ABC of Gaze and Ocular Oscillations

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Abstract

The chief goal of all eye movements is to maintain the image of an object steady on the retina especially the macula to preserve visual acuity. Gaze palsy refers to lack of the conjugate movements due to a failure of supranuclear control mechanisms. Supranuclear control is maintained by not one, but multiple eye movement systems and gaze mechanisms. Supranuclear gaze palsies can be associated with a myriad of aetiologies- from trauma or metabolic abnormalities to stroke, demyelinating disorders and space occupying lesions like tumours. Culprit lesions may be in frontal motor centres, brainstem gaze centres gaze or interconnecting segments. While the brainstem network for horizontal gaze lies in pons, that for vertical gaze is situated in midbrain. Further, ocular oscillations and nystagmus are abnormal eye movements that disrupt a steady fixation of gaze. It is prudent to be aware of various gaze pathways and their anatomical corelates in order to establish a topographic relationship of clinical findings. A systematic clinical examination may provide deep insights on the patho-physiological mechanisms along with aiding in localizing the lesion accurately. This review deals with systematic clinical approach to various gaze control systems.

Keywords: Gaze palsies, ocular movement, ocular oscillations

Introduction

A detailed knowledge of the anatomy and physiology of eye movements is important for the clinician to localize the lesion to a specific area in the brain, since the involvement of various parts of the brain (brain stem, cerebellum, or cerebral hemispheres) can produce disturbance in eye movements. Moreover, many involuntary ocular movements, like nystagmus and ocular intrusions can also occur in lesions of various parts of the brain. The key to diagnosis is a systematic clinical examination of the different types of eye movements, including eye position, range of eye movements, and various supra nuclear control systems like a smooth pursuit, saccades, gaze-holding function as well as testing for the different types of ocular oscillations. This review deals with a systematic clinical approach to these various gaze control systems and the ocular oscillations and their patho-physiological mechanisms.

Abbreviations

ANC- Abducens Nucleus Complex
APN- Acquired Pendular Nystagmus
DBN- Downbeat Nystagmus
EBN- Excitatory Burst Neurons
FOR- Fastigial Oculomotor Region
GEN- Gaze Evoked Nystagmus
INC- Interstitial Nucleus of Cajal
INO- Internuclear ophthalmoplegia
MLF- Medial Longitudinal Fasciculus
NI- Neural Integrator
PAN- Periodic Alternating Nystagmus
PPRF- Paramedian Pontine Reticular Formation
PTO- Parieto-Temporal-Occipital area
PVN- Peripheral vestibular nystagmus
riMLF- rostral interstitial nucleus of Cajal
SSN- See-Saw Nystagmus
UBN- Upbeat Nystagmus
VOR- Vestibulo-ocular Reflex

Types of eye movements

Refixation saccadic movements redirect the eye to focus the images of interest to the centre of the retina. Pursuit movements and optokinetic nystagmus stabilize the position of eye during sustained head movement and prevent the distortion of image by reducing the overflow of the image over the retina. The vestibulo-ocular reflex (VOR) stabilizes the position of eye during head movements. Convergence and divergence movements allow objects at varied distances to be centred on the retinas at corresponding locations.

Saccadic system

Saccades are rapid eye movements used to redirect the fovea from one object to another.

The essential machinery for the saccade generation is situated in the brain stem and is driven and modulated by various control systems from the cortex, cerebellum, basal ganglia, and thalamus.

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The brain stem network for horizontal saccades is situated in the pons and that for vertical saccades is situated in the midbrain. The final common pathway for horizontal saccades is from the abducens nucleus complex (ANC), which contains neurons supplying the ipsilateral lateral rectus and abducens interneurons, fibers of which cross to the opposite side and ascend in the medial longitudinal fasciculus (MLF) to innervate the contralateral medial rectus subnucleus.[1] Hence activation of the abducens nucleus results in ipsilateral horizontal conjugate gaze movement [Figure 1a].

Two mechanical elements are important for production of saccades[2,3]: a PULSE (velocity command) which aids in overcoming the resistance of various orbital tissues/ inertia of the globe and ultimately helps in changing the position of the eye in the orbit, and a STEP (position command) or change in tonic contraction of the orbital muscles helping to keep the eye in the new position.

The step innervation is provided by the neural integrator (NI), which includes the nucleus prepositus hypoglossi, medial vestibular nucleus, and neurons of the paramedian tract. The pulse-step mechanism is depicted in Figure 1b.

For horizontal saccades, the pulse is generated by excitatory burst neurons (EBN) in the paramedian pontine reticular formation (PPRF) and for vertical and torsional saccades, it is generated in the rostral interstitial nucleus of Cajal (riMLF). PPRF stimulates the ipsilateral ANC[4] [Figure 1a]. PPRF also projects to the NI for horizontal saccades.[5]

The EBN for the vertical and torsional movement is located in the riMLF and they burst for upward and downward saccades.

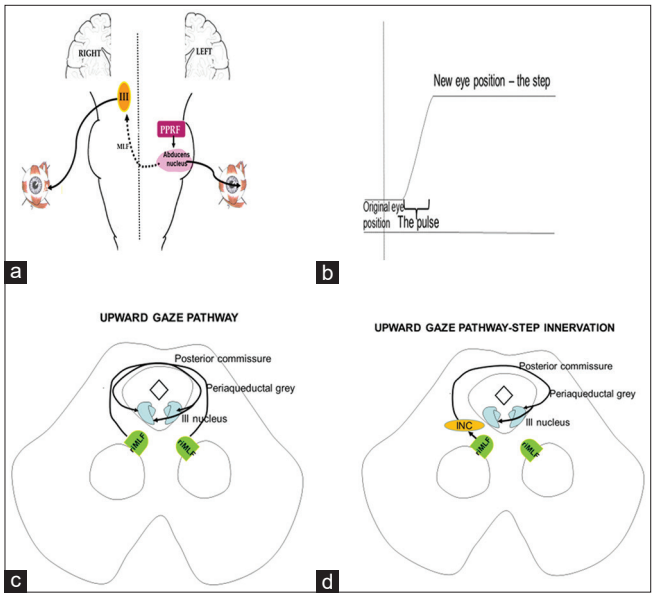

Figure 1: (a) Activation of the left abducens nucleus results in conjugate eye movement to the left side. Excitatory burst neurons in the PPRF project to the ipsilateral abducens nucleus. (b) Pulse-step mechanism of saccadic movement. (c) For upward gaze, each riMLF projects to both oculomotor nuclei. (d) The interstitial nucleus of Cajal projects through the posterior commissure to vertical motoneurons to provide the gaze-holding signal

Each riMLF contains EBN for both upward and downward movements.[6]

For upward saccades, fibers from one riMLF course dorsally and cross to the opposite side through the posterior commissure and get connected to both the oculomotor nuclei. The fibers from the other riMLF behave similarly. Hence a unilateral lesion of the riMLF produces only a transient upward gaze palsy, whereas a lesion in the posterior commissure produces an enduring upgaze palsy [Figure 1c].

Each riMLF projects bilaterally to motoneurons for elevation but only unilaterally for depression. Hence, downward gaze palsy can be produced only by bilateral lesions. Bilateral lesions of the riMLF cause loss of all vertical saccades and torsional quick phases.[7]

These vertical EBNs also project to both the interstitial nucleus of Cajal (INC) and the superior vestibular nucleus, which provide the step innervation for the vertical saccades [Figure 1d].

Omnipause cells which lie in the nucleus raphe interpositus send inhibitory projections to PPRF and riMLF. They continuously inhibit all EBN to prevent saccades. They cease discharging during any saccade as well as during eye blinks.[8] Their connections are depicted in Figure 2a.

The superior colliculus and the brainstem EBN in the PPRF and the riMLF receive input from the frontoparietal cortex, vestibular organs, cerebellum, and basal ganglia.

The cerebellum plays a major role in the control of saccadic eye movements.[9-11] The dorsal vermis and the underlying fastigial nucleus control saccadic accuracy. Flocculus and paraflocculus stabilize the NI which provides the step innervation and is also responsible for perfect matching of the pulse and step. These areas modulate the amplitude of the saccadic pulse. They drive the burst neurons for contralateral saccades and also provide a late brake for ipsilateral saccades.[12]

The oculomotor vermis projects to the caudal part of the fastigial nucleus called the fastigial oculomotor region (FOR) which modulates saccades by stimulating burst neurons during contralateral saccades and providing inhibition during ipsilateral saccades [Figure 2b]. The outflow from the FOR passes contralaterally through the uncinate fasciculus (Hook bundle of Russel) in the brachium conjunctivum to drive the contralateral PPRF and riMLF neurons [Figure 2c].

The combination of hypermetric saccades in one horizontal direction and hypometric saccades in the opposite direction is called saccadic lateropulsion (ipsipulsionand contrapulsion[13]). Since the "hook bundle of Russel" reaches the PPRF through the contralateral a lesion of this peduncle which involves the fastigial output after its decussation will cause the ipsilateral PPRF to be disfacilitated resulting in "contrapulsion." Therefore, with lesions of the SCP, the horizontal saccades away from the lesion are hypermetric and ipsilateral saccades are hypometric. On the contrary, a lesion of the inferior cerebellar peduncle causes ipsipulsion.

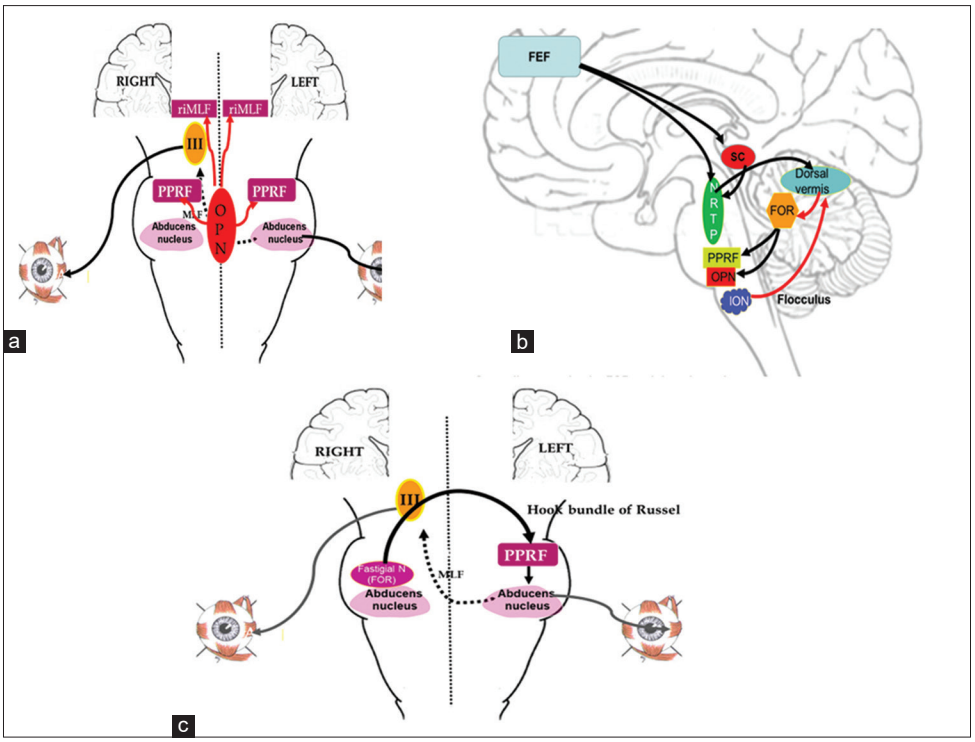

Figure 2: (a) Omnipause neurons (shown as OPN). (b) Saccadic commands from the FEF, directly and via the superior colliculus (SC) reach the nucleus reticularis tegmenti pontis (NRTP) and are transmitted to the dorsal vermis. The fastigial oculomotor region (FOR) projects to the PPRF and omnipause neurons (OPN) and modulates saccades by stimulating burst neurons during contralateral saccades and providing inhibition during ipsilateral saccades. Black lines depict excitatory pathways and red lines depict inhibitory pathways. (c) Fastigial oculomotor region (FOR) activates the contralateral PPRF though the hook bundle of Russel

The flocculus stabilizes the inherently leaky NI and mediates pulse-step matching. Lesions of the flocculus result in gaze-evoked nystagmus (GEN) due to a leaky NI and post-saccadic drift due to a defect in pulse-step matching.

Abnormalities of saccades

Absent saccades can be due to a lesion anywhere in the saccadic pathway [Figure 3a]. Since the vestibulo-ocular input mediating the VOR is to the abducens nuclear complex and not to the PPRF [Figure 3b], a PPRF lesion will spare the VOR. A similar gaze palsy can also be seen in lesions of the ventral pedunculo-tegmental pathway. If the lesion is in the frontal lobe or in the descending pathway before its crossing in the upper pons, one gets a contralateral gaze palsy but if the lesion is after crossing, then an ipsilateral gaze palsy results.[1]

Impaired initiation of saccades can be due to a lesion anywhere in the pathways mediating saccade production. Slow saccades are seen in lesions affecting the extra-ocular muscles or saccadic generators. Sometimes it can be seen in drowsy, inattentive, or sedated patients.[14]

Internuclear ophthalmoplegia

INO is due to a lesion in the MLF pathway connecting the ANC to the contralateral third cranial nerve nucleus[15] [Figure 3c]. The lesion results in weakness of the ipsilateral medial rectus, dissociated nystagmus of the contralateral abducting eye, and skew deviation with ipsilateral hypertropia.[16,17]

When there is a lesion in the PPRF or ANC and MLF on one side, one gets "one-and-half syndrome," wherein there is gaze palsy to the same side and failure of adduction of the ipsilateral eye on contralateral gaze [Figure 3d].

Vertical gaze palsy

Upward gaze palsy can be seen in lesions of bilateral riMLF as well as in lesions of the posterior commissure. Unilateral lesions of riMLF cause only transient upward gaze palsy, but bilateral riMLF lesions cause both upward and downward gaze palsy. However, vertical VOR and vertical pursuit are preserved in bilateral riMLF lesions. This finding helps to differentiate riMLF lesions from an infranuclear palsy.

Pursuit system

Images moving away from the fovea constitute the strongest stimuli for smooth pursuit. The smooth pursuit system cannot follow objects moving faster than 30–40° per second and need a visual object to be tracked.

The anatomic pathways involved in the smooth pursuit system are complex.[18] For horizontal pursuit, the control of the pursuit is ipsilateral. The intraparietal area [the parieto-temporal-occipital area (PTO)] is the main cortical center for pursuit generation. Descending pursuit pathways from the PTO run ipsilaterally through the retrolenticular internal capsule to terminate in the dorsolateral pontine nuclei (DLPN). The pathway decussates twice at the

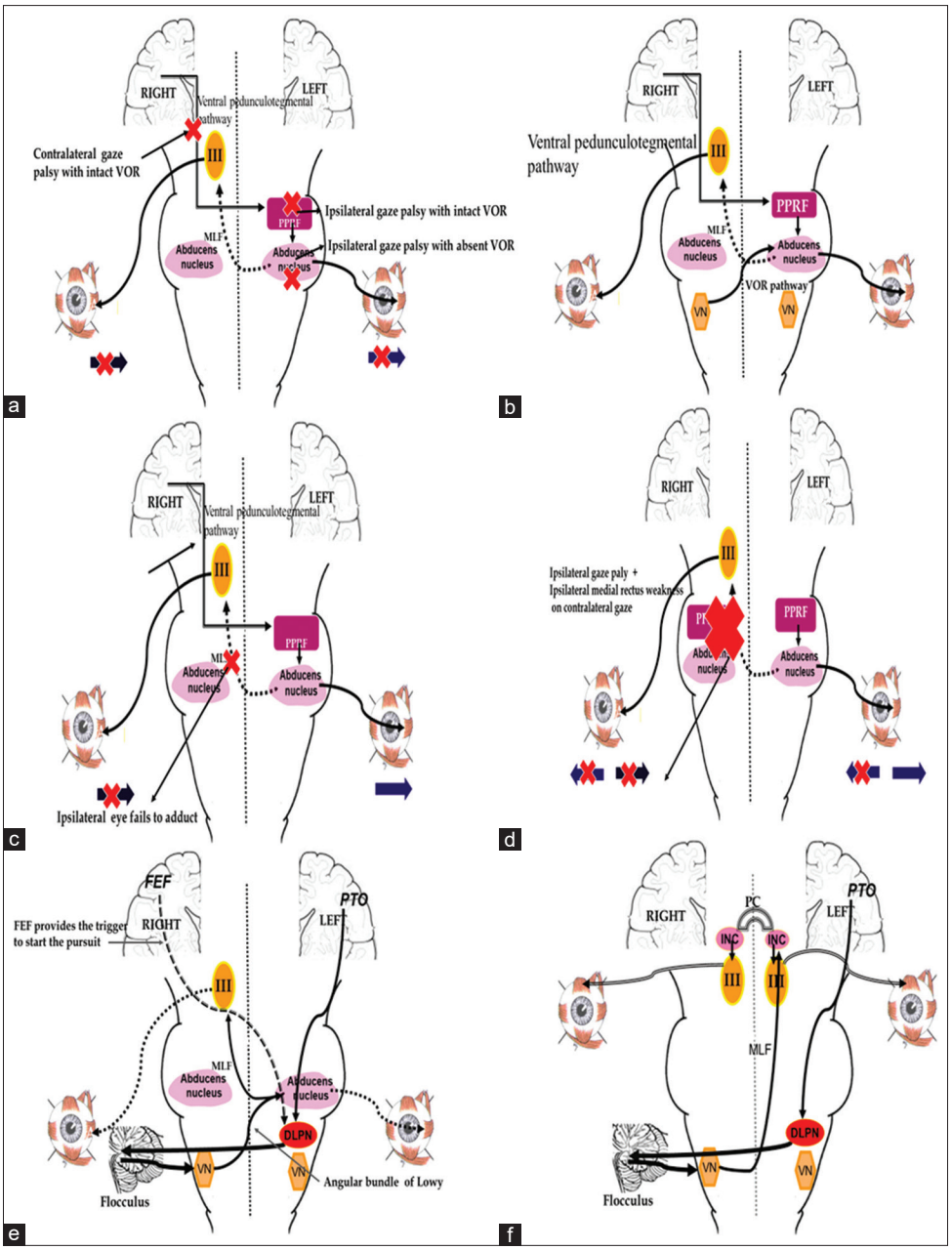

Figure 3: (a) Sites of lesions causing gaze palsy. (b) Vestibulo-ocular reflex pathway connecting the right vestibular nucleus (VN) to left abducens nucleus. (c) Right MLF lesion causing failure of adduction of ipsilateral eye. (d) Site of lesion causing "One and half syndrome". (e) Horizontal pursuit pathway. The dorsolateral pontine nucleus (DLPN) receives input from the ipsilateral parieto- temporo-occipital area and the contralateral FEF. The DLPN then projects to the contralateral flocculus and vestibular nucleus (VN) and on to the ipsilateral abducens nucleus and then via the MLF to the contralateral oculomotor nucleus (III). (f) Vertical pursuit pathway. The dorsolateral pontine nucleus (DLPN) receives input from the ipsilateral parieto- temporo-occipital area. The DLPN then projects to the contralateral flocculus and vestibular nucleus (VN) and via the MLF to the interstitial nucleus of Cajal (INC) which projects to the oculomotor nucleus (III) ipsilaterally as well as contralaterally across the posterior commissure (PC)

pontocerebellar level as shown in Figure 3e. The fibers from the DLPN cross to the opposite side and reaches the contralateral cerebellum. Impulses from the contralateral cerebellum excite the medial vestibular nucleus on the same side which recross and activates the contralateral ANC, ultimately resulting in ipsilateral control. The PPRF is not involved in smooth pursuit eye movements. The trigger for starting the smooth pursuit is provided by the FEF.

The pathway for vertical pursuit pathway follows a similar course and after synapsing in the vestibular nucleus, projects rostrally through the MLF and brachium conjunctivum and reaches the INC as shown in Figure 3f. The cerebellum plays an important role in the gain and adaptation of the pursuit movement.[19,20]

A common finding in cerebellar disease is diminished smooth pursuit gain, where pursuit will be replaced by a

Table 1: Causes of Upbeat and Downbeat nystagmus

Upbeat nystagmus	Downbeat nystagmus
Drugs	Drugs
Barbiturates	Lithium
Amitriptyline withdrawal	Amiodarone
	Metronidazole
	Antiepileptics
	Opioids
Toxins	Toxins
Nicotine	
Organophosphates	
Infectious	Infectious
Creutzfeldt-Jakob disease	Herpes simplex encephalitis
Neurocysticercosis	West Nile encephalitis
	Legionnaire's disease
	Human T-lymphotropic virus infection
	Ciguatera toxin
	Tetanus
Inflammatory	Inflammatory
Multiple sclerosis	Multiple sclerosis
Neuromyelitis optica	Neuromyelitis optica
Paraneoplastic syndrome	Paraneoplastic syndrome
Anti-GAD antibody syndrome	Anti-GAD antibody syndrome
	Miller Fisher syndrome
Vascular	Vascular
	Stroke
	Vertebrobasilar dolichoectasia
Degenerative	Degenerative
	Spine-cerebellar atrophy
	Multi-system atrophy
Other	Other
Chiari malformation	Chiari malformation
Pseudotumor cerebri	B12 deficiency
Epileptic manifestation	Hypomagnesemia
	Heat stroke
	Gluten ataxia
	Episodic ataxias

series of small, corrective saccades to keep up with the target (*saccadic pursuit* or *cogwheel pursuit)*. Generally, saccadic pursuit is non-localizing and can be caused by lesions of many neural structures.[9]

Normally the pursuit mechanism can suppress the VOR. Impaired VOR suppression suggests a defective central smooth pursuit system, usually due to a lesion of the flocculus or parafloccullus.[1,21]

Vergence system

The vergence system includes both convergence and divergence and is dysconjugate movements necessary for looking at a near target as well as far objects. The occipital areas 19 or 22 are thought to be cortical centers for the vergence system.[22] Vergence premotor neurons, also called "near response cells" lie in the midbrain, dorsolateral to the oculomotor nucleus, and in the medial nucleus reticularis tegmenti pontis. Midbrain lesions affecting these convergence neurons produce convergence paralysis.

Ocular oscillations

Abnormal eye movements that disrupt steady fixation are of two main types: pathological nystagmus and saccadic intrusions.

Nystagmus

Nystagmus is defined as a disorder of ocular posture characterized by a rhythmic, repetitive, oscillation of the eyes. Nystagmus is generally of two types: jerk nystagmus and pendular nystagmus. Jerk nystagmus has a slow phase drift followed by a rapid corrective saccade in the opposite direction. Pendular nystagmus refers to a sinusoidal oscillation with slow phases in both directions and no corrective saccades.

Nystagmus in various disease states

(i) Nystagmus in vestibular disorders

Nystagmus can be seen in peripheral as well as central vestibulopathies.

1. ***Nystagmus due to Peripheral vestibular disorder***
   Peripheral vestibular nystagmus (PVN) due to a unilateral peripheral lesion consists of either a horizontal rotary or purely horizontal nystagmus. Nystagmus does not change in direction with gaze to either side, although it increases in amplitude with gaze in the direction of the fast phase (Alexander's law). In contrast, acute central vestibular disorders cause nystagmus that changes its direction with a change in the direction of gaze. However, in some patients with medullary stroke, nystagmus may be present only when the patient is gazing in one direction, mimicking a PVN (called pseudo vestibular neuritis). Visual fixation does not affect the intensity of central vestibular nystagmus whereas PVN attenuates with visual fixation and increases by avoiding fixation [Figure 4a].
2. **Nystagmus in benign paroxysmal positional vertigo (BPPV)**
   The most common type of BPPV is the posterior canal type of BPPV. The elicited nystagmus during the Dix-Hallpike's maneuver is a mixed upbeat and torsional with the upper pole of the eyes beating toward the lower ear. In the canaolithiasis type where free-floating otolithic debris is present in the endolymph, the nystagmus usually develops with a latency of several seconds (up to 30 s) and resolves within 1 min (usually within 30 s). The nystagmus reverses direction upon sitting and tends to habituate with repeated testing (fatiguability).
3. **Central Vestibular nystagmus.**

A central vestibular dysfunction should be suspected when any one of the following findings is present:

1. Purely vertical or torsional spontaneous nystagmus
2. Horizontal–torsional nystagmus with normal head-impulse test on the side contralateral to the nystagmus
3. Positional nystagmus incompatible with canalolithiasis or cupulolithiasis
4. GEN

5. Impaired VOR suppression
6. Saccadic pursuit
7. Dysmetric or slow saccades
8. Presence of skew deviation.

(ii) Nystagmus Caused by Central Vestibular Imbalance

Upbeat nystagmus (UBN)

Upbeat nystagmus refers to nystagmus with fast phase upward. UBN typically increases with upgaze, usually diminishes with downgaze, and is unaffected by horizontal gaze. Upbeat nystagmus (UBN) has been described in lesions of the midbrain, ventral pontine tegmentum, anterior cerebellar vermis, thalamus, and medulla. When upbeat nystagmus increases in downgaze, the lesion usually involves the caudal medulla.[23]

Downbeat nystagmus (DBN)

Downbeat nystagmus refers to a jerk nystagmus with the fast phase downward, seen in the primary position. It is typically increased with convergence, with eccentric gaze, and particularly by having the patient look downward and laterally (side-pocket nystagmus). The DBN is caused by lesions of the vestibulocerebellum including the flocculus, parafloccculus, nodulus, uvula, and medulla may also be the cause.[24] DBN is a prominent manifestation of floccular and parafloccular dysfunction.

Causes of UBN and DBN are summarized in Table 1.[1]

Torsional nystagmus

Torsional nystagmus suggests a brain stem lesion. In torsional nystagmus, the eye oscillates in a purely rotary or cyclotorsional plane. It may be present in the primary position or with either head positioning or gaze deviation. It is usually the result of central vestibular pathway lesions.

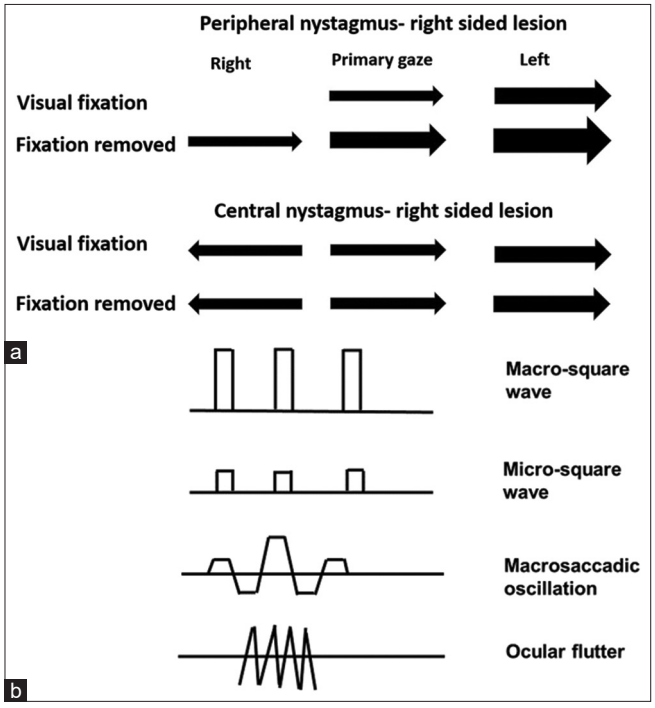

Figure 4: (a) Direction of nystagmus in peripheral and central vestibular lesion. (b) Various saccadic intrusions

Gaze evoked nystagmus (GEN)

GEN refers to the nystagmus that develops when patients look into eccentric eye positions. Here, the fast component is to the point of fixation and there is no nystagmus in the primary position.

Lesions in the NI or the flocculus which stabilizes it result in a deficit in holding the gaze in the eccentric position. This defect in gaze-holding produces a slow drift of the eyes back to the primary position, resulting in GEN. GEN is, therefore, caused by lesions affecting the NI function or the connection with the vestibulocerebellum.

Central positional nystagmus

Paroxysmal positional vertigo and nystagmus can occur in posterior fossa lesions.[13] In central lesions, one can have DBN upon supine head-hanging, UBN upon returning from supine to upright position, as well as apogeotropic horizontal–torsional nystagmus during the Dix–Hallpike or the supine head-roll test.[25] This is mainly seen with cerebellar strokes and tumors involving the nodulus and uvula.

Characteristics of nystagmus in distinguishing central and peripheral positional vertigo is given in Table 2.

Periodic alternating nystagmus (PAN)

PAN refers to nystagmus which alternates direction in the primary position.[26] The nystagmus beats in one direction for about 60–90 s with an increasing and then decreasing intensity, followed by a brief transitional period (which may be punctuated by UBN, DBN, or saccadic intrusions), and then beats in the opposite direction.[27]

PAN can be congenital or caused by cerebellar nodular dysfunction. Sometimes, PAN may be seen with the bilateral visual loss[28] and Meniere disease.[29]

Convergence-retraction nystagmus

Here there is rapid convergence with synchronous retraction of both globes caused by simultaneous contraction of all the extra-ocular muscles, followed by a slow divergent movement. It is one of many signs of Parinaud's dorsal midbrain syndrome.

See-saw nystagmus

In see-saw nystagmus (SSN), one eye moves downward and extorts while the other eye rises and intorts. SSN can

Table 2: Differences between Peripheral and Central Nystagmus

Nystagmus	Peripheral	Central
Appearance	Vertical and torsional	Pure vertical or upbeat
Latency	30-40 s	No latency
Fatigability	Yes	No
Habituation	Yes	No
Rebound	Yes	No
Reproducibility	Poor	Good
Localization	Posterior SCC or Horizontal SCC	Brainstem or cerebellum

be of the pendular type or the jerk type (*hemi-see-saw nystagmus (HSSN)*. The pendular type is usually due to a suprasellar lesion in most cases. In the jerk-waveform, half the cycle is the slow phase followed by a corrective half cycle of jerk. This is usually seen with unilateral lesions of the INC.[30] INC lesions may cause either SSN or HSSN.

Acquired pendular nystagmus (APN)

APN consists of involuntary, sinusoidal ocular oscillations typically ranging from 2 to 6 Hz that may be horizontal, vertical, or a combination thereof including circular, elliptical, or windmill-type. APN may arise from lesions affecting the dentate-rubro-olivary pathways (Guillain-Mollaret triangle), pontine tegmentum, inferior olivary nucleus, cerebellum, and medial vestibular nucleus.[1,31]

Saccadic intrusions and oscillations

Saccadic intrusions are spontaneous eye movements that intrude steady fixation. Saccadic intrusions are divided into those with an intersaccadic interval between the saccades (square-wave jerks, macro–square-wave jerks, and macrosaccadic oscillations) and those without such an interval (ocular flutter and opsoclonus) [Figure 4b].

Conclusion

Disorders of gaze are usually considered complex and their evaluation may cause apprehension to clinicians. Abnormal and involuntary eye movements can localize the lesion to various areas in the brain (brain stem, cerebellum, or cerebral hemispheres). A systematic clinical examination may provide deep insights on the patho-physiological mechanisms along with aiding in localizing the lesion accurately.

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Conflicts of interest

There are no conflicts of interest.

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