OCULAR MOTOR DISORDERS OF THE CEREBELLUM AND VESTIBULAR SYSTEM

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LEARNING OBJECTIVES

1. To better evaluate the patient at the bedside with the complaint of vertigo .
2. To better evaluate the patient at the bedside with a cerebellar disturbance
3. To better evaluate the patient at the bedside with the complaint of oscillopsia

CME QUESTIONS

1. All of the following are features of lesions of the cerebellar dorsal vermis except
   a) saccade slowing.
   b) saccade dysmetria.
   c) esodeviations.
   d) pursuit deficits.
2. All of the following are true of mastoid vibration induced nystagmus except
   a) slow phase is directed toward the paretic ear in a peripheral lesion.
   b) the slow phase can be directed vertically with a central lesion.
   c) slow phases are usually directed oppositely depending on which mastoid is vibrated in a unilateral peripheral lesion.
   d) in a peripheral lesion head shaking induced nystagmus and vibration induced nystagmus are usually directed in the same sense.
3. Smooth pursuit eye movement deficits occur with cerebellar lesions in the
   a) floccuus/paraflocculus.
   b) dorsal cerebellar vermis.
   c) nodulus/uvula.
   d) all of the above.

KEYWORDS

1. Vestibular
2. Cerebellum
3. Saccade
4. Pursuit
5. Nystagmus

INTRODUCTION

Here we present a bedside approach to patients with vestibular and cerebellar disease emphasizing clinical examination based on pathophysiology. The differentiation between peripheral and central vestibular disorders and precise anatomical localization within the cerebellum are emphasized. A number of specific manoeuvres are illustrated and evaluation of each of the different subclasses of eye movements is emphasized. The material is based upon two comprehensive and detailed review chapters on these issues cited in the reference list.

PART 1: BEDSIDE EXAMINATION OF THE PATIENT WITH A VESTIBULAR DISORDER

The successful diagnosis of a patient with vertigo or oscillopsia depends upon a careful, physiologically and anatomically based, examination of the vestibular system. The examination is guided by several key anatomical and physiological features which lead to several rules that enable one to better localize lesions. Here we concentrate upon vestibuloocular reflexes as they are relatively easy to evaluate at the bedside. The functions of the vestibuloocular reflex are clear: to stabilize the position of the eye in space, and so ensure clear vision, when we move our heads. Two reflexes are elaborated depending upon the type of head movement. If the head rotates, its motion is detected by the semicircular canals which sense angular acceleration (around all three axes, horizontal (yaw), vertical (pitch) or torsion (roll)). If the head translates or tilts (away from the direction of the pull of gravity), its motion or change in position is detected by the otolith organs, which sense linear acceleration along all three axes (side to side, up and down, or fore and aft) with gravity being the most ubiquitous form of linear acceleration.

BASIC PHYSIOLOGY

The labyrinthine receptors have a tonic discharge even when the head is still. This gives them the flexibility to either increase or decrease their discharge rate when the head motion is directed such as to excite or inhibit, respectively, the receptor within a given labyrinth. This ability to work in "push-pull" while a clear advantage because it allows one labyrinth to detect motion in any direction (albeit not as effectively as when both are working together (see Ewald's second law below)) comes with a price since with the head still the tonic level of activity in the two labyrinths (and specifically in coplanar canals such as the right anterior/left posterior (RALP) and the left anterior/right posterior (LARP)) must be perfectly balanced. If not an illusion of motion with consequent inappropriate compensatory responses can arise. In the canal system this leads to a spontaneous nystagmus with the head still and in the otolith system this leads to an ocular tilt reaction (head tilt, vertical (skew) misalignment of the eyes and ocular counterroll).

STATIC IMBALANCE IN THE CANALS: SPONTANEOUS NYSTAGMUS.

A first goal of the bedside examination then is to look for signs of 'static' imbalance. Three features of spontaneous nystagmus due to a canal imbalance help determine its cause. First is its direction (or vector). Because of the anatomical arrangement of the semicircular canals within the labyrinth (each vertical canal responds to mixtures of vertical and torsional (roll) rotation of the head and the lateral canals respond to horizontal rotation), a unilateral peripheral lesion almost never gives arise to a pure vertical or pure torsional nystagmus. In fact a complete unilateral peripheral lesion usually gives rise to a mixed horizontal torsional nystagmus. On the other hand, a pure vertical or pure torsional nystagmus is almost always central. Secondly is the effect of visual fixation on spontaneous nystagmus. When peripheral in origin, spontaneous nystagmus is suppressed by fixation. Conversely, a central nystagmus is usually unaffected by fixation. This 'Romberg' test of the vestibular system can be tested at the bedside using Frenzel lenses or occlusive ophthalmoscopy (alternating covering and uncovering one eye while watching the fundus of the other to look for the appearance, or increase in intensity of a spontaneous nystagmus. Thirdly is the effect of eye position in the orbit on the intensity of the nystagmus. With peripheral lesions the intensity of the nystagmus (slow-velocity velocity) increases when the eyes are directed to a position in the orbit opposite the direction of the slow phase (Alexander's law). With central lesions the position effect is variable but a central lesion is suggested when slow-phase velocity increases when the eyes are directed to a position in the orbit in the same direction as the slow phase.

STATIC IMBALANCE IN THE OTOLITHS: OCULAR TILT REATION (OTR).

Imbalance in static otolith inputs also leads to characteristic ocular motor sign: a skew deviation with ocular counterroll. When coupled with a head tilt this is known as the ocular tilt reaction (OTR) and reflects a phylogenetically old pattern of eye deviation to lateral tilt may. Recall that in intact lateral-eyed animals the response to a lateral tilt of the body is a 'righting reflex' comprised of a compensatory tilt of the head toward the opposite (higher) ear and a readjustment of the vertical alignment of the eyes (physiological skew deviation), in which case the eye in the relatively lower orbit (lower ear) elevates and the eye in the higher orbit (upper ear) depresses. When there is an otolith imbalance in humans the ocular tilt response (OTR) emerges as if there is a compensatory response to a lateral head tilt. The OTR consists of a vertical misalignment of the eyes (skew deviation), ocular counterroll (torsion of both eyes toward the side of the lower eye) with a consequent tilt of the visual world, and a head tilt toward the side of the lower eye.

A tilt of the subjective visual vertical (SVV) is a sensitive sign of a static disturbance in the otolith-ocular pathway., Normal individuals can position a visual linear marker in an otherwise completely dark room within 2^{o} of true vertical. Most patients with acute vestibular neuritis show an ipsilateral deviation of the SVV. Lesions in the caudal pons and rostral medullary tegmentum of the brainstem cause ipsilateral tilts (as part of the OTR) and lesions in the rostral pons and caudal mesencephalic tegmentum cause contralateral SVV tilts The so-called bucket test(adjusting a vertical line looking into a bucket) is another way to evaluate the SVV at the bedside. Along with measures of the subjective visual vertical one can evaluate the associated torsion with ophthalmoscopy looking at the relative position of the blind spot and fovea. Visual field testing with a perimeter can also be used to yield the same information. Differentiation from a superior oblique palsy is usually not difficult since the higher eye is relatively extorted in SOP and intorted in skew deviation. The vertical deviation in SOP is relatively independent of whether the patient is upright or supine whereas with skews it is diminished in the supine position.

DYNAMIC IMBALANCE IN THE CANALS: DYNAMIC VISUAL ACUITY (DVA) AND THE HEAD IMPULSE SIGN.

The second part of the bedside examination focuses on 'dynamic' abnormalities of vestibular reflexes during movement. Dynamic measures of acuity with the head moving (DVA) are important for evaluating patients who complain of oscillopsia, an illusion of visual motion often described as blurred, jumping or 'wobbly' vision. The vestibular system is usually involved when oscillopsia is brought on or exacerbated by motion of the head. DVA is measured by asking the patient to read the letters of a visual acuity chart with the head still and then oscillating horizontally, vertically, and in the roll plane from ear to shoulder, at a relatively high frequency of about two cycles per second. At this frequency visual tracking systems are too slow to help stabilize gaze, and therefore the function of the VOR can be assessed acting alone. While oscillating the head, the patient should not be allowed to stop or slow down too much at the turnaround points to 'sneak' a look at the acuity chart. Normal individuals may lose one line of acuity with head rotation, whereas patients with vestibular

abnormalities often lose more than two lines. Roll movements of the head (ear to shoulder) do not displace the fovea far from the visual target, and so cause smaller decreases in visual acuity even when vestibular function is completely lost.

Objectively, one best evaluates the amplitude (and direction) of the VOR using the head impulse maneuver. The patient is instructed to fix on the nose of the examiner, and a brief, high acceleration but low amplitude (10 or 15 deg) is applied to rotate the head. Head-impulse testing is based upon Ewald's second law which states that a better response is elicited with excitatory than inhibitory stimulation, especially at high accelerations and velocities. A corrective catch-up saccade is the sign of an underactive VOR response. An abnormally directed VOR response, for example, an upward slow-phase component followed by a downward corrective saccade with horizontal impulse testing is a sign of a cerebellar lesion. In patients with acute vestibular symptoms and a spontaneous nystagmus, a normal head impulse test suggests a central etiology whereas an abnormal head impulse occurs with both peripheral and central lesions.

The head impulse test is most consistently positive when there is a complete loss of labyrinthine function involving the lateral canal. The test, however, can be positive with a partial loss of function. Patients with chronic loss of labyrinthine function may appear to have an intact impulse response because very early in the head movement they have learned to trigger preprogrammed compensatory saccades which is complete by the time the head stops moving, making them hard to discern (covert saccades).

DYNAMIC IMBALANCE IN THE OTOLITHS: THE HEAD HEAVE SIGN.

The head heave maneuver (a high acceleration side to side translational movement), is used to evaluate the translational VOR and in turn the function of utricle. the finding of an asymmetric response to horizontal translation is more useful for identifying an abnormality Because normal individuals frequently show a corrective saccade, in both directions, an asymmetrical response is of better diagnostic use.. Unlike the head impulse sign, which is permanent if there is a complete loss of labyrinthine function, the head heave asymmetry is usually rapidly compensated and so only apparent in the first days after unilateral loss of function. A positive head heave sign, however, predicts a delayed or less complete recovery.

PROVOCATIVE TESTS: HEAD-SHAKING INDUCED NYSTAGMUS (HSN).

Head-shaking induced nystagmus (HSN) is a useful sign of imbalance of dynamic vestibular function. To perform the head-shaking maneuver, after establishing a comfortable range of motion of the head and while wearing Frenzel goggles, the head of the patient is shaken rapidly back and forth from side to side, but through a small excursion, for about 10 -15 seconds. Immediately afterwards the examiner looks for the induced nystagmus. With a unilateral loss of vestibular function, a vigorous nystagmus with slow phases directed initially toward the affected side will usually appear followed by a reversal phase with slow phases directed toward the intact side. In patients with vestibular imbalance, there is an asymmetry of peripheral inputs during high-velocity head rotations (Ewald's second law) which lead to an unequal accumulation of activity in the central velocity-storage mechanism within the vestibular nuclei. Immediately after head shaking, the initial phase of HSN appears as a result of a decay of activity within the velocity-storage mechanism. HSN can be also induced in the vertical and roll planes. With unilateral peripheral lesions, vertical head shaking may cause a small-amplitude horizontal nystagmus with slow phases directed toward the intact ear (away for the affected side). Immediately after a unilateral loss of labyrinthine function there may be no horizontal HSN. because the velocity storage mechanism is inhibited centrally much as one may lose the caloric response on the intact side in the first few days after a unilateral loss of labyrinthine function. Some patients with peripheral lesions may show horizontal HSN with slow phases directed away from the affected side. The mechanism may be related to 'recovery' nystagmus which refers to the appearance of a nystagmus with slow phases emanating from the lesioned ear. When there has been a prior adaptive rebalancing of vestibular tone after a unilateral lesion, and the tone from the paretic side is suddenly restored or increases as peripheral function recovers, the new level of spontaneous activity on the paretic side becomes excessive relative to the central state of compensation. This leads to a new imbalance causing a spontaneous nystagmus with slow phases directed toward the intact year. As with the horizontal head impulse sign, a cross-coupled HSN such as a vertical nystagmus following horizontal head shaking usually indicates a cerebellar disturbance.

PROVOCATIVE TESTS: VIBRATION-INDUCED NYSTAGMUS.

Vibration applied to the mastoid tip may bring out nystagmus in patients with unilateral loss of vestibular function. Vibration on either mastoid or on the vertex can elicit a nystagmus with a slow phase toward the paretic ear. This direction of nystagmus usually is independent of the site of stimulation as the vibration impulses are transmitted throughout the skull to both labyrinths. Because of this symmetry, normal individuals show little or no vibration-induced nystagmus. In patients with a unilateral loss of labyrinthine function, stimulating with a vibrator is comparable to a hot water caloric irrigation to the intact ear. When vibration elicits a vertical nystagmus a central lesion should be suspected.

PROVOCATIVE TESTS: HYPERVENTILATION.

Hyperventilation may induce a variety of symptoms is patients with anxiety and phobic disorders but usually does not produce nystagmus. Patients with demyelinating lesions of the vestibular nerve due to compression by a tumor(e.g., acoustic neuroma) or small blood vessels (microvascular compression) or with demyelination in

central pathways (e.g., in multiple sclerosis) may develop nystagmus with hyperventilation. The alkalosis and change in ionized calcium caused by hyperventilation can improve conduction on demyelinated axons leading to a recovery nystagmus (slow phases directed toward in the intact ear). Hyperventilation may induce nystagmus in patients with a prior labyrinthitis (with the slow phase usually directed toward the paretic ear) which may reflect a decompensation of adaptive rebalancing of vestibular tone. Hyperventilation may also enhance spontaneous downbeat nystagmus in cerebellar patients which is likely mediated through metabolic effects on calcium channels of Purkinje cells. Moreover, hyperventilation may induce nystagmus by changing intracranial pressure in patients with cranio-cervical junction anomalies or with abnormal connections between the subarachnoid space and the inner ear as occurs with a perilymph fistula or canal dehiscence.

PROVOCATIVE TESTS: VALSALVA MANEUVERS.

The Valsalva maneuver can induce nystagmus either by increasing intracranial pressure (straining against closed glottis as with lifting weights) or by increasing pressure in the middle ear (attempting to blow out against pinched nostrils). The nystagmus may be induced in patients with Ménière's disease, cranio-cervical junction anomalies such as Arnold-Chiari malformation, ossicular chain abnormalities, perilymph fistula, or superior canal dehiscence. Tragal compression can also provoke nystagmus by changing the middle-ear pressure (Hennebert's sign). Increasing the pressure in the middle ear, however, is better with a pneumatic otoscope.

PROVOCATIVE TESTS: POSITIONAL MANEUVERS.

Benign positional vertigo of the posterior semicircular canal due to misplaced otoconia is the most common cause of vertigo. Positional vertigo may also be a prominent feature of migraine induced dizziness, perhaps the second most common cause of vertigo. For positional testing the patient is first moved from the sitting position to the Hallpike position (the head is turned 45 degree to the left and then the patient is moved backward) to stimulate the left posterior SCC and look for the pattern of nystagmus (mixed vertical torsional with the quick phases directed upward and counterclockwise (using the patient as the reference)). The patient is then brought back to the sitting position. The maneuver is repeated with the head turned 45 degree to the right to stimulate the right posterior SCC. Finally, the head is placed in the straight back hanging position to look for a vertical nystagmus and then the patient is turned 90 degree to the left ear down and then 180 degree to the right ear down positions to stimulate the lateral canals. Characteristics which point to a central cause of positional nystagmus are a lack of a latency, lack of fatigability with repetitive testing, an unusual direction of the nystagmus which sometimes change direction, and a pure vertical or pure torsional nystagmus, though other more typically peripheral patterns of positional nystagmus are very occasionally associated with a central lesion.

PART 2: OCULAR MOTOR DISORDERS ASSOCIATED WITH CEREBELLAR DISEASE:

The cerebellum plays a central role in the control of every type of eye movements It has both immediate, on-line functions to make each individual movement accurate, and long-term, adaptive functions to keep ocular motor responses correctly calibrated for optimal motor behavior. Here we take an anatomical approach to the types of eye movement disorders that appear with lesions within specific parts of the cerebellum.

VESTIBULOCEREBELLUM: FLOCCULUS/ PARAFLOCCULUS (TONSILS).

The flocculus and paraflocculus (or tonsil) together with the caudal portions of the cerebellar vermis (nodulus and uvula) are part of the archicerebellum, also called the vestibulocerebellum. Lesions of the flocculus/paraflocculus impair many ocular motor functions. First, smooth tracking of a moving target, either when the head is still or moving (VOR cancellation) can be impaired. A second cardinal feature of lesions of the flocculus/paraflocculus is impaired gaze holding with the eyes drifting centripetally after eccentric eye movements, resulting in a gaze-evoked nystagmus. Thus the flocculus/paraflocculus functions in the control of the brain stem circuits (nucleus prepositus and medial vestibular nuclei for horizontal movements and superior vestibular nuclei and interstitial nucleus of Cajal for vertical eye movements) that convert (mathematically integrate) velocity into position commands for all types of conjugate eye movements; the ocular motor integrator. The paramedian tracts and their associated neurons may also be part of this integrator network, and there are rich interconnections between the cerebellum and these structures. A third distinctive feature of lesions in the flocculus/paraflocculus is downbeat nystagmus, in which the eyes drift up (slow phase) and are brought back to the fixation target by a corrective downward saccade (quick phase). This form of nystagmus can be linked to the damage of physiologic 'up-down' asymmetry of the floccular Purkinje cells (with predominant downward facilitation) resulting in upward slow drift or the tonic inhibition by the flocculus upon the upward VOR (by inhibitory projections to the superior vestibular nucleus), and lack of corresponding projections from the flocculus to the brain stem structures that mediate downward vestibulo-ocular responses. The upward drift waveform is variable from subject to subject and occasionally may be velocity increasing. These variable waveforms suggest that for the vertical integrator the flocculus/paraflocculus has a more subtle, modulator role, possibly related to the long-term adaptation capability of an individual animal. In other words, based upon the animal's own ocular motor history (e.g., trauma or disease) and genetic makeup, the inherent brain stem vertical neural integrator could be relatively leaky or relatively unstable, and the cerebellar lesion then unmasks the 'default' behavior (3,4-Diaminopyridine (3,4-DAP) and 4-Aminopyidine (4-AP), potassium channel blockers, can diminish downbeat nystagmus associated with cerebellar lesions). Rebound nystagmus is also typically seen in patients with cerebellar syndromes is rebound nystagmus.

The nystagmus is short-lived and occurs when the eyes are returned to the central position following sustained eccentric gaze. The rebound nystagmus beats oppositely to the prior gaze-evoked nystagmus, i.e., the slow phase is toward the prior eccentric gaze position. Similar to gaze-evoked nystagmus, rebound nystagmus is linked to the gaze-holding neural integrator controlled by the vestibulocerebellum. In extreme cases the mechanism producing rebound nystagmus becomes unstable leading to a centripetal-beating nystagmus on eccentric gaze in which slow phases are directed outwards. Postsaccadic drift, a brief drift of the eyes lasting several hundred milliseconds following each saccade, is another feature of the floccular/parafloccular syndrome. The postsaccadic drift reflects a mismatch between the pulse (phasic) and the step (tonic) components of innervation that produce saccades. The flocculus and parafloccculus are not critical for generating a compensatory response to head rotations since the VOR is still present after a lesion there but its amplitude and direction may be incorrect. This implicates the flocculus and parafloccculus in the adaptive mechanism that keeps the VOR properly calibrated in response to changing environmental conditions.

During rotation of the head around an earth-vertical axis, patients with diffuse cerebellar lesions may show a dynamic upward bias so that the eyes move up as well as horizontally, producing a 'cross-coupled' VOR There are also inappropriate torsional components and the responses in the two eyes are disconjugate. A release of inhibition upon anterior semicircular canal pathways within the brain stem (which produce upward slow phases) is a possible explanation. In line with this hypothesis, patients with cerebellar disease have an asymmetric vertical VOR with higher gain for downward head impulses (consistent with increased anterior semicircular canal stimulation) .These results implicate the cerebellum, and likely the flocculus/parafloccculus, in generating movements of each eye that have the correct amplitude and direction for perfect VOR compensation.

VESTIBULOCEREBELLUM: NODULUS/VENTRAL UVULA.

These structures mainly contribute to the control of the rotational and the translational VOR though pursuit deficits, especially vertical, may also be seen with lesions in this region. Lesions in the nodulus/ventral uvula commonly lead to spontaneous downbeat nystagmus and periodic alternating nystagmus. The nodulus/ventral uvula projects directly to the brain stem velocity storage mechanism which is dependent upon Purkinje cell inputs for its proper actions. The velocity storage mechanism has several functions. First it extends the duration of the VOR response beyond that expected from the mechanical properties of the cupula-endolymph system within the semicircular canals. This perseverating (integrating) action slows the decay of nystagmus that normally occurs during a constant-velocity rotation in the dark. Secondly, during sustained 'off-vertical axis' rotation of the head, when there is an imposed changing linear acceleration due to the continuous reorientation of the head relative to the pull of gravity, the velocity-storage mechanism modulates the direction of compensatory slow phases, reorienting the axis of eye rotation towards earth vertical. It thus serves an orienting function so the brain can know the position of the head relative to the pull of gravity, as well as determine whether a sensed linear acceleration of the head is from gravity or an imposed translation of the head. Lesions of the nodulus/uvula alter the velocity-storage mechanism for the horizontal VOR and increase the duration of vestibular responses to a constant-velocity input around an earth-vertical axis (i.e., the VOR time constant is increased). Lesions of the nodulus/uvula also disrupt the spatial orientation function of the velocity-storage mechanism; the VOR no longer reorients the axis of eye rotation toward upright during off-vertical axis rotation.. With nodulus/uvula lesions, there is also a loss of the normal habituation of the time constant of the VOR to repetitive stimulation as well as loss of tilt suppression of post-rotary nystagmus, the phenomenon by which the decay of post-rotary nystagmus is hastened with pitching the head down immediately following the end of a constant-velocity rotation. Periodic alternating nystagmus (PAN), a horizontal jerk nystagmus that changes direction every few minutes, may appear following lesions of the nodulus and its adjacent paravermal region. PAN reflects the combined actions of a (1) disinhibited brain stem vestibular velocity-storage mechanism (due to loss of inhibition from Purkinje cells in the nodulus that project to the vestibular nuclei) and (2) an intact adaptive mechanism that acts to null any sustained unidirectional nystagmus, thus allowing PAN to change direction. Because Purkinje cell inhibition is mediated through $GABA_B$ receptors, treatment with baclofen (a $GABA_B$ agonist) disengages the velocity-storage mechanism and stops PAN. Memantine may also be of use in treating this disorder. Note that as for rebound nystagmus, the adaptive mechanism that leads to the reverse of the direction of PAN is intact or possibly increased after lesions in the cerebellum. Downbeat nystagmus is also reported with nodulus and uvula lesions. The slow-phase velocity of this nystagmus, unlike that with flocculus lesions, is independent of orbital position (i.e., nystagmus does not change intensity with up and down gaze nor increase with lateral gaze) and can be suppressed with visual fixation. Changing the orientation of the head with respect to gravity may also alter the nystagmus. Thus the downbeat nystagmus with nodulus/uvula lesions could be due to a bias in the vestibular system (either the t-VOR or r-VOR mechanisms) and need not reflect changes in the gaze-holding neural integrator.

DORSAL VERMIS AND FOR (FASTIGIAL OCULOMOTOR REGION): SACCADES.

The dorsal vermis (lobules V–VII, also called the oculomotor vermis; OMV) and the underlying posterior fastigial nucleus (also called the fastigial oculomotor region; FOR) is especially important for the control of saccades. Lesions in the OMV cause changes in the accuracy, latency, trajectory, and dynamic properties (speed and acceleration) of saccades. Purkinje cells in the OMV discharge before saccades, and

stimulation of this same area can elicit saccades. Transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), and mapping of lesions supports a role for the participation of the OMV in the generation of saccades. The OMV also plays an important role in saccade adaptation, a mechanism that detects errors in motor performance and updates saccade commands to accurately move the eye toward a target. OMV lesions impair adaptation of saccade amplitude. Neurons in the FOR also discharge in relation to saccades and supply a presaccadic burst for contraversive saccades and a 'braking' discharge, late during the saccade, for ipsiversive saccades. Thus, each FOR acts to facilitate contraversive saccades and contributes to the termination of ipsiversive saccades. Consequently, lesions in the FOR cause ipsiversive saccadic hypermetria (overshoot) and contraversive hypometria (undershoot) and bilateral FOR lesions cause bilateral hypermetria. Purkinje cells in the OMV behave similarly to those of the FOR, though, as predicted from their inhibitory nature, their 'sign' is opposite. Thus, each side of the vermis acts to facilitate ipsiversive saccades and contributes to the termination of contralateral saccades. Accordingly, OMV lesions lead to hypometric ipsiversive and hypermetric contraversive saccades and bilateral lesions in OMV cause hypometric saccades in both horizontal directions. Vertical saccades show ipsipulsion (oblique trajectory toward the side of inactivation) with experimental lesions of the FOR Ipsipulsion is also a feature of Wallenberg's syndrome, presumably due to a functional lesion of the FOR resulting from interruption of the climbing fiber input (within the inferior cerebellar peduncle) to the OMV and a consequent increased inhibition by Purkinje cells upon the underlying FOR Other areas, such as the interposed nucleus (emboliform and globose) and paraflocculus (tonsils), may also be important in the generation of vertical saccades. The central role of the cerebellum in the control of saccades is reflected in the different ways it can influence the trajectory of the saccade but how does the cerebellum modulate the brain stem circuits that generate saccades? There are many targets in the brain stem by which the cerebellar output, via the FOR, could influence saccades including excitatory burst neurons (EBN) for saccade initiation and inhibitory burst neurons (IBN) and omnipause neurons (OPN) for saccade termination. Projections to the fixation zone of the rostral pole of the superior colliculus are another route by which the FOR could help bring the saccade to an end.

DORSAL VERMIS AND FOR (FASTIGIAL OCULOMOTOR REGION): PURSUIT.

The OMV and FOR also participate in the generation of pursuit eye movements. Electrical stimulation of the OMV in monkeys can enhance contraversive or impair ipsiversive pursuit, and transcranial magnetic stimulation of the skull over the posterior cerebellum in humans can influence pursuit eye movements in the same pattern. There are neurons in the FOR that discharge early during contraversive pursuit and late for ipsilateral pursuit, analogous to activity associated with saccades. Thus, each FOR can facilitate contraversive pursuit and can contribute to the termination of ipsiversive pursuit. Purkinje cells in the OMV probably behave in a similar way to those of the FOR, though, as predicted from their inhibitory nature their 'sign' is opposite. Each side of the vermis would act to facilitate ipsiversive pursuit and contribute to the termination of contralateral pursuit. The pursuit deficits reported after experimental lesions in the OMV and the FOR are largely in accord with the physiological findings. With a lesion in the FOR contralateral pursuit is impaired, and with a lesion in the OMV ipsilateral pursuit is impaired. Vertical pursuit is little affected following OMV lesions whereas FOR lesions reduce downward pursuit more than upward pursuit. Bilateral lesions of the OMV in monkeys produce horizontal pursuit deficits in both directions though bilateral FOR lesions leave pursuit relatively intact; this is also seen in patients with bilateral FOR lesions. These finding suggest the pursuit deficit is due to imbalance between opposing drives of the two FOR. Therefore, with bilateral FOR inactivation, and no FOR imbalance, the pursuit movements remain intact. Lesions of OMV and FOR mainly affect eye acceleration during the initial period of pursuit (the first 100 ms of tracking after a target has started moving or has changed its speed) and have a smaller effect during the sustained tracking period. As noted above the flocculus/paraflocculus contribute to smooth pursuit. One possible division of labor between these two regions is that the OMV/FOR is more concerned with the initiation and termination of the preprogrammed initial 'open-loop' portion of pursuit (when retinal slip is high), and the vestibulocerebellum is more concerned with pursuit during sustained tracking.

CEREBELLUM AND BINOCULAR CONTROL.

Patients with cerebellar damage sometimes show a skew deviation, a vertical misalignment of the eyes that cannot be attributed to a simple ocular muscle weakness. Most commonly the abducting eye is higher as the patient looks from far right to far left. The source of the skew may be an imbalance in otolith-ocular reflexes and patients with cerebellar skew deviation have reduced and disconjugate counterroll gains that depend on the direction of the head tilt. Note that a skew deviation is commonly observed in Wallenberg's syndrome but this is probably attributed to involvement of the caudal portions of the vestibular nuclei in the brain stem. The dentate nucleus has been also implicated in cerebellar skew deviation based on MRI/CT lesion analysis. Patients with cerebellar lesions can also show misalignment of the eyes during the r-VOR and during saccades. An esotropia (the eyes turn inward), sometimes attributed to a divergence paralysis since the esodeviation is usually greater at distance, also occurs in cerebellar disease and probably reflects involvement of the dorsal vermis. Patients with acute cerebellar lesions can show impaired slow but relatively intact fast vergence. Moreover, divergence, but not convergence, can be affected particularly with the lesions in the OMV. Patients with vestibulocerebellar lesions may also show a divergence-beating nystagmus (convergent slow phases with divergent quick phases. These abnormalities

hint at an excess of convergence tone with some cerebellar lesions. In sum, the cerebellum is involved in almost every facet of the control of eye movements and a careful examination of the different subclasses of eye movements in patients with cerebellar disease provides precise localizing diagnostic information.

CME ANSWERS

1. a
2. c
3. d

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OCULAR MOTOR DISORDERS OF THE CEREBRUM AND BRAINSTEM

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LEARNING OBJECTIVES

1. To be able to apply basic concepts of the control of gaze by the brainstem and cerebrum to the bedside diagnosis of abnormal eye movements
2. To learn of new insights, provided by eye movements, into motor control, visual perception and balance
3. To be aware how current research is revising standard notions of the way that the brain governs eye movements—from the extraocular muscles to the cortical eye fields

CME QUESTIONS

1. Hering's law of equal innervations for horizontal eye movements depends upon:
   a) Abducens motoneurons
   b) Abducens internuclear neurons
   c) Medial rectus motoneurons
   d) The sum of the above (A-C)
   e) None of the above
2. A unilateral lesion of the right RIMLF causes:
   a) Loss of vertical saccades in the right eye
   b) Loss of vertical gaze-holding ability
   c) Unidirectional loss of torsional quick phases (extorsion of right eye, intorsion of left eye)
   d) Loss of convergence
   e) Loss of vertical dolls-head responses (vestibulo-ocular reflex)
3. Akinetopsia:
   a) Is a disturbance of motion perception
   b) Occurs with posterior cerebral lesions
   c) May be a transient symptom
   d) Is associated with impaired visual tracking defects in the contralateral visual hemifield
   e) All of the above
   f) None of the above

KEYWORDS

1. Abducens nucleus
2. Medial longitudinal fasciculus (MLF)
3. Gaze palsy
4. Internuclear ophthalmoplegia
5. Rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF)
6. Interstitial nucleus of Cajal
7. Parinaud syndrome
8. Convergence retraction nystagmus
9. Frontal eye field
10. Parietal eye field
11. Ocular motor apraxia
12 Akinetopsia

VISUAL REQUIREMENTS OF EYE MOVEMENTS[1]

Clear vision of an object requires that its image be held steadily on the retina; best vision is possible when the image lies on the fovea (macula), which has the highest photoreceptor density. It follows that excessive motion of images on the retina degrades vision and leads to the illusion of movement of the visual environment (oscillopsia). Eye movements evolved to aid vision. Eye movements serve two distinct functions: gaze holding and gaze shifting and, within these categories, several functional classes of eye movements can be identified, each with a set of properties that suit it for a specific function (Table 1). Each functional class of eye movements depends, in part, on a distinct neural substrate. Knowledge of the purpose and properties of each functional class of eye movements guides the clinical examination. Knowledge of the neural substrate of each class of eye movements aids topological diagnosis, which is the focus of this syllabus. A recent detailed account is available.[2]

TABLE 1. FUNCTIONAL CLASSES OF HUMAN EYE MOVEMENTS*

Class of Eye Movement	Main Function
Vestibular	Holds images of the seen world steady on the retina during brief head rotations or translations
Visual Fixation	Holds the image of a stationary object on the fovea by minimizing ocular drifts

Optokinetic	Holds images of the seen world steady on the retina during sustained head rotation
Smooth Pursuit	Holds the image of a small moving target on the fovea; or holds the image of a small near target on the retina during linear self-motion; with optokinetic responses, aids gaze stabilization during sustained head rotation
Nystagmus quick phases	Reset the eyes during prolonged rotation and direct gaze towards the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions so that images of a single object are placed or held simultaneously on the fovea of each eye

*Modified from Leigh and Zee.[1]

BRAINSTEM CONTRIBUTIONS TO HORIZONTAL CONJUGATE MOVEMENTS

The brainstem circuits that co-ordinate horizontal conjugate eye movements is summarized in Figure 1.[3-5] The abducens nucleus contains *abducens motoneurons*, which innervate the lateral rectus muscle, and *abducens internuclear neurons*, which project via the contralateral medial longitudinal fasciculus (MLF) to contact medial rectus motoneurons of the oculomotor nucleus. This simple circuit is the neural basis for Hering's law of equal innervation for horizontal movements. Abducens motoneurons and internuclear neurons show some morphological,[6] pharmacological,[7-10] and electrophysiological differences.[11]

How do signals for each functional class of eye movement (Table 1) project to the abducens nucleus? Excitatory saccadic commands originate from burst neurons that lie in the ipsilateral paramedian pontine reticular formation (PPRF), which lies rostral to the abducens nucleus.[12-15] Inhibitory saccadic commands arise from burst neurons in the contralateral rostral medullary reticular formation, caudal to the abducens nucleus. Omnipause neurons, lying in the pontine raphe, inhibit both sets of burst neurons except during saccades, when they play a role in initiating these fast movements. Pursuit signals from posterior cortical areas are relayed via the cerebellum, vestibular and fastigial nuclei.[16,17] The output of the gaze-holding network (neural integrator), to which the cerebellum makes important contributions, reaches the abducens nucleus from the nucleus prepositus hypoglossi (NPH) and adjacent medial vestibular nucleus (MVN).[18,19] Vestibular and optokinetic inputs reach the abducens nucleus from the vestibular nuclei.[20] Note that medial rectus motoneurons receive inputs for vergence eye movements from neurons in the mesencephalic reticular formation, independent of the MLF.[21,22]

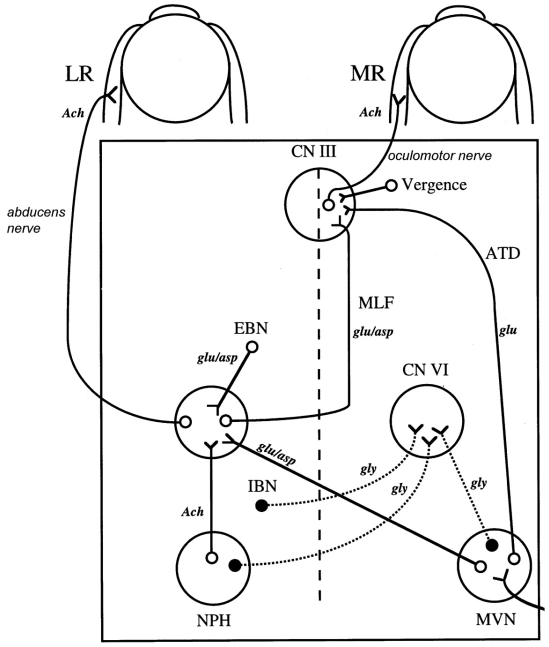


Figure 1. Anatomic scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR), and abducens internuclear neurons that send an ascending projection in the contralateral medial longitudinal fasciculus (MLF) to contact medial rectus (MR) motoneurons in the contralateral third nerve nucleus (CN III). From the horizontal semicircular canal, primary afferents on the vestibular nerve project mainly to the medial vestibular nucleus (MVN), where they synapse and then send an excitatory connection to the contralateral abducens nucleus and an inhibitory projection to the ipsilateral abducens nucleus. There is also a vestibular projection to CN III via the ascending tract of Deiters (ATD), but its functional significance in humans is uncertain. Saccadic inputs reach the abducens nucleus from ipsilateral excitatory burst neurons (EBN) and contralateral inhibitory burst neurons (IBN). Eye position information (the output of the neural integrator) reaches the abducens nucleus from neurons within the nucleus prepositus hypoglossi (NPH) and adjacent MVN. The medial rectus motoneurons in CN III also receive vergence command. Putative neurotransmitters for each pathway are shown: Ach: acetylcholine; asp: aspartate; glu: glutamate; gly: glycine. Adapted from Leigh and Zee.[1]

EFFECTS OF DISCRETE LESIONS ON BRAINSTEM PATHWAYS FOR HORIZONTAL GAZE

It is possible to use the anatomic scheme shown in Figure 1 to account for effects of discrete lesions on the coordination of horizontal gaze. *Lesions of the abducens nucleus* produce paralysis of both the ipsilateral lateral rectus and contralateral medial rectus for all conjugate eye movements.[23-27] Vergence is spared, since these movements mainly depend on projections that pass directly to medial rectus motoneurons. Saccadic, pursuit, optokinetic, and vestibular movements are still present in the contralateral hemifield, but are impaired when

directed towards the side of the lesion. Contraversive saccades are preserved because they depend on the intact abducens nucleus, which receives projections from excitatory burst neurons in the ipsilateral PPRF. Saccades directed towards the side of the lesion are also present in the contralateral hemifield of movement, but they are slow.

Lesions of the medial longitudinal fasciculus produce *internuclear ophthalmoplegia* (INO), which is characterized by paresis of adduction for conjugate movements on the side of the lesion.[28-30] Adduction is still possible with convergence, because of direct vergence inputs to medial rectus motoneurons (see Figure 1). Thus, when INO is produced experimentally by lidocaine blockade of the MLF between the levels of the trochlear and abducens nuclei, the vergence response is preserved or even increased.[30] More rostral lesions of the MLF may impair vergence if the medial rectus motoneurons, or their vergence inputs, are involved. With complete lesions of the MLF, the eye does not adduct across the midline with any conjugate movements, implying that extra-MLF pathways, such as the ascending tract of Deiters, can only play a minor role in the horizontal vestibulo-ocular reflex. Peripheral disorders, such as myasthenia gravis, can imitate INO.[31] A combined lesion of one MLF and the abducens nucleus on the same side produces paralysis of all conjugate movements save for abduction of the eye contralateral to the side of the lesion—"one-and-a-half" syndrome.[32,33] This syndrome has also been attributed to an infarction that bilaterally affects the MLF and the abducens nucleus on one side.[34] Failure of development of crossing pathways in the brainstem may cause horizontal gaze palsy and scoliosis.[35]

Discrete *lesions of the paramedian pontine reticular formation (PPRF)* cause loss of saccades and quick phases of nystagmus to the side of the lesion.[36,37] Experimental lesions in the PPRF that spare axons of passage leave smooth pursuit, the vestibulo-ocular reflex, and gaze-holding ability intact;[37] similar sparing is sometimes encountered with clinical lesions, including saccadic palsy following cardiac surgery.[38-41] Spinocerebellar ataxia type 2 (SCA2, formerly called olivopontocerebellar atrophy) is characterized by slowing of horizontal saccades and loss of burst neurons from the PPRF.[42] Often, however, lesions affecting the PPRF also involve axons conveying vestibular and pursuit inputs to the abducens nucleus.[43] Furthermore, lesions that affect the excitatory burst neurons may also affect omnipause neurons, which lie in the adjacent nucleus raphe interpositus, close to the midline at the level of the abducens nerve,[44-46] and which inhibit all burst neurons except during saccades.[47] Lesions of omnipause neurons may account for slowing of vertical, as well as horizontal, saccades after bilateral pontine lesions.[37,38,48] Bilateral, experimental lesions of the nucleus prepositus hypoglossi -medial vestibular (NPH-MVN) region—abolish the gaze-holding mechanism (neural integrator) for eye movements in the horizontal plane.[49,50] Vertigo, falls, facial palsy, and gaze-evoked nystagmus may occur with NPH-MVN lesions in humans.[51]

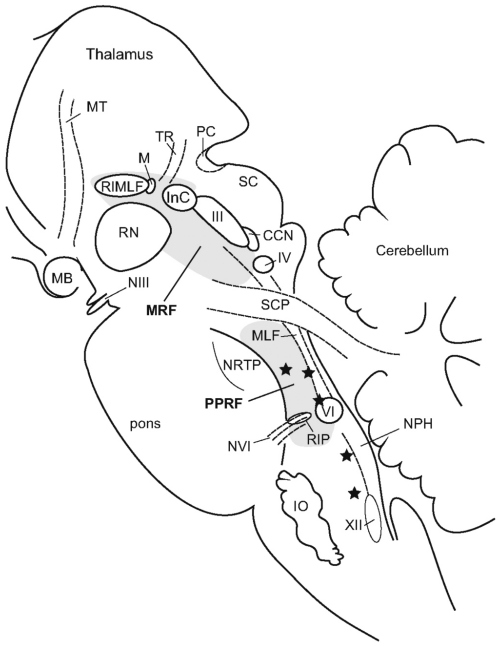


Figure 2. A sagittal section of the human brain stem showing the location of regions important for the control of vertical and horizontal gaze: the mesencephalic reticular formation (MRF) contains the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF), the M-group (M) and interstitial nucleus of Cajal (INC) controlling vertical gaze and accompanying lid movements. The paramedian pontine reticular formation (PPRF) contains the excitatory and inhibitory burst neurons for horizontal gaze as well as the omnipause neurons in the nucleus raphe interpositus (RIP). The nucleus prepositus hypoglossi (NPH) stretches between the nucleus hypoglossus (XII) and the abducens nucleus (VI). The asterisks indicate the location of cell groups of the paramedian tracts (PMT), which relay information to the flocculus. III: oculomotor nucleus; IV: trochlear nucleus; VI: abducens nucleus; CCN: central caudal nucleus; InC: interstitial nucleus of Cajal; IO: inferior olive; M: M-group; MB: mammillary body; MLF: medial longitudinal fascicle; MT: mammillothalamic tract; NIII: rootlets of the oculomotor nerve; NVI: rootlets of the abducens nerve; NPH: nucleus prepositus hypoglossi; NRTP: nucleus reticularis tegmenti pontis; PC: posterior commissure; RN: red nucleus; SC: superior colliculus; SCP: superior cerebellar peduncle; TR: tractus retroflexus.. (Figure reproduced with permission of Dr. Anja Horn).

BRAINSTEM CONTRIBUTIONS TO VERTICAL AND TORSIONAL MOVEMENTS

Ocular motoneurons for vertical and torsional eye movements lie in the oculomotor nucleus and trochlear nucleus (Figure 2).

Vertical saccadic commands and gaze-holding (neural integrator) innervation are generated in the midbrain, but vestibular and pursuit signals arise from the lower brainstem.[4]

Vertical and torsional saccades are generated in the *rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF)*, in the rostral mesencephalon (prerubral fields), rostral to the tractus retroflexus and caudal to the mammillothalamic tract (see Figure 2).[52-54] The RIMLF contains excitatory burst neurons for vertical and torsional saccades and quick phases.[55-59] Each RIMLF contains neurons that burst for upward or downward eye movements, but for torsional quick phases in only one direction. Thus, the right RIMLF discharges for quick phases that are directed clockwise with respect to the subject (top poles of both eyes rotate toward the right side).[56,57] Each RIMLF projects predominantly to the ipsilateral oculomotor and trochlear nuclei; however, projections to motoneurons innervating the elevator muscles appear to be bilateral, with axon collaterals probably crossing to the opposite side at the level of the motoneurons, and not in the posterior commissure.[56-58] Furthermore, each burst neuron in the RIMLF sends axon collaterals to motoneurons supplying yoke muscle pairs; this appears to be the neural substrate for Hering's law of equal innervation for vertical saccades.[60,61] Axons from the RIMLF neurons also send collaterals to the interstitial nucleus of Cajal (bilaterally for upward burst neurons), and to the paramedian tract (PMT) cell groups,[62] which project to the cerebellum. The RIMLF receives an ascending projection from omnipause neurons in the pons.[53,63] The central mesencephalic reticular formation (cMRF) also plays an important role in the control of saccades.[64]

A critical structure for *vertical gaze holding* (the neural integrator) is the *interstitial nucleus of Cajal (INC)*. The INC projects to vertical motoneurons in the oculomotor and trochlear subnuclei on the contralateral side of the brainstem via the *posterior commissure*;[65] thus, the effects of a posterior commissure lesion on vertical gaze is tantamount to a bilateral INC lesion. The neural signals necessary for vertical vestibular and pursuit eye movements as well as contributions to the vertical gaze-holding command ascend from the medulla and pons to the midbrain. The MLF is important route for these projections, but the brachium conjunctivum (superior cerebellar peduncle) and other pathways, including the ventral tegmental tract, which crosses at the rostral pole of the nucleus reticularis tegmenti pontis,[66] also contribute.

EFFECTS OF DISCRETE LESIONS ON SUBSTRATE FOR VERTICAL SACCADES

Unilateral, *experimental lesions of the RIMLF* that spare axons cause a mild defect in vertical movements, consisting of slowing of downward saccades.[67] This slowing probably occurs because each nucleus contains burst neurons for both upward and downward movements, but projections to motoneurons innervating depression are ipsilateral, whereas those innervating the elevators may be bilateral.[56-58] Conversely, a severe, specific defect of torsional quick phases is produced.[67] For example, with a lesion of the right RIMLF, torsional quick phases, clockwise from the point of view of the subject (extorsion of the right eye and intorsion of the left eye—with top poles rotating towards the side of the lesion) are lost. Bilateral experimental lesions of the RIMLF in monkeys abolish vertical and torsional saccades,[67] but vertical gaze-holding, vestibular eye movements, and pursuit are preserved, as are horizontal saccades. Patients with discrete, bilateral infarction in the region of the RIMLF usually show deficits of either downward saccades or both upward and downward saccades.[68,69] Selective involvement of burst neurons in RIMLF occurs in Neimann-Pick type C disease,[70] and may also occur in progressive supranuclear palsy (PSP). *Pharmacological inactivation of the INC* with muscimol causes impaired vertical and torsional gaze holding after a saccade carries the eye to a tertiary (oblique) position.[71,72] Vertical saccades become smaller (hypometric) but not slow.[73] Experimental *inactivation of the posterior commissure* with lidocaine causes failure of vertical gaze-holding function, with centripetal drifts of the eyes following vertical saccades.[74] Larger destructive lesions severely limit vertical eye movements, especially upward;[75,76] it is possible that such lesions also affect other structures, such as the nucleus of the posterior commissure.[58] *Bilateral lesions of the medial longitudinal fasciculus* cause bilateral INO, and impair vertical vestibular and smooth-pursuit movements, but spare vertical saccades.[29,77]

ROLE OF CEREBRAL CORTEX IN THE CONTROL OF GAZE

Cerebral cortical areas contributing to the control of gaze are summarized in Figure 3.[78] Primary visual cortex (V1) is the gateway for vision; without it, humans cannot make accurate visually guided eye movements.[79] Cortical areas concerned with motion vision lie in cortex at the junction of areas 19, 37, and 39, close to the intersection of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus. These areas correspond to the middle temporal visual area (MT, or V5), and the medial superior visual temporal area (MST) in the monkeys; experimental lesions impair eye movements to moving targets.[80] Patients with lesions affecting the homologue of MT/MST report akinetopsia (loss of motion vision), which may be transient, and show impaired eye movements (saccades and pursuit) to targets moving in the contralateral visual hemifield; saccades to stationary targets may be normal. Patients with lesions involving the homologue of MST show impaired smooth pursuit for targets moving ipsilateral to the lesion.[1]

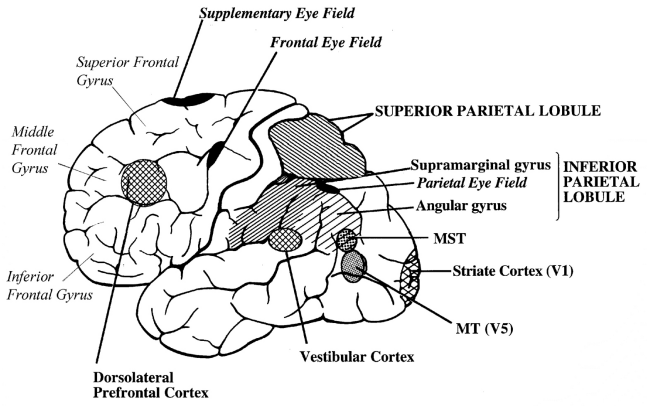


Figure 3. Human cortical areas important for eye movement control. Adapted from Leigh and Zee.[1]

In monkey, posterior parietal cortex (area 7a) contains neurons that variously discharge during active visual fixation, in relation to saccades, or during smooth pursuit. A neural network of neurons in this area could play an important role in transforming visual signals from retinal into spatial or craniotopic coordinates.[81] A homologous region to area 7a in the human brain probably corresponds to portions of the Brodmann areas 39 and 40, including parts of the supramarginal gyri and angular gyri (Figure 4).[82,83] Acute parietal lobe lesions, especially affecting the right hemisphere, produce a classic syndrome of contralateral hemineglect that contributes to an ipsilateral gaze preference. The accuracy of saccades to contralateral targets may also be impaired, but a more impressive dysmetria occurs when patients are required to respond to a double-step stimulus, in which the target jumps twice before a response can be initiated. If the target jumps first into the contralateral hemifield and then into the ipsilateral field, patients cannot make accurate saccades to the final target position, even though it lies in the "intact" hemifield. This finding has been taken as evidence that the parietal lobe plays a pivotal role in computing target position from both visual stimuli and an internal (efference) copy of eye movements (in this case, the change in eye position due to the first saccade). Bilateral posterior parietal lesions cause Balint's syndrome,[84] features of which are disturbance of visual attention (simultanagnosia), inaccurate arm pointing (optic ataxia) and difficulty initiating voluntary saccades to visual targets (ocular motor apraxia). Ocular motor apraxia involves all types of voluntary movements: saccades, vergence, and pursuit. The pulvinar contributes to visual attention,[85] and lesions affect the latency of saccades made to a series of targets.[86]

The frontal eye field (FEF) is important for generating voluntary saccades and suppression of saccades during steady fixation.[87,88] There are also subregions of the FEF concerned with vergence and smooth pursuit.[89,90] Acute lesions that involve the FEF may produce an ipsilateral gaze deviation.[91] With more chronic FEF lesions, saccades made in response to the overlap paradigm, during which the fixation light remains on when the target light is presented, show increased reaction time, both ipsilaterally and contralaterally (see slide presentation).[1]

The supplementary eye fields (SEF), and adjacent pre-supplementary motor cortex, guide saccades during complex tasks, such as sequences of movements and responses when the instructional set changes. SEF also contribute to predictive smooth pursuit.[92] Patients with SEF lesions cannot make a sequence of saccades to an array of visible targets in the order that they were turned on.[93,94] Another effect of SEF lesions is difficulty in changing the direction of saccades as part of a reversal of a previously established pattern of response.[95] In other words, the SEF seems to play an important role in shifting from a more automatic to volitional behavior. The area immediately rostral to SEF (pre-supplementary motor areas, pre-SMA) also seems important for switching from automatic to more voluntary behavior.[96]

The dorsolateral prefrontal cortex (DLPC) is important for memory-guided saccades and lesions in this region impair both this function and saccades made to the imagined mirror-image of a visual target (antisaccades—see slide presentation).[97] When normal subjects attempt to make saccades to the remembered location of a target that they viewed a few seconds before, they do so with accuracy almost as good as if the target were visible. Neurons in DLPC of monkey, show an ability to hold in memory specific visuospatial coordinates represented in a topographical memory map.[98] Pharmacological inactivation of DLPC with D1-dopamine antagonists impairs the accuracy of monkeys in making contralateral memory-guided saccades.[99] In humans, there is activation of DLPC when subjects make memory-guided saccades.[100] Repetitive transcranial magnetic stimulation (TMS) over DLPC in normal subjects also impairs the accuracy of memory-guided saccades.[101] Patients with lesions affecting this area show increased variable error of memory-guided saccades.[102] Based on TMS studies, it seems possible to track the flow of neural information during programming of memory-guided saccades. Thus, the right posterior parietal cortex is involved at about 300 ms after the target presentation when it contributes to visual-spatial integration stage.[103] Both DLPC are involved during the memorization phase (around 1 second after the target presentation). The FEF is involved in triggering of the memory-guided saccade, possibly with a contribution from the parietal lobe (PEF).[104] Although most studies of memory-guided saccades have concerned short-term or working memory, saccades have also be used to probe aspects of medium-term spatial memory (with delays of 20 seconds—2 minutes), which may depend on perirhinal cortex,[105] and longer-term memory, which appears to depends on the parahippocampal cortex formation in humans.[106]

Recent research has indicated that proprioceptive inputs from the extraocular muscles project to primary somatosensory cortex, where they may modulate visual responses by eye movements in parietal cortex.[107]

PROJECTIONS OF CORTICAL EYE FIELDS TO BRAINSTEM CIRCUITS FOR GAZE

There are no direct projections from the cortical eye fields to the ocular motoneurons. Two important pathways (Figure 4) are: (1) via the superior colliculus and brainstem reticular formation, and (2) via the pontine nuclei and cerebellum. The superior colliculus seems important for initiating saccades.[108,109] The cortical areas encode visual and ocular motor signals in a "place map" such that each cortical point corresponds to a visual location or the size and direction of an eye movement.[110] In contrast, ocular motoneurons and premotor neurons, such as saccadic burst cells, encode eye movements in terms of discharge properties.[111] Thus, a spatial-to-temporal transformation of signals is necessary and may be achieved by connections between superior colliculus and adjacent brainstem reticular formation. The superior colliculi

are also important for triggering saccades, and lesions permanently increase saccade latency.[112] The projection from cortical eye fields via pontine nuclei and cerebellum seems most important for making eye movements accurate, so that the eye gets on target during gaze shifts. The cerebellum may achieve this by sending a "stop" signal when the eye is on target.[113,114]

Two regions of the cerebellum contribute to the control of eye movements. The vestibulocerebellum (flocculus, paraflocculus, nodulus) are important for normal smooth pursuit (eye alone or eye-head tracking), eccentric gaze holding, and adjustment of the VOR so that it is optimised to guarantee clear vision. These latter functions are all impaired in patients with vestibulocerebellar lesions such as Chiari malformation; downbeat nystagmus is also often present.[1] The second cerebellar region, comprising the dorsal vermis and the fastigial nucleus to which it projects, is important for saccades to be accurate. Thus, dorsal vermis lesions cause saccadic hypometria (undershoots), and fastigial nucleus lesions cause hypermetria (overshoots).[115]

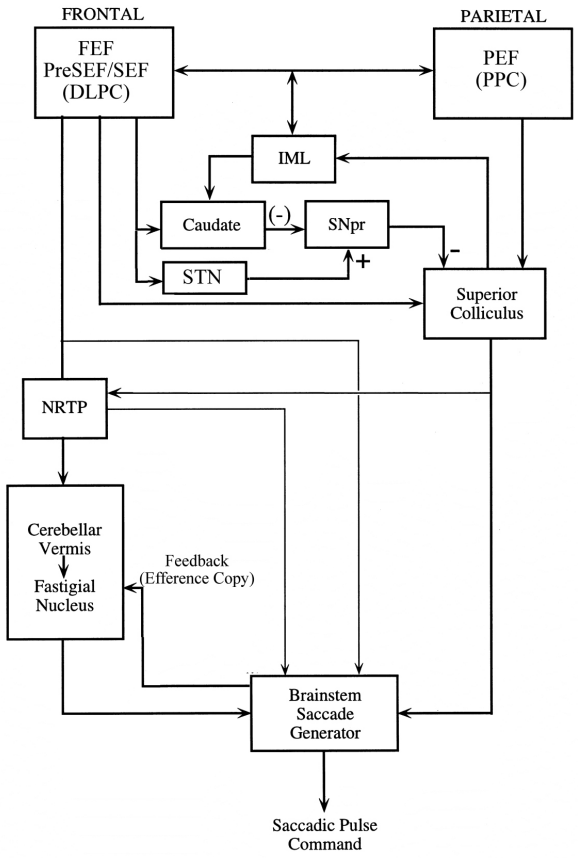


Figure 4. Block diagram of the major structures that project to the brainstem saccade generator (premotor burst neurons in PPRF and riMLF). Also shown are projections from cortical eye fields to superior colliculus. DLPC—dorsolateral prefrontal cortex; FEF—frontal eye fields; IML—intramedullary lamina of thalamus; NRTP—nucleus reticularis tegmenti pontis; PEF—parietal eye fields; PPC—posterior parietal cortex; SEF—supplementary eye fields; SNpr—substantia nigra, pars reticulata; STN—subthalamic nucleus. Not shown are the pulvinar, which has connections with the superior colliculus and both the frontal and parietal lobes, projections from the caudate nucleus to the subthalamic nucleus via globus pallidus, and the pathway that conveys efference copy from brainstem and cerebellum, via thalamus, to cerebral cortex. Adapted from Leigh and Zee.[1]

A simplified view of the basal ganglia pathway is that it is composed of two serial, inhibitory links: a caudo-nigral inhibition, which is phasically active, and a nigro-collicular inhibition, which is tonically active. If frontal cortex causes caudate neurons to fire, then the nigro-collicular inhibition is removed and the superior colliculus can activate a saccade.[116] Studies of the effects of pharmacologically inactivating the nuclei in this pathway have supported this hypothesis. However, stimulation of caudate neurons can produce either suppression or facilitation of SNpr neurons, suggesting that the facilitation may be due to a multisynaptic pathway, perhaps via the subthalamic nucleus, whereas inhibition is due to the direct pathway from caudate to SNpr.[117] Thus, the means by which the frontal eye field influences the superior colliculus is complex and might produce difficulties in either initiating or suppressing saccades. Both deficits have been described in patients with disorders affecting the basal ganglia, such as Huntington's disease.[118] Recent work has emphasized the role that the basal ganglia play in programming eye movements and other behaviors that are rewarded;[119] the habenula may play a key role in rewarded behaviors.[120]

CME ANSWERS

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NYSTAGMUS

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LEARNING OBJECTIVES

1. The attendee will be able to identify acquired types of spontaneous nystagmus.
2. The attendee will be able to differentiate between peripheral and central causes of vestibular nystagmus.
3. The attendee will be able to list the common causes of each type of acquired spontaneous nystagmus and describe its localization and pathogenesis, where known.

CME QUESTIONS

1. A 34-year-old woman presents with a 2-month history of blurring of vision in both eyes. Three years earlier, she had developed bilateral leg numbness that lasted a few months. Examination demonstrates low-amplitude upbeat nystagmus in central gaze. The site of the lesion is most likely:

   a) medial medullary tegmentum
   b) superior cerebellar vermis
   c) interstitial nucleus of Cajal
   d) both central tegmental tracts in the pons
   e) both anterior semicircular canals

2. A deficiency of which of the following is least likely to cause downbeat nystagmus:

   a) pyridoxine
   b) magnesium
   c) thiamine
   d) vitamin B12

3. A 57-year-old woman presents with sudden vertical diplopia. Examination shows a left hypertropia and a slight head tilt to the right. There is a fine torsional nystagmus that beats toward the right shoulder. There is also binocular slowing and limitation of downward and upward saccades. These findings signify dysfunction of:

   a) left INC
   b) left vestibular nucleus
   c) left riMLF
   d) right INC
   e) right vestibular nucleus
   f) right riMLF

KEYWORDS

1. Nystagmus
2. Ocular Oscillations
3. Ocular Tilt Reaction
4. Vestibular Function
5. Oculopalatal Tremor

INTRODUCTION

Nystagmus is a rhythmic eye oscillation that usually has a jerk or pendular waveform. Congenital nystagmus often comprises more complex waveforms. The slow phase of nystagmus is the fundamental "driving" component. It typically arises from dysfunction of the vestibular or gaze-holding system but nystagmus also may be produced by dysfunction of other slow-eye-movement systems, such as the smooth pursuit, optokinetic and vergence systems. In contrast to nystagmus, saccadic oscillations and intrusions are initiated by quick eye movements and generally originate in the saccadic system (see Wray, this syllabus).

Simple inspection of the eyes may fail to detect low-intensity nystagmus, even at close range. Ophthalmoscopy may reveal otherwise occult nystagmus but detection depends on consciously resisting the natural impulse to ignore retinal movement. Fixation often suppresses nystagmus and can be prevented during ophthalmoscopy by having the patient cover the fellow eye or, during inspection, by covering one eye and shining a bright handlight in the other eye. Frenzel goggles (illuminated +20-diopter lenses) also magnify and illuminate the eyes while inhibiting fixation. Their use enables the examiner to prevent fixation while observing for nystagmus in different eye and head positions and during provocative tests (see Zee, this syllabus).

Nystagmus is depicted by a box-diagram, using arrows to denote its trajectory, quick-phase direction (if jerk nystagmus) and nystagmus intensity (amplitude x frequency) in each gaze position, as viewed by the examiner (Fig. 1). The effect of convergence also should be noted. The trajectory of nystagmus is described in terms of its horizontal, vertical and torsional components. Describing the direction of torsional jerk nystagmus as clockwise or counter-clockwise is inherently ambiguous. It is clearer to state that the nystagmus beats torsionally toward the left or right shoulder.

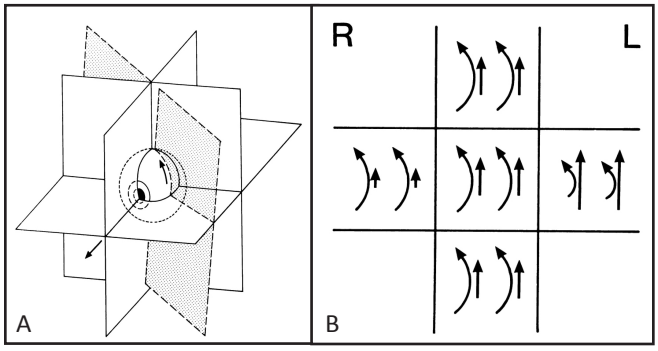


Figure 1. A. Drawing showing jerk nystagmus in a plane that comprises mainly a combination of vertical and torsional vectors. Nystagmus plane and direction (*curved arrow*) approximate that produced by stimulation of the right posterior semicircular canal (e.g., in benign postional vertigo). **B.** Box diagram of nystagmus shown in **A.** *Lines with arrowheads* indicate trajectory and direction of quick phases for each eye and lengths of lines depict relative intensity of vertical and torsional components in each gaze position. For pendular nystagmus, arrowheads are placed at both ends of the lines.

Nystagmus may be congenital or acquired. Acquired nystagmus may be present spontaneously in central gaze (spontaneous nystagmus), evoked by eccentric gaze (gaze-evoked nystagmus) or triggered by a change of head position (positional nystagmus). This review will consider only acquired spontaneous nystagmus, which encompasses jerk nystagmus arising from peripheral or central vestibular dysfunction (including periodic alternating nystagmus) and various types of pendular nystagmus. Contemporary reviews of nystagmus are available (Thurtell and Leigh, 2011; Brodsky, 2010; Leigh and Zee, 2006). The management of nystagmus is reviewed by Thurtell in this syllabus.

PERIPHERAL VESTIBULAR NYSTAGMUS

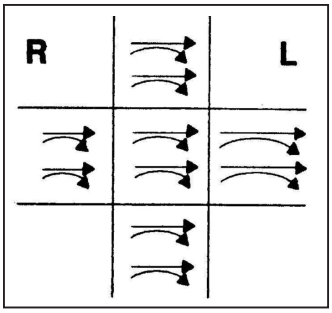


Figure 2. See text.

Pathological peripheral vestibular nystagmus results from disease of the labyrinth or vestibular nerve whereas central vestibular nystagmus arises from dysfunction of vestibular pathways in the brainstem or cerebellum. The slow phase of vestibular nystagmus, whether peripheral or central, usually has a steady velocity, in contrast to the increasing-velocity slow phase seen in congenital nystagmus and the decreasing-velocity slow phase seen in gaze-evoked nystagmus. Lesions of the end-organ or nerve usually disrupt input from all three semicircular canals. The resulting imbalance of resting input causes unidirectional nystagmus that beats away from the side of the lesion. The trajectory is typically horizontal, with a smaller torsional component (Fig. 2), reflecting the combined rotational vector of the three canals (Fig. 3). Peripheral vestibular nystagmus obeys Alexander's law: the intensity of nystagmus increases when gaze is directed toward the side of the quick phase and decreases with gaze in the direction of the slow phase (Fig. 2). This phenomenon allows division of vestibular nystagmus into three grades of intensity: *first degree* nystagmus occurs only on gaze in the direction of the quick phase, *second degree* also involves primary position and *third degree* affects all gaze positions. First degree vestibular nystagmus may be indistinguishable clinically from unilateral gaze-evoked nystagmus.

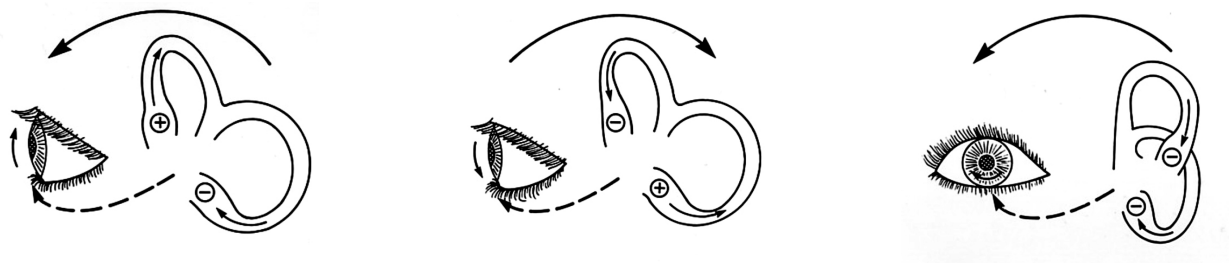


Figure 3. Schematic diagram of eye and vertical semicircular canals in sagittal and frontal planes, showing how vertical-canal geometry and hair cell polarization contribute to the pattern of peripheral vestibular nystagmus. During normal head movement, endolymph flow directed toward vertical-canal ampullae causes inhibition of the tonic discharge of hair cells and contributes to the generation of slow phases of physiological nystagmus (which stabilize the eyes in space). Inhibition of input from the posterior canal caused by forward pitch of the head **(left)** generates compensatory upward slow phases. Similarly, inhibition of input from the anterior canal caused by backward pitch **(middle)** generates downward slow phases. Inhibition of input from both canals caused by rolling the head to the opposite side **(right)** generates pure torsional slow phases (upper poles rotate toward the same side). Inhibiting each canal at the same time cancels the other canal's effect on vertical eye movement while adding to the effect on torsional eye movement. Since unilateral lesions simulate an inhibitory stimulus and usually disrupt the signals from both vertical canals, the resulting pathological nystagmus has a torsional component but no vertical component. The torsional component of the quick phase beats toward the opposite shoulder. It is added to a horizontal component that also beats toward the opposite side due to disrupted horizontal-canal output (as in Fig.2).

CENTRAL VESTIBULAR NYSTAGMUS

Central vestibular nystagmus is distinguished from peripheral vestibular nystagmus by the trajectory of eye rotation and other features as outlined in Table 1.

Table 1. Features of spontaneous vestibular nystagmus: peripheral vs central

Peripheral	Central
Mixed horizontal-torsional	Purely vertical Purely torsional Purely horizontal or mixed
Unidirectional	Unidirectional or reverses direction with gaze
Suppressed by vision	Not suppressed by vision
Subsides in days	Often persists
Associated Features	
Prominent vertigo	Mild vertigo
Possible hearing loss or tinnitus	No hearing loss or tinnitus
No brainstem/cerebellar features	Possible brainstem/ cerebellar features

Nystagmus resulting from peripheral lesions is usually suppressed by fixation and subsides spontaneously within a few days to weeks. Disappearance of nystagmus in the face of peripheral damage is due to central rebalancing of tonic activity in the vestibular nuclei. The enduring nature of central vestibular nystagmus may result from disruption of shared pathways that mediate fixation suppression and smooth pursuit and impaired adaptive networks that normally restore vestibular balance.

Although the above features usually distinguish peripheral from central disorders, lesions of the cerebellum or the vestibular nerve fascicle in the pons may produce nystagmus that mimics peripheral nystagmus. This is of particular concern when presented with an elderly patient who has an isolated acute vestibular syndrome. In this situation, a peripheral-type nystagmus may not always differentiate a peripheral cause such as vestibular neuronitis from a small cerebellar or pontine infarct. In such cases, the presence of a negative head impulse test (see Zee, this syllabus) or skew deviation is a strong indicator of a central lesion (Kattah et al, 2009; Newman-Toker et al, 2008). On the other hand, a positive head impulse test does not entirely rule out a central lesion.

DOWNBEAT NYSTAGMUS

Downbeat nystagmus is the most common type of central vestibular nystagmus. Its intensity typically increases with lateral gaze and downward gaze and decreases in upward gaze (obeying Alexander's law). Convergence often makes it worse. It may be visible only with ophthalmoscopy or slit-lamp exam. Prone positioning and Dix-Hallpike maneuvers may intensify downbeating.

Downbeat nystagmus is usually accompanied by impaired horizontal smooth pursuit and VOR suppression and by horizontal gaze-evoked nystagmus. Skew deviation also may be seen, often with alternating hypertropia of the abducting eye. In one series of patients with downbeat nystagmus, roughly one third of the patients who had caloric or head-impulse testing showed bilateral loss of vestibular function and one fourth of all patients had idiopathic polyneuropathy (Wagner et al, 2008). In darkness, normal subjects may show a slight upward ocular drift and occasional downbeat that disappears with fixation (Leigh and Zee, 2006)

Downbeat nystagmus usually signifies disease of the cerebellum, particularly the flocculus or tonsils (paraflocculus). Rarely, a lower brainstem lesion generates downbeating (Wagner et al, 2009). The commonest causes are cerebellar degeneration, including that induced by paraneoplasic or other autoantibodies, and structural lesions, particularly Chiari malformations and posterior fossa vascular lesions (Thurtell and Leigh, 2010; Wagner et al, 2008; Wagner et al, 2009; Fletcher, 1993; Halmagyi et al, 1983). Other causes include multiple sclerosis, tumors, chronic lithium therapy, anticonvulsant or amiodarone toxicity and deficency of thiamine, magnesium or vitamin B_{12}. The cause of downbeat nystagmus remains undiagnosed in 20%–40% of all patients and in the majority of patients over 70 years of age (Wagner et al, 2008).

A variety of mechanisms has been proposed to explain downbeat nystagmus. It can be produced in monkeys by flocculectomy, which disinhibits anterior semicircular canal projections but not posterior canal projections. Similarly, experimental lesions that disrupt posterior, but not anterior, canal projections in the brainstem cause downbeating. In humans, cerebellar disease that causes disinhibition of anterior canal projections or a brainstem lesion that selectively disrupts posterior canal projections bilaterally could cause a tonic upward bias of vestibulo-ocular drive and downbeat nystagmus. Other proposed mechanisms include an imbalance in otolith-ocular reflexes (Marti et al, 2005) and dysfunction of the vertical neural integrator—the interstitial nucleus of Cajal (INC) (Glasauer et al, 2003). Integrator function may be perturbed by damage to a feedback circuit comprising the flocculus, the INC and discrete cell groups located between the fascicles of the MLF in caudal pons (cell groups of the paramedian tract).

UPBEAT NYSTAGMUS

Upbeat nystagmus may resolve in the prone or supine position and may convert to downbeat nystagmus with convergence. Occasionally, it changes spontaneously to downbeat nystagmus over weeks to months, particularly when caused by Wernicke's encephalopathy (Suzuki et al, 2005). The Dix Hallpike maneuver rarely may trigger purely upbeating nystagmus due to bilateral posterior canal benign positional vertigo (Beyea and Parnes, 2010).

Spontaneous upbeat nystagmus has been reported most commonly with lesions in the medial medullary tegmentum or ventral pontine tegmentum (Tilikete et al, 2008; Pierrot-Deseilligny, 2009), less often with lesions of the brachium conjunctivum (which may cause upbeat-torsional nystagmus; Thurtell et al, 2009), and rarely with lesions of the superior cerebellar vermis, rostral brainstem or thalamus. In monkeys, bilateral inactivation of interstitial nucleus of Cajal (INC) in rostral midbrain can cause upbeat nystagmus (Helmchen et al, 1998).

The most common diseases causing upbeat nystagmus are multiple sclerosis, brainstem infarction, cerebellar degeneration and various tumors (Fletcher, 1993). Other etiologies include thiamine deficiency (Wernicke's encephalopathy), meningitis and encephalitis. In infancy, upbeating nystagmus often indicates a congenital retinal dystrophy, mandating investigation with ERG (Brodsky, 2010). Upbeat nystagmus occurs rarely in Infantile Nystagmus Syndrome and may be familial. Nicotine (cigarette smoking) can induce low-intensity upbeating in darkness.

Various mechanisms have been proposed to explain upbeat nystagmus. Lesions of the pontomedullary tegmentum may disrupt upward VOR signals (from the anterior semicircular canals) ascending in the brachium conjunctivum or in a nearby crossed ventral tegmental tract (Ranalli and Sharpe, 1988; Zwergal et al, 2009; Pierrot-Deseilligny, 2009). Medial medullary lesions may disrupt vertical eye position input (coming from the INC) to perihypoglossal nuclei (nucleus intercalatus and nucleus pararaphales), located between the fascicles of the medullary paramedian tract (which includes the caudal MLF).

NYSTAGMUS WITH A PROMINENT TORSIONAL COMPONENT

Purely torsional nystagmus may be difficult to detect and may be mistaken for vertical nystagmus during ophthalmoscopy; the optic disc of one eye beats upward while the other disc beats downward. When spontaneous, it almost always indicates brainstem damage but peripheral vestibular lesions occasionally cause predominantly torsional nystagmus (the horizontal component may become apparent only when fixation is removed). Torsional nystagmus often arises from lesions near the vestibular nuclei in upper medulla and lower pons (Lopez et al, 1992). The nystagmus typically beats toward the opposite shoulder, although ipsiversive nystagmus has been described with syringobulbia (Nogués M et al, 2010). Rostral midbrain lesions involving the riMLF also may produce contraversive torsional nystagmus, often combined with a vertical component, either upward or downward (Helmchen et al, 2002). Isolated INC lesions are seen less commonly but may cause an ipsiversive torsional quick phase and a contraversive ocular tilt reaction (OTR). The OTR comprises a skew deviation with tilt of the head and eyes toward the lower skewed eye. The pattern seen with medullary lesions is the usually opposite to that seen with INC lesions: contraversive nystagmus and ipsiversive OTR. Ipsiversive torsional nystagmus is also seen rarely with unilateral MLF lesions.

Rarely, a unilateral mesodiencephalic lesion leads to paroxysmal or intermittent torsional nystagmus and OTR, both directed toward the side of the lesion. Typically, the cause is a hemorrhage and the syndrome begins months after the acute event. In these patients, the conjugate torsional components of the quick phases may be combined with smaller disjunctive vertical components; the eye with the intorting quick phases beats upward and the eye with the extorting quick phases beats downward. This is called ***jerk seesaw or hemi-seesaw nystagmus***. Medullary infarcts, syringobulbia and Chiari malformations may produce spontaneous jerk seesaw nystagmus but the torsional component typically beats away from the side of the lesion. Subthalamic stimulation for Parkinson's disease also may cause contraversive torsional nystagmus (Poisson et al, 2008).

Paroxysmal torsional nystagmus with vertical components may be produced by pathological excitation of individual vertical semicircular canals, such as that triggered by Dix-Hallpike maneuvers in posterior-canal benign positional vertigo (Fig. 1), or by sound (Tullio's phenomenon) in the anterior canal dehiscence syndrome. The torsional quick phase is directed toward the affected side.

PERIODIC ALTERNATING NYSTAGMUS

Acquired periodic alternating nystagmus (PAN) follows a crescendo-decrescendo pattern of intensity and reverses direction every 80-120 seconds,. Recognition of its alternating character depends on prolonged observation. Between the right beating cycle and the left beating cycle, there is a 5- to 20-second null period when the eyes are still or show downbeating nystagmus. PAN is encountered in patients with Chiari malformations, spinocerebellar degenerations, multiple sclerosis, fourth ventricle tumors, and drug toxicity (anticonvulsants and possibly lithium). There are a few reports of PAN occurring with peripheral vestibular disease (Mirofushi et al, 2008) and following bilateral anterior visual loss without neurological disease.

PAN is produced experimentally in monkeys by removing the cerebellar nodulus and uvula. These structures normally reduce the duration of vestibular responses by inhibiting the "velocity-storage" mechanism in the vestibular nucleus (see Zee, this syllabus). GABA mediates this inhibition. Baclofen, a GABA-β agonist, is an effective treatment for acquired PAN.

ACQUIRED PENDULAR NYSTAGMUS

ACQUIRED PENDULAR NYSTAGMUS IN MULTIPLE SCLEROSIS (APNMS)

APNMS is a common form of acquired pendular nystagmus and is distinct from other types of pendular nystagmus (Aschoff et al, 1974; Tilikete et al, 2011). It often exhibits a combination of

horizontal, vertical and torsional components and may have a diagonal, circular or elliptical trajectory, depending on the phase difference between the horizontal and vertical components. APNMS has a high frequency (2 - 6 Hz) and small amplitude (< 3 degrees). The amplitude, trajectory and phase are often different in the two eyes (Fig. 4). APNMS may vary in amplitude in different gaze positions, pause momentarily after a saccade and abate under closed lids.

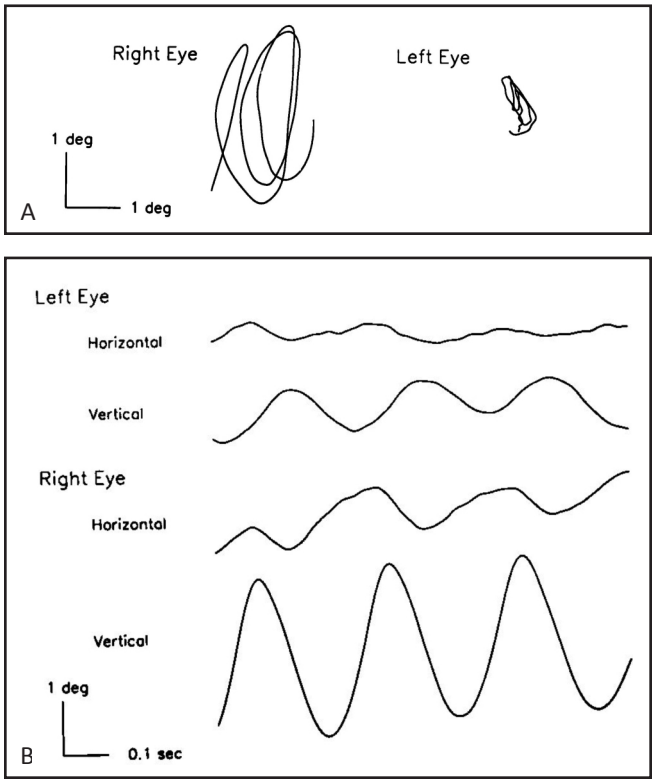


Figure 4. Eye movement recording illustrating APNMS. X-Y plot (**A**) shows marked dissociation of nystagmus amplitude in the two eyes. The elliptical trajectory is caused by differences in amplitude and phase of the horizontal and vertical components of each eye. These differences are shown in the tracings of eye position over time (**B**). The bottom panel (**B**) also shows that the vertical components of the oscillation of the two eyes are out of phase.

Most patients have oscillopsia, impaired vision and associated optic atrophy. Other common findings include internuclear ophthalmoplegia, tremor of the head or limbs and truncal or limb ataxia. When the amplitude of nystagmus is different in the two eyes, optic atrophy is usually worse in the eye with the greater oscillation. MRI typically shows several areas of abnormal signal in brainstem and cerebellum, with no consistent single area of involvement.

No specific neural lesion has been shown to generate this form of APN. The frequent association with cerebellar dysfunction and experimental modeling of APN suggest a disturbance of a brainstem-cerebellar feedback network that regulates the neural integrator (Das et al, 2000). Less common causes of APN include cerebellar degeneration, toluene abuse and, in children, leukodystrophies such as Pelizaeus-Merzbacher disease.

OCULOPALATAL TREMOR (OPT; OCULOPALATAL MYOCLONUS)

OPT also comprises a distinct form of pendular nystagmus associated with oscillations of the palate. Vertical or torsional eye motion usually predominates. The palatal oscillation is synchronous in most patients but not all. Compared to APNMS, OPT has a lower frequency (1 to 3 Hz) and higher amplitude (2 to 12 degrees) and is more irregular, often showing variable amplitude and frequency over sequential cycles (Kim et al, 2007, Tilikete et al, 2011). Occasionally, there is associated rhythmic contraction of the orofacial muscles, vocal cords, diaphragm or limb muscles. OPT is typically caused by a hemorrhage or infarct of brainstem tegmentum. Uncommon causes include demyelination, trauma and a variety of other conditions. Due to the lesion location, patients present often with a horizontal gaze palsy, one-and-a-half syndrome or ocular bobbing. OPT often does not begin until several weeks or months after the acute lesion. The MRI hallmark is T2-hyperintensity of one or both inferior olives (the "pimento sign"), caused by degenerative olivary hypertrophy.

Olivary hypertrophy is induced transynaptically by disruption of the crossed dentato-olivary pathway. The dentate projections cross in the superior cerebellar peduncle and, without synapsing in the red nucleus, descend in the opposite central tegmental tract to reach the inferior olive. Symmetric OPT is usually caused by pontine or upper medullary lesions that damage one or both central tegmental tracts. Unilateral lesions of the central tegmental tract, or rarely the dentate nucleus, may give rise to asymmetric ocular oscillations and, less commonly, asymmetric palatal tremor. In these cases, the oscillations are usually more prominent on the side opposite the olivary hypertrophy (Kim et al, 2007, Tilikete et al, 2011). The more affected eye often intorts as it rises and extorts as it falls while the other eye shows a pure torsional oscillation.

The mechanism of OPT production is unclear. Disruption of the dentato-olivary pathway removes inhibitory modulation of olivary dendro-denditic gap junctions. Over time, deafferented neurons become larger and develop abnormal soma-somatic gap junctions. They also show spontaneous rhythmic discharges. The increased electrotonic coupling together with decreased inhibition may lead to synchronous firing of large numbers of neurons. Computer modeling of such discharges coming irregularly from multiple groups of olivary neurons together with normal cerebellar conditioning simulates most of the features of OPT (Shaikh et al, 2010)

PENDULAR SEESAW NYSTAGMUS

Pendular seesaw nystagmus comprises reciprocal upward-intorting and downward-extorting eye movement similar to jerk seesaw, but with a sinusoidal rather than jerk waveform.

The oscillation is typically rapid but ranges in frequency from 1 to 4 Hz. Most patients have bitemporal hemianopia caused by a tumor, head trauma or, rarely, hydrocephalus. The post-traumatic variety typically begins several months or years after injury. When caused by tumor, the nystagmus usually resolves after surgical resection. Pendular seesaw nystagmus may also occur with congenital achiasma (Hertle et al, 2001; Prakash et al, 2010) and septo-optic dysplasia (Rudich and Lesser, 2009) and may develop rarely in the setting of progressive vision loss without chiasmal or brainstem disease. Thus, loss of crossing visual input seems to be important in the genesis of this nystagmus, perhaps by depriving feedback circuits of information needed to calibrate vestibular responses to head rotations in roll (Leigh and Zee, 2006)

PENDULAR VERGENCE OSCILLATIONS

Pendular vergence oscillations are a rare form of nystagmus in which the horizontal oscillations of each eye are 180 degrees out of phase, producing alternating convergence and divergence. Pendular vergence nystagmus at a frequency of about 1 Hz together with vertical gaze palsy and synchronous jaw contractions comprise *Oculomasticatory myorhythmia*, a syndrome pathognomonic for Whipple's disease (Schwartz et al, 1986; Grotta et al 1987). Multiple sclerosis and brainstem stroke also may cause pendular vergence oscillations. In some patients, the oscillation is present only during convergence. Convergence also may amplify or induce upbeat or downbeat nystagmus or cause it to reverse direction.

CME ANSWERS

1. a) medial medullary tegmentum
2. b) pyridoxine
3. c) left riMLF

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SACCADIC OSCILLATIONS AND INTRUSIONS

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LEARNING OBJECTIVES

1. The importance of the examination of the stability of fixation in evaluating eye movements.
2. The recognition of saccadic intrusions as a sign of cerebellar disease
3. How to distinguish paraneoplastic opsoclonus from parainfectious opsoclonus and the appropriate workup

CME QUESTIONS

1. Is oscillopsia a symptom of square-wave jerks ?
2. Are square-wave jerks a side effect of depakote, an anticonvulsant drug ?
3. Is opsoclonus usually visible under closed eyelids ?

KEYWORDS

1. Oscillopsia
2. Intrusive saccades
3. Square wave jerks
4. Ocular flutter
5. Opsoclonus

INTRODUCTION

Saccadic oscillations and intrusions are unwanted saccades that occur spontaneously. Several types of saccadic intrusions are recognized and four are selected for discussion.

- Square-wave jerks
- Macrosaccadic oscillations
- Ocular flutter
- Opsoclonus

The characteristics of these disorders are:

1. They are inappropriate saccades
2. They take the eye away from the target and disrupt steady fixation
3. The movements are saccadic (with different amplitudes) with or without an intersaccadic interval
4. They may disrupt overall tracking but not necessarily impair normal pursuit
5. They are due to disorders of saccadic control
6. All are signs primarily of disease of the cerebellum

SQUARE-WAVE JERKS

Normally, *microsaccades*, which are typically less than a third of a degree in amplitude, aid vision during fixation and are suppressed during visual tasks that demand steady fixation such as threading a needle.

Intrusive horizontal *square-wave* jerks are small saccades, (typically 0.5 degrees) that take the eyes away from the target and after an intersaccadic interval of approximately 250 ms, a corrective saccade brings the eyes back to refix the target. Square-wave jerks are usually asymptomatic, visible on inspection of the eyes 'fixing' and easily detected during ophthalmoscopy. In a number of diseases of the central nervous system they may occur almost continuously and have been called *square-wave oscillations* which can, on occasions, be mistaken for nystagmus.

It is very important to bear in mind that *square-wave jerks* can occur in normal healthy subjects with a frequency in the range of up to 20 per minute or greater. They are more common in normal elderly subjects and are reported to increase in frequency in cigarette smoking. Normal subjects have no accompanying disorders of the saccadic eye movement system.

Square-wave jerks are a sign of cerebellar disease and are prominent in certain hereditary ataxic syndromes especially Friedreich's ataxia.

Square-wave jerks are also relatively common in patients with neurodegenerative disease, in particular progressive supranuclear palsy (PSP). In these disorders square-wave jerks may be due to dysfunction of saccadic control by the superior colliculus or its inputs. The superior colliculus and the mesencephalic reticular formation are involved in PSP. Pallidotomy for Parkinson's disease is also reported to increase the frequency of square-wave jerks, perhaps by disrupting projections from the basal ganglia to the superior colliculus.

A cautionary note: Patients with dementia (PSP or Alzheimer's disease) may show excessive distractibility wherein novel visual targets evoke inappropriate saccades. This *excessive distractibility* disrupts steady fixation in these patients and should be distinguished from fixation instability due to square-wave jerks.

The etiology of square-wave jerks is shown in Table 1.

Table 1. Etiology of Square-Wave Jerks

Cerebellar Disease

- Hereditary spinocerebellar ataxia (SCA) - Dominant
  - SCA 3 Machado–Joseph Disease
  - SCA 6 Holmes type – Harding ADCA3
  - SCA 8 (vermis atrophy)
  - SCA 20 (palatal tremor)
- Hereditary spinocerebellar ataxia - Recessive
  - Friedreich's ataxia
  - Ataxia telangiectasia
  - SCA with saccadic intrusions
- Neoplasm
- Multiple sclerosis
- Cerebellar degeneration

Neurodegenerative Disease

- Parkinson's disease
- Post-pallidotomy in Parkinsons
- Progressive supranuclear palsy
- Multisystem atrophy

Cerebral Cortical Disorder

- Hemisphere strokes or hemorrhage

MACROSACCADIC OSCILLATIONS

Macrosaccadic oscillations are another form of intrusions that disrupt steady fixation. They are regarded as an extreme form of saccadic hypermetria secondary to cerebellar dysfunction involving the fastigial nucleus or its output.

Macrosaccadic oscillations oscillate around the fixation point and both the primary saccade that takes the eye away from fixation and the corrective saccade that returns the eye to the target are hypermetric and overshoot the target continuously in both directions. They may have vertical or torsional components and occasionally the vertical may be prominent clinically. Patients with macrosaccadic oscillations may have difficulty in reading because the print goes 'out of focus' due to oscillopsia.

Macrosaccadic oscillations occur in association with:

1. Lesions affecting the fastigial nucleus of the cerebellum or its outflow
2. Some forms of hereditary SCA with intrusions
3. Rarely with focal pontine lesions
4. Occur during an injection of edrophonium (tensilon) in patients with myasthenia gravis.

OCULAR FLUTTER AND OPSOCLONUS

Saccadic oscillations made up of back-to-back saccades without an intersaccadic interval can be subdivided into three forms. The first is *voluntary nystagmus* which can be initiated voluntarily by some individuals as a burst of high-frequency oscillations, primarily as a party trick.

The other forms are two symptomatic saccadic oscillations flutter (including microsaccadic flutter) and opsoclonus.

Microsaccadic flutter is a rare symptomatic saccadic oscillation that had only been reported twice previously, in advance of Ash et al's description of five patients with this disorder in 1991.

Microsaccadic flutter is horizontal with a frequency of 15 to 30 Hz and a very small amplitude of 0.1 to 0.5 degrees. These oscillations can not be seen with the unaided eye. The patients reported are typically young and healthy and complain of 'shimmering' vision or 'jiggling', 'wavy' vision lasting for seconds to hours, sometimes associated with dizziness or disequilibrium.

Sharpe and Fletcher and also Carlo published separate reports of similar patients. Sharpe and Fletcher's case was a patient with cerebellar degeneration. They called the oscillations microflutter. Carlo reported a case the same year with a long history of oscillopsia and oscillations seen only with an ophthalmoscope. His case had no information regarding an underlying neurological disorder. He also termed the oscillations microflutter.

The co-authors on Ash's paper included Zee and Shatz who called the oscillations microsaccadic flutter and attributed them to a benign malfunction of the brainstem omnipause neurons unassociated with neurologic disease. Clearly this terminology is open for discussion.

Ocular flutter is far from being benign. It is characterized by bursts of back-to-back horizontal saccades, about 1 to 5 degrees, often precipitated by a change in gaze. It is noteworthy that *ocular flutter* and *opsoclonus* are closely related and maybe seen in the same patient during the course of an illness. The two together or alone immediately suggest a potential diagnosis of parainfectious brainstem encephalitis or a paraneoplastic syndrome; for example neuroblastoma in children and cancer of the lung, breast or uterus, among others in adults.

Opsoclonus, first described by Orzechowski in 1913 is characterized by chaotic, 'unpredictable', large-amplitude randomly directed saccades occurring in the horizontal, vertical and torsional planes. Orzechowski originally described opsoclonus in six patients with epidemic encephalitis.

Digre reported three new cases in 1986 and reviewed opsoclonus in children and 58 previously reported cases in adults. At that time there were already 119 pediatric cases of opsoclonus in the literature dating back to 1926. (Digre K. Archives of Neurology 1986; 43:1165-1175).

A number of other associations are reported by Leigh and Zee. The Neurology of Eye Movements, Fourth Edition, Oxford University Press, New York 2006.
A modified list of the *etiology of ocular flutter and opsoclonus* is shown in Table 2.

Table 2. Etiology of Ocular Flutter and Opsoclonus

Parainfectious viral brainstem encephalitis

Myoclonic encephalopathy - 'Dancing eyes and dancing feet'

Paraneoplastic Syndromes

Neuroblastoma/neural crest tumors
Cerebellar syndromes – lung, breast, ovary
Brainstem 'toxic-T-cell syndromes – pancreas, prostate, testes

Metabolic – toxic states

Hyperosmolar coma
Chlordecone, thallium, strychnine, toluene and organophosphates

- side effects

Lithium, amitriptyline, cocaine, phenytoin with diazepam

Central Nervous System diseases – including

Multiple sclerosis
AIDS
Thalamic hemorrhage
Hydrocephalus

CLINICAL DISTINCTIVE FEATURES OF PARANEOPLASTIC OPSOCLONUS VS. PARANEOPLASTIC OPSOCLONUS

- Patients are usually under the age of 40 years
- Parainfectious opsoclonus is high frequency, horizontal > multivectorial and suppressed by convergence and/or sustained upgaze
- Associated with marked trunkal ataxia and myoclonic jerks
- Cerebrospinal fluid has an encephalopathic profile – increased protein, cell count and positive oligoclonal bands
- Usually good response to IVIg

WORKUP

1. Take a detailed history with attention to visual symptoms (oscillopsia), medications, alcohol and drug use, and known systemic and neurological disease
2. Neuro-ophthalmological examination – evaluate stability of fixation and eye movements under closed eyelids
3. Neurological examination – remember to test gait
4. Selected investigations:

    - Paraneoplastic markers e.g. Ri, Yo, Hu, Ma1, Ma2, amphiphysin, CV2, CRMP-5 neurophilaments.
    - (The presence of antibodies confirm the diagnosis but their absence does not exclude it).
    - Cerebrospinal fluid examination include oligoclonal bands, test for syphilis, and culture
    - Electroencephalogram
    - Brain MRI
    - Whole body positron emission tomography and other studies.

ILLUSTRATIVE CASES

- Square-wave jerks
- Neonatal opsoclonus
- Neonatal ocular flutter
- Paraneoplastic ocular flutter
- Parainfectious opsoclonus
- Paraneoplastic opsoclonus/flutter

PATHOGENESIS

This brief overview of saccadic oscillations and intrusions suggests that there may be two distinct mechanisms. One causing small oscillations such as microsaccadic flutter and one causing larger oscillations such as flutter and opsoclonus.

Leigh and Zee suggest that small amplitude oscillations might be provoked simply by lowering the tone in pause cells which might account for the deliberate production of saccadic oscillations of *voluntary nystagmus* or may occur involuntarily and be the cause of *microsaccadic flutter*.

They also suggest the disruption of pause cells and *saccadic pulse generator interconnections* may cause flutter and opsoclonus. This disruption might be at the level of the neurotransmitter, glycine, and glycinergic dysfunction might be the underlying mechanism for opsoclonus.

Also open for discussion regarding pathogenesis of opsoclonus, is the single functional MRI report by Helmchen et al in 2003. They reported two patients with atypical opsoclonus in that the opsoclonic movements stopped under closed eyelids. They obtained functional MRI with or without eyes closed and reported activation of the fastigial nucleus

in the cerebellum with eyes open, suggesting that this nucleus is the generator of opsoclonus. Leigh and Zee have commented that it might simply reflect increased frequency of saccades. This study is open to discussion.

(Helmchen et al Ann N.Y. Acad Sci 2003;1004;229-240).

TREATMENT

To be discussed by Matthew Thurtell, M.B.B.S, FRACP

CME ANSWERS

1. no
2. yes
3. yes

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TREATMENT OF NYSTAGMUS AND SACCADIC OSCILLATIONS

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LEARNING OBJECTIVES

1. The attendee will be able to understand the goals of treating nystagmus and saccadic oscillations.
2. The attendee will be able to list treatment options for acquired and congenital forms of nystagmus.
3. The attendee will be able to list treatment options for saccadic oscillations.

CME QUESTIONS

1. Which of the following is most likely to be effective for suppressing acquired pendular nystagmus?

    a) Baclofen
    b) Acetazolamide
    c) Gabapentin
    d) 4-aminopyridine
    e) Carbamazepine

2. Which of the following is least likely to be effective for improving vision in infantile nystagmus syndrome?

    a) Gabapentin
    b) Contact lenses
    c) Prisms to induce convergence
    d) Scopolamine patches
    e) Strabismus surgery

3. Which of the following is most likely to be effective for suppressing macrosaccadic oscillations?

    a) Memantine
    b) Acetazolamide
    c) Trihexyphenidyl
    d) 4-aminopyridine
    e) Carbamazepine

KEYWORDS

1. Nystagmus
2. Saccadic Intrusions
3. Eye Movement Disorders
4. Oscillopsia

INTRODUCTION

Nystagmus is often encountered in neuro-ophthalmic practice, having a prevalence of about 24 per 10,000 in the general population.[1] Unlike physiologic nystagmus, where the slow phases of nystagmus serve to *minimize* retinal image slip, the slow phases of pathologic forms of nystagmus *cause* retinal image slip. Retinal image slip of greater than 5 degrees per second can produce a decline in visual acuity, partly because the image of the object of interest no longer lies on the fovea, and illusory motion of the visual environment (*oscillopsia*).[2,3] Saccadic oscillations can also cause visual symptoms, since they consist of inappropriate saccadic eye movements that take the eye off target so that the image of the object of interest no longer lies on the fovea.[2]

Goals of Treatment

The primary goal of treatment is to reduce the patient's visual symptoms (blurred vision and/or oscillopsia) by reducing the speed of the nystagmus slow phases or by suppressing the saccadic oscillations. Treatments that stop the eyes from moving altogether (e.g., Botulinum toxin injections) are not ideal, because they cause oscillopsia during head movements (due to impairment of the vestibulo-ocular reflex) and diplopia (due to impairment of vergence eye movements).[2] Consequently, treatments that suppress the abnormal eye movements without affecting normal eye movements are preferred. Note that certain types of nystagmus (e.g., gaze-evoked nystagmus) and saccadic intrusions (e.g., square-wave jerks) do not give rise to visual symptoms and, thus, do not require specific treatment.

General Approaches to Treatment

A variety of treatments for nystagmus have been proposed, including medical, optical, surgical, and other miscellaneous treatments (Table 1), but few have been evaluated in prospective masked clinical trials.[2,4] Likewise, a variety of treatments for saccadic oscillations have been proposed, but few have been evaluated in prospective masked clinical trials.[2] Most treatments aim to suppress the abnormal eye movements without affecting normal eye movements, whereas others aim to negate the visual consequences of the abnormal eye movements rather than suppress them. The most appropriate choice of treatment depends on the type of nystagmus or saccadic oscillation and its characteristics. While some patients will derive benefit from one treatment approach (e.g., medication), others require a combination of treatments (e.g., medication and surgery) to improve their visual symptoms.[2,4]

TABLE 1: PROPOSED TREATMENTS FOR NYSTAGMUS[4]

Treatment Approach	Examples
Medical	Gabapentin Memantine 4-aminopyridine and 3,4-diaminopyridine Baclofen Clonazepam Valproate Trihexyphenidyl Benztropine Scopolamine Isoniazid Carbamazepine Barbiturates Alcohol Acetazolamide Brinzolamide (topical) Cannabis
Optical	Contact lenses Contact lens and spectacle combinations Prisms (base-in or base-out) Electro-optical devices
Surgical	Anderson-Kestenbaum procedure Cuppers divergence procedure Recession of rectus muscles Tenotomy and reattachment procedure
Other (Miscellaneous)	Botulinum toxin Acupuncture Biofeedback Cutaneous stimulation

TREATMENT OF ACQUIRED FORMS OF NYSTAGMUS

Medical treatments are often the most effective for suppressing acquired forms of nystagmus, but optical, surgical, and other treatments can sometimes be helpful. The dosing and common side-effects of medical treatments for acquired forms of nystagmus are summarized in Table 2.[5] Treatment approaches to specific acquired forms of nystagmus are discussed below.

Peripheral Vestibular Nystagmus

Acquired nystagmus can result from diseases of the peripheral vestibular system, such as vestibular neuritis, Ménière's disease, and benign paroxysmal positional vertigo. In most cases, the nystagmus is short-lived and/or intermittent. Furthermore, the associated vertigo, nausea, and vomiting are often more distressing to the patient than are the visual symptoms from the nystagmus. Consequently, the nystagmus is best managed with treatments directed towards the underlying peripheral vestibular disorder.[6]

Downbeat Nystagmus

Downbeat nystagmus often causes visual symptoms, such as vertical oscillopsia, and many affected patients seek treatment. Medications that have been reported to improve downbeat nystagmus include agents that act via GABA. Clonazepam, a $GABA_A$-agonist, has been shown to improve downbeat nystagmus in two uncontrolled trials.[7,8] Baclofen, a $GABA_B$-agonist, was thought to suppress downbeat nystagmus,[9,10] but it did not produce a consistent improvement in a subsequent double-masked trial.[11] Gabapentin, now thought to act an $\alpha 2\delta$-1 calcium channel

TABLE 2: DRUG TREATMENTS FOR ACQUIRED NYSTAGMUS[5]

Nystagmus Type	Treatment (dose, frequency)	Common Side-Effects
Peripheral Vestibular Nystagmus	Treatment of underlying vestibular disorder	Not applicable
Downbeat Nystagmus	4-aminopyridine (5-10mg, tid) 3,4-diaminopyridine (10-20mg, tid) Clonazepam (0.5-1mg, bid)	Dizziness, paresthesias, incoordination Dizziness, paresthesias, incoordination Drowsiness, dizziness, incoordination
Upbeat Nystagmus	Memantine (10mg, qid) 4-aminopyridine (5-10mg, tid) Baclofen (5-10mg, tid)	Lethargy, dizziness, headache Dizziness, paresthesias, incoordination Drowsiness, dizziness, lethargy
Torsional Nystagmus	Gabapentin (300mg, qid)	Dizziness, incoordination, drowsiness
Seesaw Nystagmus	Alcohol Clonazepam (0.5-1mg, bid) Memantine (10mg, qid)	Drowsiness, incoordination, vomiting Drowsiness, dizziness, incoordination Lethargy, dizziness, headache
Periodic Alternating Nystagmus	Baclofen (5-10mg, tid) Memantine (5-10mg, qid)	Drowsiness, dizziness, lethargy Lethargy, dizziness, headache
Acquired Pendular Nystagmus in MS	Gabapentin (300mg, qid) Memantine (10mg, qid)	Dizziness, incoordination, drowsiness Lethargy, dizziness, headache
Acquired Pendular Nystagmus in OPT	Gabapentin (300mg, qid) Memantine (10mg, qid) Trihexyphenidyl (5-20mg, tid)	Dizziness, incoordination, drowsiness Lethargy, dizziness, headache Dry mouth, blurred vision, dizziness

Abbreviations: bid, twice daily; MS, multiple sclerosis; OPT, oculopalatal tremor; qid, four times daily; tid, three times daily

antagonist[12] and N-methyl-D-aspartate (NMDA) receptor antagonist,[13] also failed to consistently improve downbeat nystagmus.[11] Anticholinergic agents were also suggested as a potential treatment, after intravenous scopolamine was observed to reduce downbeat nystagmus.[14] However, a prospective double-masked trial showed that trihexyphenidyl (an oral anticholinergic agent) produced only a modest improvement with significant side-effects.[15]

Recent trials have demonstrated that the aminopyridine potassium channel blockers are an effective treatment for downbeat nystagmus. Both 3,4-diaminopyridine and 4-aminopyridine have been shown to suppress downbeat nystagmus, although they are more effective in patients with cerebellar degenerations and less effective in those with downbeat nystagmus due to focal cerebellar lesions.[16,17] 4-aminopyridine has been found to be more effective than 3,4-diaminopyridine for suppressing downbeat nystagmus.[18] Both drugs are well tolerated, although they can cause seizures if high dosages are given and cardiac arrhythmias in patients with QT interval prolongation. The mechanism by which they suppress downbeat nystagmus is unclear, although they might work by increasing the activity and excitability of cerebellar Purkinje cells, thereby restoring normal levels of cerebellar inhibition of vertical vestibular eye movements.[19] 3,4-diaminopyridine has been shown to modulate the gravity-dependence of downbeat nystagmus and, thus, might suppress downbeat nystagmus by modulating otolithic pathways.[20] An extended-release formulation of 4-aminopyridine is now available in the United States and is approved for the treatment of gait difficulties in multiple sclerosis (MS) patients.[21] At present, the aminopyridines are considered first-line treatment for downbeat nystagmus (recommended dosages are given in Table 2). In those who do not respond, a trial of clonazepam could be considered (Table 2). Surgery (e.g., tenotomy and reattachment) might also have a role in the treatment of severe intractable oscillopsia in patients with downbeat nystagmus, either alone or in combination with medical therapy,[22] but clinical trials are yet to be performed.

Upbeat Nystagmus

Although upbeat nystagmus can produce pronounced vertical oscillopsia, it often resolves spontaneously. Thus, long-term treatment is only required if it is persistent. There have been few clinical trials evaluating proposed treatments for upbeat nystagmus. One uncontrolled trial reported a beneficial effect with baclofen.[9] A prospective double-masked cross-over trial reported reduction of upbeat nystagmus (or upbeat components of nystagmus) with memantine, a non-competitive NMDA receptor antagonist, but not with gabapentin.[23] In another study, 4-aminopyridine suppressed upbeat nystagmus in one patient.[24] A therapeutic trial with memantine, 4-aminopyridine, or baclofen could therefore be considered in patients with visual symptoms from persistent upbeat nystagmus (recommended dosages are given in Table 2).

Torsional Nystagmus

Torsional nystagmus can be persistent and can cause disabling oscillopsia. However, there have been few clinical trials evaluating proposed treatments. A double-masked cross-over trial reported a modest reduction in torsional nystagmus with gabapentin, but little response to memantine, in a single patient.[23] While further studies are required to identify medications that are effective in suppressing torsional nystagmus, a trial of gabapentin could be considered in patients with visual symptoms from persistent torsional nystagmus (the recommended dosage is given in Table 2).

Seesaw Nystagmus

Acquired seesaw nystagmus is rarely encountered in clinical practice, but can give rise to disabling oscillopsia. Several small studies have suggested that the pendular form can be suppressed by alcohol or clonazepam in individual patients.[25-27] A double-masked cross-over trial reported that the jerk form, hemi-seesaw nystagmus, can be suppressed with gabapentin or memantine.[23] Thus, treatment with clonazepam, gabapentin, or memantine could be considered in patients with visual symptoms from persistent seesaw nystagmus (recommended dosages are given in Table 2).

Periodic Alternating Nystagmus

Patients with the acquired form of periodic alternating nystagmus often complain of oscillopsia. Although no masked or randomized trials have been performed to date, several studies have reported complete suppression of the nystagmus with the $GABA_B$-agonist baclofen.[28-30] The efficacy of baclofen in treating periodic alternating nystagmus has been confirmed in a primate model.[31] A beneficial effect from memantine has also been reported in a single patient whose nystagmus was refractory to baclofen treatment.[32] At present, baclofen is considered first-line treatment for acquired periodic alternating nystagmus, while memantine could be considered in those patients who do not respond to baclofen (recommended dosages are given in Table 2).

Acquired Pendular Nystagmus in Multiple Sclerosis

Acquired pendular nystagmus (APN) can occur in patients with multiple sclerosis (MS) and is often responsible for disabling visual symptoms. The hypothesis that APN arises due to instability of the ocular motor neural integrator led to testing of drugs with presumed effects on GABA- and glutamate-mediated mechanisms. Those with GABAergic effects (e.g., clonazepam, valproate, and isoniazid) were found to help some patients in early studies.[33,34] The effects of gabapentin, which was initially thought to have GABAergic effects, were compared with those of baclofen, a $GABA_B$ agonist, in a double-masked study including patients with APN.[11] Across all subjects, visual acuity improved with gabapentin, but not baclofen, and only gabapentin reduced median nystagmus slow phase speed. However, some patients had no response to gabapentin or reported

side-effects (e.g., ataxia). Gabapentin was subsequently compared with vigabatrin, which is known to be more purely GABAergic.[35] While gabapentin suppressed APN, vigabatrin did not, suggesting that gabapentin might suppress APN by a non-GABAergic mechanism; gabapentin is now thought to exert its effect via the $\alpha 2\delta$-1 calcium channel subunit[12] and NMDA receptors.[13] Two recent prospective masked trials have confirmed that gabapentin is often effective in suppressing APN in patients with MS, although not all patients respond.[23,36]

Several prospective masked trials have demonstrated that memantine, a non-competitive NMDA receptor antagonist, can also suppress APN in patients with MS when given in doses of 40-60mg per day.[23,36,37] Indeed, it can reduce APN in patients who do not respond to gabapentin.[23,37] However, patients with MS can develop a reversible exacerbation of their MS symptoms when receiving 30mg or more of memantine per day[38] and, thus, gabapentin may be the preferred initial treatment for APN in MS. The recommended dosages for gabapentin and memantine are given in Table 2. There is a potential role for combining drug therapies (e.g., gabapentin and memantine), but no clinical trials have been conducted to date. Surgery (e.g., tenotomy and reattachment) might also be effective in suppressing APN in patients with severe intractable oscillopsia,[22] but should not be routinely recommended as clinical trials are yet to be performed.

Acquired Pendular Nystagmus in Oculopalatal Tremor

The nystagmus of oculopalatal tremor (OPT) often causes severe intractable oscillopsia and, consequently, many affected patients request treatment. Several studies have evaluated the effect of anticholinergic agents on the nystagmus of OPT. Although individual patients can show a response to trihexyphenidyl,[39,40] it was found to be only modestly effective in a prospective masked trial.[15] A prospective double-masked trial comparing intravenously-administered scopolamine, benztropine, and glycopyrrolate found that scopolamine reduced the nystagmus of OPT and improved vision, whereas benztropine was less effective, and glycopyrrolate had no effect.[14] However, treatment with intravenous scopolamine resulted in significant side-effects and is not practical for day-to-day treatment. Transdermal scopolamine was also found to be unreliable for treating the nystagmus of OPT, given that it can make the nystagmus worse or cause significant side-effects in some patients.[41] Two prospective double-masked cross-over trials have demonstrated that gabapentin and memantine can suppress the nystagmus of OPT in some patients.[11,23] Although the nystagmus of OPT is often more refractory to treatment with gabapentin and memantine than is APN due to MS, a trial of therapy is worthwhile and usually well tolerated (the recommended dosages of these medications are given in Table 2). There is a potential role for combined drug therapies (e.g., gabapentin and memantine) or surgery (e.g., tenotomy and reattachment), but these treatment approaches have not yet been evaluated in clinical trials.

TREATMENT OF CONGENITAL FORMS OF NYSTAGMUS

Treatment approaches to congenital forms of nystagmus vary depending on the severity of visual symptoms, severity of any associated afferent visual system anomalies, and the characteristics of the nystagmus itself.[2,4] Some patients do not have visual symptoms, especially if "foveation periods" are well developed, and most do not complain of oscillopsia.[42] Those with impaired vision might have so due to associated afferent visual system anomalies (e.g., due to optic nerve hypoplasia),[2] such that suppression of the nystagmus does not produce a significant improvement in vision. However, those with visual symptoms with intact afferent visual systems can potentially benefit from treatments that suppress the nystagmus.[2,4]

Infantile Nystagmus Syndrome

Infantile nystagmus can be treated using optical, surgical, and medical approaches.[2,4] Optical treatments are relatively simple, safe, and may be all that is required to bring about a substantial improvement in vision. For example, correction of refractive error alone might bring about an appreciable improvement in vision.[43,44] Use of contact lenses might be preferred over spectacle lenses, because contact lenses appear to further suppress infantile nystagmus by an uncertain mechanism.[45] However, spectacle lenses might be preferred in patients whose nystagmus suppresses with convergence, because prism can be added to induce convergence, and thereby suppress the nystagmus and improve visual acuity, during viewing of far targets.[46] Adequate convergence can be produced by a pair of 7 diopter base-out prisms with -1 diopter sphere added to compensate for the accompanying accommodation.

Several surgical procedures can be considered for the treatment of patients with infantile nystagmus. The Anderson-Kestenbaum procedure aims to move the attachments of the extraocular muscles, so that the null point of the nystagmus is shifted to the straight ahead position.[47,48] The Anderson-Kestenbaum procedure also lead to decreased nystagmus intensity outside of the null zone and may improve head posture.[49-51] However, selection of patients who will benefit entails measuring visual acuity and nystagmus in different gaze positions. Cuppers' divergence procedure can be effective in patients whose nystagmus suppresses with convergence; the procedure aims to diverge the eyes, such that the patient is required to converge during far viewing.[52,53] In selected patients, combining the Anderson-Kestenbaum and Cuppers' divergence procedures can produce a better outcome than either procedure alone.[53] Another surgical approach involves large recessions of the horizontal rectus muscles,[54-58] sometimes in combination with other procedures,[59] to produce suppression of the nystagmus. However, the nystagmus can increase in severity following an initial improvement, due to adaptive changes. It has been observed that some suppression of the nystagmus and broadening of the null zone follows almost every surgical procedure for infantile nystagmus, which led to the suggestion that merely detaching the muscles, dissecting

the perimuscular fascia, and re-attaching them at the same site ("tenotomy and reattachment") might suppress infantile nystagmus.[60] Experimental studies in a canine model support this hypothesis.[61] Clinical trials indicate that some patients treated with tenotomy and reattachment show improvement in some measures of visual and ocular motor function following horizontal rectus surgery,[62-64] but not all reports agree.[65] Since the operation may have its effects by disrupting extraocular proprioceptive feedback signals, variations on the original procedure have been proposed.[66] Carefully selected patients with infantile nystagmus can benefit from surgical treatments that are geared to their individual visual and ocular motor findings: (1) if there is a narrow eccentric null zone, then the Anderson-Kestenbaum procedure should be considered; (2) if the nystagmus is greatly reduced with convergence, then Cuppers' divergence procedure often reduces the nystagmus; and (3) if neither of these conditions apply, then tenotomy and reattachment may help some patients by broadening the null zone. Patients with infantile nystagmus and associated afferent visual system anomalies (e.g., oculo-cutaneous albinism) are less likely to benefit from surgical intervention.[67]

Medical treatments of infantile nystagmus are generally less favorable, since they would need to be given life-long and can produce significant side-effects. A randomized, controlled, double-masked trial comparing gabapentin and memantine found that nystagmus intensity and visual acuity improved in both treatment groups.[68] However, those with associated afferent visual system anomalies only derived a small benefit. Recent studies have reported that infantile nystagmus might be suppressed with carbonic anhydrase inhibitors; both oral acetazolamide and topical brinzolamide appear to have an effect.[69,70] Infantile nystagmus can also be reduced after smoking cannabis.[71] Lastly, gene therapy holds the potential for treatment of nystagmus associated with congenital retinal disorders. For example, in an animal model of Leber's congenital amaurosis, successful gene therapy restored vision and reduced the associated nystagmus.[72-75]

Other Congenital Forms of Nystagmus

The treatment options for other congenital forms of nystagmus are more limited. Treatment for fusional maldevelopment nystagmus syndrome (latent nystagmus) consists of measures to improve vision, such as correction of refractive error and patching for amblyopia.[2,4] Spasmus nutans syndrome typically resolves spontaneously and does not require specific intervention.[2,4]

TREATMENT OF INTRACTABLE NYSTAGMUS

There are several treatment options for patients with nystagmus that does not respond to the treatment approaches listed above. Optical devices that negate the visual effects of the nystagmus can be useful. One such approach consists of using high-plus spectacle lenses in combination with high-minus contact lenses.[2,4,76] While the visual effects of the nystagmus can be effectively negated using this approach, it is only useful when the patient is stationary and viewing monocularly, since the visual effects of normal eye movements (e.g., vestibulo-ocular reflex and vergence) are also negated.[77] Another approach involves the use of an electro-optical device, which measures the ocular oscillations and incorporates image-shifting optics to negate their visual effects in real-time.[78] Electo-optical devices are best suited for patients with pendular forms of nystagmus, since the abnormal eye movements can be more easily distinguished from normal eye movements (e.g., saccades), but these devices remain experimental. Treatments to stop the eyes from moving altogether, such as Botulinum toxin injections into the extraocular muscles or retrobulbar space, can also be considered in patients with intractable nystagmus. While such treatments can lead to reduced oscillopsia and improved visual acuity, patients often develop ptosis and diplopia that can be more troublesome than the visual consequences of the nystagmus itself.[79-84] Furthermore, normal eye movements are impaired and the treatment is only effective for a period of weeks to months, making Botulinum toxin injections limited in their therapeutic value.[2,4]

TREATMENT OF SACCADIC OSCILLATIONS

The treatment of saccadic oscillations depends on the presence and severity of associated visual symptoms. Some forms of saccadic oscillation, such as square-wave jerks, are not associated with visual symptoms and, thus, do not require specific treatment.[2] In those forms of saccadic oscillation in which there are associated visual symptoms, medical treatments are often the most effective.[2]

Macrosaccadic Oscillations

Macrosaccadic oscillations often result in difficulty with reading, but there are few clinical trials investigating the merit of proposed treatments. Memantine was shown to reduce the frequency of the oscillations and improve reading ability in one family with macrosaccadic oscillations due to cerebellar ataxia and, thus, could be considered for a therapeutic trial in patients with symptomatic macrosaccadic oscillations.[85]

Ocular Flutter and Opsoclonus

Ocular flutter and opsoclonus can produce severe disabling oscillopsia. When due to brainstem encephalitis, treatment with intravenous immunoglobulin, corticosteroids, azathioprine, or monoclonal antibodies directed against B-lymphocytes can hasten recovery.[86-88] In adults with opsoclonus in association with cancer, treatment of the tumor itself can lead to improvement in the oscillations.[87] Plasmapheresis, intravenous immunoglobulin, and immunoadsorption therapy can sometimes be effective.[89-91] Opsoclonus in children with neural crest tumors often responds to corticosteroids[92] and sometimes to intravenous immunoglobulin.[93] New therapies with monoclonal antibodies directed against B-lymphocytes may also prove effective.[88] Occasional patients derive a benefit from medications, such as gabapentin,[94] but formal clinical trials have not yet been completed.

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CME ANSWERS

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