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Acquired nystagmus

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Abstract

Nystagmus is the repetitive to and fro movement of the eyes, which may be physiological or pathological. The movements can be horizontal, vertical, torsional or a combination of these movements. It starts by a slow movement of the eye away from the visual target. The second movement brings the eye back to the visual target. If this second movement is quick, the nystagmus is called jerk nystagmus. If the second movement is slow, the nystagmus is said to be pendular. Maintaining steady gaze is dependent upon visual fixation, the vestibulo-ocular reflex and the gaze-holding neural integrator system. Pathological nystagmus typically presents with the symptom of oscillopsia, which is the illusory movement of the surrounding environment. Nystagmus that develops outside of early infancy is termed acquired nystagmus. There may be serious underlying pathology that will require further investigation and management. This article reviews the terminology, pathophysiology, causes and treatment of acquired nystagmus.

Key words: Acquired nystagmus; Conjugate nystagmus; Horizontal nystagmus; Nystagmus; Oscillopsia; Rotational nystagmus; Vertical nystagmus

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Introduction

Nystagmus is defined as a repetitive to and fro movement of the eyes. The prevalence of nystagmus is estimated to be 24 per 10 000 individuals, being more common in the white European population (Sarvananthan et al, 2009). Nystagmus may be physiological or pathological. Physiological nystagmus preserves clear vision during self-rotation. Pathological nystagmus can degrade vision and produce oscillopsia. A decline in visual acuity can occur if there is retinal image slip (the image is no longer focused on the fovea) of greater than 5° per second (Thurtell and Leigh, 2011). The impact on visual function can be substantial and many adults with nystagmus have low visual function comparable with that of patients with age-related macular degeneration (Pilling, 2005). Oscillopsia is defined as the illusion of an unstable (oscillating) visual world. Oscillopsia is a symptom of acquired nystagmus and uncommon in early onset nystagmus.

In nystagmus there is a slow movement away from fixation that is corrected either by a fast movement (jerk nystagmus) or by another slow movement (pendular nystagmus). The direction of jerk nystagmus is named according to the direction of the quick phases, even though it is the slow phases that are abnormal.

This article focuses on the terminology, pathophysiology, causes and treatment of acquired adult-onset nystagmus. The classification is shown in Figure 1.

Pathophysiology

There are three main mechanisms which are involved in maintaining steady gaze (Stahl, 2000):

1. Visual fixation is the visual system's ability to detect retinal image slip and programme corrective eye movements and the ability to suppress unwanted saccades that would take the eye away from the target
2. The vestibulo-ocular reflex by which steady gaze is maintained during head movements
3. Gaze-holding system (the neural integrator) is a network of neurones required to hold the eyes in eccentric gaze. A constant level of fine tuning of muscle activity is needed to counteract the elastic pull of the extraocular structures (eg fat, muscles), which would tend to return the eye toward a central position in the orbit.

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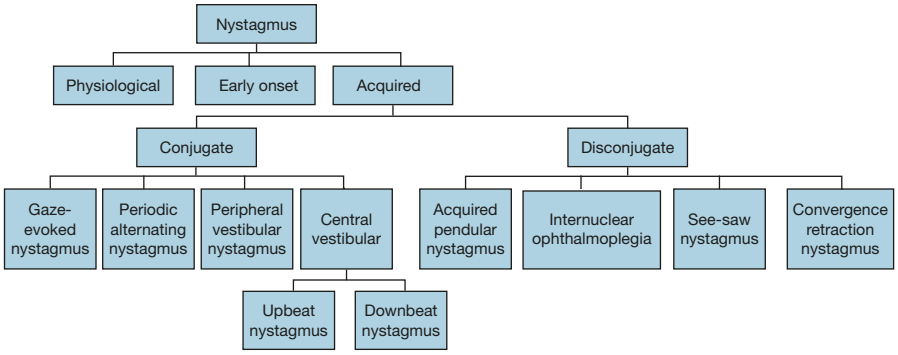

Figure 1. Classification of acquired nystagmus can be broadly divided into conjugate and disconjugate nystagmus. Conjugate nystagmus implies that both eyes have identical movements, whereas disconjugate implies separate movements.

Table 1. Common terms used to describe nystagmus

Frequency	How often the eye oscillates per second; this can be broadly divided into high, moderate or low
Amplitude	How far the eyes move; this can be fine or coarse
Alexander's law	Nystagmus increases in amplitude and frequency as the patient looks in the direction of the fast phase
Null point	A particular direction of gaze where the nystagmus has a lower intensity. If the null point is not the primary gaze position, the patient may develop a head turn in an effort to reduce the nystagmus
Dissociated nystagmus	The two eyes having nystagmus with the same direction but with differing amplitudes
Foveation period	A brief period of time during nystagmus when visual acuity is the best as the eye is pointed at the object of interest with minimum velocity

Any interruptions of the above systems can lead to the development of nystagmus. Common terms used to describe nystagmus are listed in Table 1.

Acquired nystagmus – conjugate

Gaze-evoked nystagmus

Gaze-evoked nystagmus is induced by turning the eye to an eccentric position in the orbit. It is a term that includes both physiological (end-point) and pathological nystagmus.

Maintaining horizontal gaze in a particular direction for a sustained period requires repeated signals from a neural integrator to the relevant extraocular muscles (Abadi, 2002). However, if this gaze-holding system is disrupted, the eyes will tend to drag into a 'primary position', that is straight ahead (Stahl, 2000; Abadi, 2002). This movement is the slow phase in gaze-evoked nystagmus. The slow phase causes the image on the retina to slip, stimulating a compensatory fast saccadic movement of the eye back in the direction of intended gaze, re-centring the image. For example, on looking to the left the patient will develop jerking eye movements with the fast phase to the left.

Gaze-evoked nystagmus tends to start at a smaller angle (<45°) than physiological end-point nystagmus (Denniston and Murray, 2018). Unfortunately, it is not a particularly useful localising sign. The central neural integrator is made up of a network of nuclei from the midbrain, pons and medulla, with the cerebellum playing an independent role in sustaining gaze in a given direction. Disease processes affecting any of these areas, such as stroke, demyelination or compressive lesions, can cause gaze-evoked nystagmus, which is usually unilateral and asymmetric. When present in both horizontal and upgaze, gaze-evoked nystagmus usually signifies a toxic metabolic process secondary to alcohol, barbiturates, ketamine or pharmacological causes (carbamazepine, lithium, phenytoin, amiodarone, morphine) (Table 2) (Denniston and Murray, 2018).

Table 2. Pharmacological agents that induce nystagmus	
Antiepileptics	Carbamazepine
	Phenytoin
	Barbiturates
	Valproic acid
	Lamotrigine
	Topiramate
	Benzodiazepines
	Gabapentin
Drugs of abuse	Ethanol
	Barbiturates
	Morphine
	Amphetamines
	Ecstasy
	Lysergic acid diethylamide (LSD)
	Toluene
	Ketamine
Miscellaneous	Lithium
	Amiodarone
	Salicylates
	Selective serotonin-reuptake inhibitor
	Pyridostigmine
	Nitrofurantoin
	Lidocaine
	Neostigmine

Periodic alternating nystagmus

This is a horizontal jerk nystagmus present in primary position where the direction changes roughly every 2 minutes (Dibartolomeo and Yee, 1988; Stahl, 2000). Starting in a particular direction the nystagmus will get worse then better in a crescendo-decrescendo pattern, before eventually stopping or converting into a vertical nystagmus for roughly ~10 s (Thurtell and Leigh, 2011). It then proceeds in the opposite direction. The hallmark of periodic alternating nystagmus is a shifting null point.

Acquired periodic alternating nystagmus usually indicates a lesion of the cervicomedullary junction, particularly of the cerebellar nodulus or uvula. Common causes are outlined in Table 3 (Leigh and Zee, 2015).

Peripheral vestibular nystagmus

Normal gaze control relies in part on balanced signals from the vestibular apparatus to the respective nuclei on each side (Abadi, 2002). Less activity on a particular side is interpreted by the brain as the head turning away from that side, causing a compensatory movement of the eyes towards the side with less vestibular input (Stahl, 2000). This is the slow phase. Image slip on the retina then triggers a fast eye movement in the opposite direction, resulting in a horizontal jerk nystagmus. For example, a lesion impairing the vestibular apparatus on the right-hand side will cause a slow phase towards the right and a fast phase towards the left. An overactive right vestibular system on the other hand will produce a slow phase towards the left and a fast phase to the right. Examples of lesions impairing vestibular function include labyrinthitis and demyelination, while overactivity is produced by Ménière's disease and benign paroxysmal positional vertigo (Thurtell and

Table 3. Common causes of periodic alternating nystagmus
Chiari malformations and other hindbrain abnormalities
Multiple sclerosis
Cerebellar space-occupying lesions
Cerebellar degenerations

Table 4. Common causes of upbeat nystagmus
Brainstem and cerebellar stroke
Wernicke encephalopathy
Multiple sclerosis
Brainstem and cerebellar tumours
Drugs, for example organophosphate toxicity, tobacco, amitriptyline withdrawal

Leigh, 2011). Patients typically experience other vestibular symptoms such as vertigo, unsteadiness, nausea, vomiting, tinnitus or hearing loss.

Patients experiencing peripheral vestibular nystagmus can improve their control by fixating on a target or looking in the direction of the slow phase, that is towards the underactive side. This is because vestibular control over eye movements can be overridden by visually mediated or voluntary controls (Stahl, 2000; Thurtell and Leigh, 2011).

Central vestibular nystagmus

These forms of nystagmus arise as a result of dysfunction of the many interconnections between the central vestibular structures and the neural integrators. In contrast to peripheral vestibular nystagmus, no improvement is seen by visual fixation (Stahl, 2000).

Upbeat nystagmus

This is a type of central vestibular nystagmus that is usually caused by lesions by lower brainstem pathology or the cerebellum (Denniston and Murray, 2018). It is a vertical jerk-waveform nystagmus with a slow downward drift and quick corrective upward saccade. It usually increases in upgaze (Alexander's law), but not on lateral gaze, and fixation does not dampen it. Convergence may enhance or suppress upbeat nystagmus and may even convert it to downbeat nystagmus (Kim et al, 2006). Common causes are listed in Table 4.

Several mechanisms have been proposed for upbeat nystagmus. These include an imbalance in the vertical vestibulo-ocular reflex pathway, dysfunction of the neural integrator involved in vertical gaze holding, and an impairment of the upward smooth pursuit (Kim et al, 2006).

Downbeat nystagmus

This is the most common form of central vestibular nystagmus. There is a pathological upward drift of the eyes that is then corrected with a downward saccade with sometimes debilitating vertical oscillopsia. It is usually caused by pathology of the craniocervical junction or drug-induced (Table 5). This form of nystagmus follows Alexander's law and is pronounced by downgaze and least in upgaze. It is also increased by convergence and lying prone (Strupp et al, 2014).

Acquired nystagmus – disconjugate

Acquired pendular nystagmus

This type of nystagmus has a sinusoidal waveform, that is slow phases in both directions without corrective quick phases. It can have horizontal, vertical and torsional components with the same frequency. Pendular nystagmus may also be dissociated, and this tends to occur when one eye has impaired visual function (Pavan-Langston, 2008). It can also

Table 5. Common causes of downbeat nystagmus
Cerebellar degenerations (for example hereditary, paraneoplastic)
Chiari malformation and other hindbrain abnormalities
Cerebellar dysfunction (for example mass lesions, stroke)
Drugs (for example lithium, anticonvulsants, alcohol)

be bilateral, associated with brainstem and cerebellar disease, most commonly multiple sclerosis. Acquired pendular nystagmus occurring in combination with a palatal tremor is termed oculopalatal myoclonus. Common causes are brainstem infarction and haemorrhage and the oculopalatal tremor follows the neurological injury by several months, whereas the nystagmus may be apparent sooner. The key pathological feature is olivary hypertrophy (Pane et al, 2017). Acquired pendular nystagmus can also be caused by drug toxicity from sedatives or anticonvulsants, and is also reported in toluene abuse (a substance used in industrial solvents) (Pavan-Langston, 2008). Further causes are Whipple's disease, serotonin syndrome and neurosarcoidosis. Owing to the wide differential diagnoses, a thorough neurological and systemic investigation is necessary in these cases.

Internuclear ophthalmoplegia

Disruption of the medial longitudinal fasciculus in the pons or midbrain results in an internuclear ophthalmoplegia characterised by an ipsilateral adduction deficit and contralateral abducting nystagmus. This is caused by a lesion affecting the communication of the sixth cranial nerve with the third cranial nerve on the contralateral side. Internuclear ophthalmoplegia is most commonly associated with multiple sclerosis, but it is also important to consider a partial third nerve palsy and myasthenia gravis in the differential diagnosis as they may mimic internuclear ophthalmoplegia (Pane et al, 2017). Internuclear ophthalmoplegia can also be associated with one and a half syndrome, which is an ipsilateral gaze palsy and contralateral internuclear ophthalmoplegia. Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) can also occur with bilateral medial longitudinal fasciculus lesions, resulting in exotropia in primary gaze and bilateral internuclear ophthalmoplegia.

See-saw nystagmus

This nystagmus subtype is of slow to medium frequency with a pendular waveform. The nystagmus is vertical and torsional, with one eye being elevated and intorted, while the other is depressed and extorted. This cycle then alternates between the eyes in a slow fashion. This condition is associated with expanding lesions in the suprasellar area or the third ventricle, which cause damage to the midbrain reticular nuclei (Pavan-Langston, 2008). It can be caused by parasellar tumours accompanied by visual field defects such as bitemporal hemianopia, and also syringobulbia and a brainstem stroke (Salmon, 2019). In children, seesaw nystagmus is most commonly seen with craniopharyngiomas (Pavan-Langston, 2008). It is an extremely rare condition, with less than 100 cases reported in the literature. Urgent neuro-imaging is indicated and a full systemic history warranted, especially with regards to any irradiation or trauma that the patient may have suffered (as these are potential causes).

Convergence retraction nystagmus

Convergence retraction nystagmus is commonly produced by lesions of the mesencephalon that damage the posterior commissure, such as pineal tumours. It is characterised by irregular, jerky, quick phases that converge or retract the eyes on attempted upgaze, and can be elicited by asking the patient to make an upward saccade or by moving the stripes of an optokinetic drum downwards (Leigh and Zee, 2015). It is associated with lesions in the dorsal midbrain, and most classically seen in patients with Parinaud's syndrome (dorsal midbrain syndrome). This syndrome also has a variety of other features, including defective upgaze, lid retraction and light-near dissociation. Causes generally vary with age: in younger patients, tumours and hydrocephalus are most common, whereas in middle age it is multiple sclerosis, and older patients, stroke.

Nystagmoid eye movements

Another group of disorders that disrupt steady gaze are saccadic intrusions. Saccadic intrusions are inappropriate, involuntary, spontaneously generated and conjugate saccades that disrupt steady fixation. Subtypes include square wave jerks, macrosaccadic oscillations, ocular flutter and opsoclonus.

Superior oblique myokymia

This is a rare condition that is usually unilateral. It is a high frequency monocular oscillation produced by spontaneous firing of one superior oblique muscle. It is characterised by brief sudden episodes of oscillopsia and diplopia in one eye (Salmon, 2019). It may be reported as 'shimmering' in the vision, or double vision, sometimes precipitated by looking downward (Pane et al, 2017). The episodes usually occur for around 10 seconds and may be difficult to detect without slit lamp examination. The condition is usually idiopathic, but there have been reported cases after head injury, in brainstem tumours, multiple sclerosis, following a superior oblique palsy and from compression of the trochlear nerve root by the adjacent superior cerebellar artery (Salmon, 2019).

Treatment of nystagmus

The treatment of nystagmus is often difficult, as the outcomes are often less than desirable at achieving control. A variety of factors influence the choice of treatment. These factors include the type of nystagmus, symptoms such as oscillopsia, and visual or ocular factors such as visual potential in the eye(s) and the location of the null point. Treatment plans are tailored to the patient. Treatment arms can be broadly classified into optical devices, pharmacological and surgical treatments.

Optical devices

Optical devices such as high plus spectacle lenses and high minus contact lens use simultaneously can help to stabilise the eye (Rushton and Cox, 1987). In patients whose nystagmus is suppressed by convergence, prisms can be used to induce convergence for viewing distant targets.

Pharmacological treatment

Pharmacological treatments can be used, but their side-effect profile generally limits their use as long-term therapy. These medications generally aim to reduce abnormal eye movements while preserving normal movement, or aim to reduce the visual effects of excessive, unwanted eye movements. It is felt that γ-aminobutyric acid (GABA) and glutamate are important neurotransmitters involved in gaze functioning, and therefore drugs with actions on these have been investigated in controlling nystagmus. Baclofen is regarded as an effective therapy for periodic alternating nystagmus (Comer et al, 2006). Both gabapentin and memantine have been used in acquired pendular nystagmus (Thurtell et al, 2010). Memantine has also been reported in an open label study to help in acquired pendular nystagmus associated with multiple sclerosis (Starck et al, 1996). Gabapentin is also useful in pendular nystagmus and has been investigated in a double-blind clinical trial (Averbuch-Heller et al, 1997).

Other types of nystagmus have been targets for drug use. For example, clonazepam and the potassium-channel blockers 3,4 diaminopyridine (Strupp et al, 2003) and 4-aminopyridine in downbeat nystagmus (Claassen et al, 2013), memantine and baclofen in upbeat nystagmus and gabapentin in torsional nystagmus (Thurtell et al, 2011).

Surgical treatment

Surgical interventions are generally aimed at moving and broadening the null point in patients with an eccentric null point, correcting an anomalous head posture and diverging the eyes in patients with nystagmus that suppresses with convergence. Surgery is directed at the extraocular muscles, and these are weakened or strengthened to move the eyes into a desirable position.

Key points

- Nystagmus is a repetitive to and fro movement of the eyes, which may be physiological or pathological, and is initiated by a slow phase (drift).
- Nystagmus can develop when the three main mechanisms for steady gaze are interrupted. These are visual fixation, vestibulo-ocular reflex and the neural integrator system.
- Oscillopsia is an illusory sensation that the surrounding environment is constantly in motion, when it is in fact stationary. It is a symptom seen in acquired nystagmus.
- A thorough history and examination specifically analysing the morphology of the nystagmus can provide important clues towards the diagnosis.
- In general, nystagmus associated with oscillopsia is caused by a new-onset inner ear or brain pathology and requires urgent neuro-imaging.

Botulinum toxin can be injected into individual extraocular muscles or the retrobulbar space to temporarily treat acquired forms of nystagmus. Common complications include ptosis, diplopia (as a result of ocular misalignment), and oscillopsia during head movements (as a result of loss of vestibulo-ocular reflex function), but these are temporary. Electrical devices that work on movement based or biofeedback principles are an emerging therapy for patients with oscillopsia (Averbuch-Heller et al, 1997).

Conclusions

Nystagmus can be a daunting topic but a thorough appreciation of the morphology of nystagmus, together with a detailed history and examination, can aid diagnosis. Any disruption of the systems that maintain a steady gaze can result in nystagmus. Oscillopsia and image degradation are common features of acquired nystagmus.

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Conflicts of interest

The authors declare no conflicts of interest.

References

Abadi RV. Mechanisms underlying nystagmus. J R Soc Med. 2002;95(5):231–234. https://doi.org/10.1258/jrsm.95.5.231

Averbuch-Heller L, Tusa RJ, Fuhry L et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. Ann Neurol. 1997;41(6):818–825. https://doi.org/10.1002/ana.410410620

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum:

- Managing an acute specialty-related take
- Managing patients in an outpatient clinic, ambulatory or community setting, including management of long-term conditions
- Managing medical problems in patients in other specialties and special cases.

Claassen J, Spiegel R, Kalla R et al. A randomised double-blind, cross-over trial of 4-aminopyridine for downbeat nystagmus—effects on slowphase eye velocity, postural stability, locomotion and symptoms. J Neurol Neurosurg Psychiatry. 2013;84(12):1392–1399. https://doi.org/10.1136/jnnp-2012-304736

Comer RM, Dawson ELM, Lee JP. Baclofen for patients with congenital periodic alternating nystagmus. Strabismus. 2006;14(4):205–209. https://doi.org/10.1080/09273970601026045

Denniston AKO, Murray PI. Oxford handbook of ophthalmology. 4th edn. Oxford: Oxford University Press; 2018

Dibartolomeo JR, Yee RD. Periodic alternating nystagmus. Otolaryngol Head Neck Surg. 1988;99(6):552–557. https://doi.org/10.1177/019459988809900603

Kim JS, Yoon B, Choi K-D et al. Upbeat nystagmus: clinicoanatomical correlations in 15 patients. J Clin Neurol. 2006;2(1):58–65. https://doi.org/10.3988/jcn.2006.2.1.58

Leigh RJ, Zee DS. The neurology of eye movements. 5th edn. Oxford: Oxford University Press; 2015

Pane A, Miller N, Burdon M. The neuro-ophthalmology survival guide. 2nd edn. Amsterdam: Elsevier; 2017

Pavan-Langston D., Manual of ocular diagnosis and therapy. 6th edn. Philadelphia (PA): Lippincott Williams and Wilkins; 2008

Pilling RF. Social and visual function in nystagmus. Br J Ophthalmol. 2005;89(10):1278–1281. https://doi.org/10.1136/bjo.2005.070045

Rushton D, Cox N. A new optical treatment for oscillopsia. J Neurol Neurosurg Psychiatry. 1987;50(4):411–415. https://doi.org/10.1136/jnnp.50.4.411

Salmon JF. Kanski's clinical ophthalmology: a systematic approach. 9th edn. Amsterdam: Elsevier; 2019

Sarvananthan N, Surendran M, Roberts EO et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. Invest Ophthalmol Vis Sci. 2009;50(11):5201–5206. https://doi.org/10.1167/iovs.09-3486

Stahl JS. Acquired nystagmus. Arch Ophthalmol. 2000;118(4):544–549. https://doi.org/10.1001/archopht.118.4.544

Starck M, Albrecht H, Pöllmann W, Straube A, Dieterich M. Drug therapy for acquired pendular nystagmus in multiple sclerosis. J Neurol. 1996;244(1):9–16. https://doi.org/10.1007/PL00007728

Strupp M, Schuler O, Krafczyk S et al. Treatment of downbeat nystagmus with 3,4-diaminopyridine: a placebo-controlled study. Neurology. 2003;61(2):165–170. https://doi.org/10.1212/01.WNL.0000078893.41040.56

Strupp M, Kremmyda O, Adamczyk C et al. Central ocular motor disorders, including gaze palsy and nystagmus. J Neurol. 2014;261(S2):542–558. https://doi.org/10.1007/s00415-014-7385-9

Thurtell MJ, Leigh RJ. Nystagmus and saccadic intrusions. In: Handbook of Clinical Neurology. 2011:333–378. https://doi.org/10.1016/B978-0-444-52903-9.00019-4

Thurtell MJ, Joshi AC, Leone AC et al. Cross-over trial of gabapentin and memantine as treatment for acquired nystagmus. Ann Neurol. 2010;67(5):676–680. https://doi.org/10.1002/ana.21991

Thurtell MJ, Rucker JC, Tomsak RL et al. Medical treatment of acquired nystagmus. Expert Rev Ophthalmol. 2011;6(3):307–314. https://doi.org/10.1586/eop.11.22