HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. *Stroke* 2009; 40: 3504–10.
3. Leigh RJ, Zee D: *The neurology of eye movements* (4th ed.). Oxford, New York: Oxford University Press 2006.
4. Brandt T, Dieterich M, Strupp M: *Vertigo – Leitsymptom Schwindel*. Darmstadt: Steinkopff, 2. Auflage, 2011.
5. Thömke F: *Augenbewegungsstörungen*. Stuttgart, Thieme Verlag 2001.
6. Buttner-Ennever JA: Anatomy of the oculomotor system. *Dev Ophthalmol* 2007; 40: 1–14.
7. Zwergal A, Rettinger N, Frenzel C, Frisen L, Brandt T, Strupp M: A bucket of static vestibular function. *Neurology* 2009; 72: 1689–92.
8. Wagner JN, Glaser M, Brandt T, Strupp M: Downbeat nystagmus: aetiology and comorbidity in 117 patients. *J Neurol Neurosurg Psychiatry* 2008; 79: 672–7.
9. Wagner J, Lehnen N, Glasauer S, et al.: Downbeat nystagmus caused by a paramedian ponto-medullary lesion. *J Neurol* 2009; 256: 1572–4.
10. Strupp M, Schuler O, Krafczyk S, et al.: Treatment of downbeat nystagmus with 3,4-diaminopyridine: a placebo-controlled study. *Neurology* 2003; 61: 165–170.
11. Helmchen C, Sprenger A, Rambold H, Sander T, Kompf D, Straumann D: Effect of 3,4-diaminopyridine on the gravity dependence of ocular drift in downbeat nystagmus. *Neurology* 2004; 63: 752–3.
12. Bense S, Best C, Buchholz HG, et al.: 18F-fluorodeoxyglucose hypometabolism in cerebellar tonsil and flocculus in downbeat nystagmus. *Neuroreport* 2006; 17: 599–603.
13. Kalla R, Glasauer S, Buttner U, Brandt T, Strupp M: 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain* 2007; 130: 2441–51.
14. Etzion Y, Grossman Y: Highly 4-aminopyridine sensitive delayed rectifier current modulates the excitability of guinea pig cerebellar Purkinje cells. *Exp Brain Res* 2001; 139: 419–25.
15. Alvina K, Khodakhah K: The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. *J Neurosci* 2010; 30: 7258–68.
16. Dieterich M, Straube A, Brandt T, Paulus W, Buttner U: The effects of baclofen and cholinergic drugs on upbeat and downbeat nystagmus. *J Neurol Neurosurg Psychiatry* 1991; 54: 627–32.
17. Glasauer S, Kalla R, Buttner U, Strupp M, Brandt T: 4-aminopyridine restores visual ocular motor function in upbeat nystagmus. *J Neurol Neurosurg Psychiatry* 2005; 76: 451–3.

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REVIEW ARTICLE

Central Oculomotor Disturbances and Nystagmus

A Window Into the Brainstem and Cerebellum

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CASE ILLUSTRATION

A 65-year-old male patient with diabetes mellitus and arterial hypertension presents to the doctor's surgery as an emergency. He reports severe rotatory vertigo, with sudden onset on the morning of the same day. He also complains of blurred vision, jumping images, and a tendency to fall to the right. He also has symptoms of nausea and vomiting.

In terms of a differential diagnosis, his medical history would lead you to assume one of two causes: an acute unilateral vestibular disturbance (by diagnosis of exclusion) or a central lesion. In most cases, the clinical examination would allow differentiation between the two.

During the clinical examination, you discover a nystagmus, which beats to the left and has a rotational component. The intensity of the nystagmus does not increase when you use Frenzel's spectacles, that is, when "switching off" the fixation. The cover test shows that the right eye is lower than the left (vertical divergence). Furthermore, the patient has gaze-evoked nystagmus to the right, that is, when looking in the opposite direction of the fast phase of the nystagmus. The patient's pursuit is horizontally saccadic. Visual fixation suppression of the vestibulo-ocular reflex is impaired.

These oculomotor disturbances (especially the fixation nystagmus and the vertical divergence) indicate a central lesion in the brainstem region. The specialist physician in private practice therefore refers the patient as an emergency case to the hospital with suspected brainstem infarction. On computed tomography scanning, no signs of hemorrhage are found. Doppler/Duplex tests and electrocardiogram are normal. The patient is admitted to a stroke unit and treated with Aspirin and a lipid-lowering drug. Diffusion-weighted magnetic resonance imaging (MRI) of the skull shows an infarction on the right side in the transitional area between pons and medulla oblongata, where the vestibular nerve enters. The clinically suspected diagnosis of central vestibular pseudoneuritis on the right side is confirmed by MRI.