DIPLOPIA: SUPRANUCLEAR AND INTERNUCLEAR

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INTRODUCTION

Brainstem ocular motility: an overview

A significant amount of information is now known about brainstem neural networks and pathophysiologic mechanisms governing eye movements.[1, 2] Baseline understanding and systematic examination of the types of normal eye movements are essential to diagnosing supranuclear and internuclear eye movement problems. All normal eye movements have a shared goal of maintaining clear, single vision by placing and maintaining an object of visual interest on the fovea, the retinal region with the best visual acuity and highest density of photoreceptors. Several functional classes of eye movements with distinct anatomic substrates exist to meet this goal. Many supranuclear disorders affect a specific type, or functional class, of dynamic eye movement and may affect each eye symmetrically; thereby minimizing visual symptoms such as diplopia. Diplopia in supranuclear disorders occurs more often when the deficits have acute onset, such as with infarction. An exception to this generalization is a skew deviation, a common supranuclear eye movement problem with which vertical diplopia is most often the presenting manifestation, regardless of etiology or temporal onset.

Functional classes of eye movements

The functional classes of eye movements include saccades, smooth pursuit, vergence, optokinetic responses, and vestibular reflexes. The presence of distinct anatomic substrates for each type of eye movement refers primarily to the premotor or supranuclear command networks in the cerebral hemispheres, cerebellum, and brainstem. For each class of eye movements, these premotor or supranuclear networks converge upon a “final common pathway” that includes the ocular motoneuron, neuromuscular junction, and extraocular muscle.

Comprehensive coverage of supranuclear eye movement disorders is far beyond the scope of this talk and syllabus. The focus will be on two broad categories of brainstem supranuclear problems: skew deviation and supranuclear saccadic gaze palsies. The internuclear eye movement abnormality internuclear ophthalmoplegia will also be covered.

SUPRANUCLEAR AND INTERNUCLEAR OCULAR MOTILITY DISORDERS

The eye movement abnormalities discussed below may be caused by any lesion affecting the structure described. The eye movements themselves are exquisitely localizing, but their presence alone does not indicate the underlying etiology. When acute in onset, brainstem ischemia, hemorrhage, demyelination, or encephalitis are common causative pathologies. The abnormal eye movement may occur in isolation with a small lesion or may be accompanied by other neurologic signs, such as hemiparesis or ataxia. When in isolation, it is possible for the tiny localizing lesion to be radiographically silent on MRI.

I. SKEW DEVIATION

Skew deviation, a very common cause of vertical binocular diplopia, is an acquired vertical misalignment of the eyes due to a lesion in the supranuclear pathways connecting the vestibular apparatus to the vertical ocular motor cranial nerve nuclei.[3] Vertical diplopia is the most common patient complaint and examination discloses a vertical ocular misalignment. Exam typically also reveals a pathologic head tilt and inappropriate torsion of the eyes. This triad of findings comprises the ocular tilt reaction (OTR).

In normal vestibular function, head motion is detected by the vestibular apparatus (semicircular canals and the otolith organs – the saccule and utricle) and neural signals directing the eyes to move in a compensatory opposite direction are generated to allow gaze stabilization during head movement. Semicircular canals detect angular head acceleration, while the otolith organs detect linear acceleration. The OTR is a physiologic reaction mediated

by the otolith organs in response to head or body tilt from side-to-side. The reaction consists of vertical eye deviation, compensatory head tilt, and torsional eye movements. In healthy humans, this reaction is largely unnecessary and is generally suppressed. With lesions of the supranuclear vestibular pathways, it resurfaces.

Signals from the utricle on one side project to the ipsilateral vestibular nuclei and then decussate within the pons and ascend in the medial longitudinal fasciculus (MLF). A lesion along this pathway or in the cerebellar connections to this pathway results in a pathologic OTR and skew deviation. A lesion below the pontine decussation will result in a lower eye ipsilateral to the lesion. A lesion above the pontine decussation will result in a higher eye ipsilateral to the lesion.[4]

The range of eye movements is normal with skew deviation. The diagnosis lies in detection of the pattern of vertical ocular misalignment. Often, the misalignment (and the diplopia) is comitant – or the same size in all directions of gaze. However, skew deviations may also be incomitant. The head and superior poles of both eyes rotate toward the lower eye. Thus the higher eye is incyclotorted and the lower eye is excyclotorted. This is in distinct contrast to the excyclotorsion of the higher eye in a fourth nerve palsy. Fundoscopic examination allows assessment for ocular torsion via comparison of the relationship between the optic disc and macula (Fig. 1). Because bedside undilated ocular fundoscopic examination makes assessment of ocular torsion difficult, thereby precluding accurate topographical diagnosis, skew deviation should be considered in the differential diagnosis of any vertical misalignment with a full range of eye movements when the misalignment does not conform to the pattern expected for a fourth nerve palsy.

Figure 1. Ocular torsion component of the ocular tilt reaction in a patient with a skew deviation. In an eye with no ocular torsion, a straight line can be drawn between the optic disc and fovea. With torsion, this line is tilted up or down. In this patient with skew deviation and a right hypertropia, the right higher eye is incyclotorted (left photo) and the lower left eye is excyclotorted (right photo).

II. SUPRANUCLEAR SACCADIC GAZE PALSIES

Saccades and bedside recognition of supranuclear (premotor) lesions

Of the functional classes of eye movements, saccades, smooth pursuit, and vestibular reflexes are the most important for identification of supranuclear gaze palsies. The focus of this section is utilization of these to distinguish supranuclear (premotor) gaze palsies from other localizations causing ophthalmoplegia.

Saccades are rapid, conjugate eye movements with which we explore our visual world and shift our gaze to objects of visual interest. Saccades must be very quick (300-500 degrees/second) to prevent deterioration of vision during the movement.[5] A high degree of accuracy is required for the saccade to "land the eye on target". These features of saccades make them a complex task for the brain and, thereby, prone to error. Execution of a saccade requires a sudden, intense neural discharge provided by burst neurons in the brainstem to the cranial nerve nucleus and motoneuron (Fig. 2).[6] For horizontal saccades, the burst neurons are located in the pontine paramedian reticular formation (PPRF) in the caudal, dorsal pons – just rostral to the abducens nucleus. For vertical saccades, most of the burst neurons are located in the rostral interstitial medial longitudinal fasciculus (riMLF) in the midbrain rostral to the oculomotor nucleus. Some are located in the interstitial nucleus of Cajal (INC), just caudal to the riMLF.[7] Inhibition of burst neurons is required at all times other than when a saccade is occurring. This is provided by omnipause neurons located in the nucleus raphe interpositus (RIP) in the caudal pons.[8, 9] The neural connections and anatomic pathways governing smooth pursuit are less well understood than those governing saccades.

A clinical hallmark of a supranuclear gaze palsy is disproportionate involvement of saccades. Smooth pursuit may be affected, but usually to a lesser extent than saccades. Vestibular eye movements (Doll's eyes, vestibular ocular reflex = VOR) are typically spared (Fig. 3). This is especially true for disorders of vertical gaze due to midbrain lesions. In contrast to supranuclear disorders, nuclear and infranuclear (cranial nerve, neuromuscular junction, and extraocular muscle) processes affect saccades, smooth pursuit, and vestibular reflexes equally. The caveat to the above discussion is that, with acute catastrophic lesions (ischemia or hemorrhage), supranuclear eye movement lesions may affect all classes of eye movements – but the deficits still tend to affect saccades most dramatically.

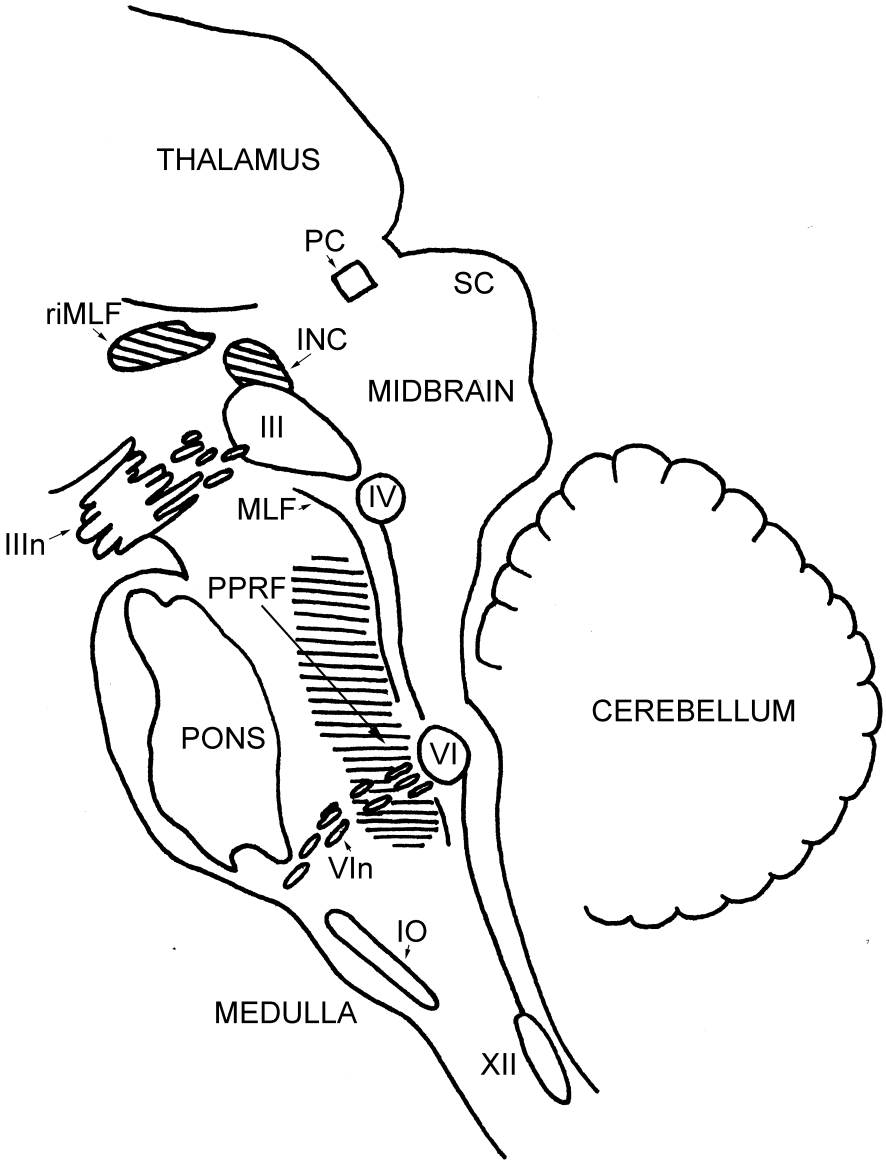

Figure 2. Drawing of a sagittal brainstem view showing the localization of ocular motor-related nuclei. Within the midbrain, premotor burst neurons for vertical saccades are located within the riMLF. The INC likely also contains vertical premotor burst neurons. The shaded region in the pons is the PPRF, containing premotor burst neurons for horizontal saccades, with an arrow showing the approximate location of these neurons in the caudal PPRF.

Abbreviations: PC = posterior commisure; riMLF = rostral interstitial medial longitudinal fasciculus; INC = interstitial nucleus of Cajal; SC = superior colliculus; IIIn = oculomotor nerve fascicle; III = oculomotor nucleus; IV = trochlear nucleus; MLF = medial longitudinal fasciculus; PPRF= paramedian pontine reticular formation; VI = abducens nucleus; VIn = abducens nerve rootlets; IO = inferior olive; XII = hypoglossal nerve. Drawing based on Buttner U, Buttner-Ennever JA. Prog Brain Res 2005;151:1-42.

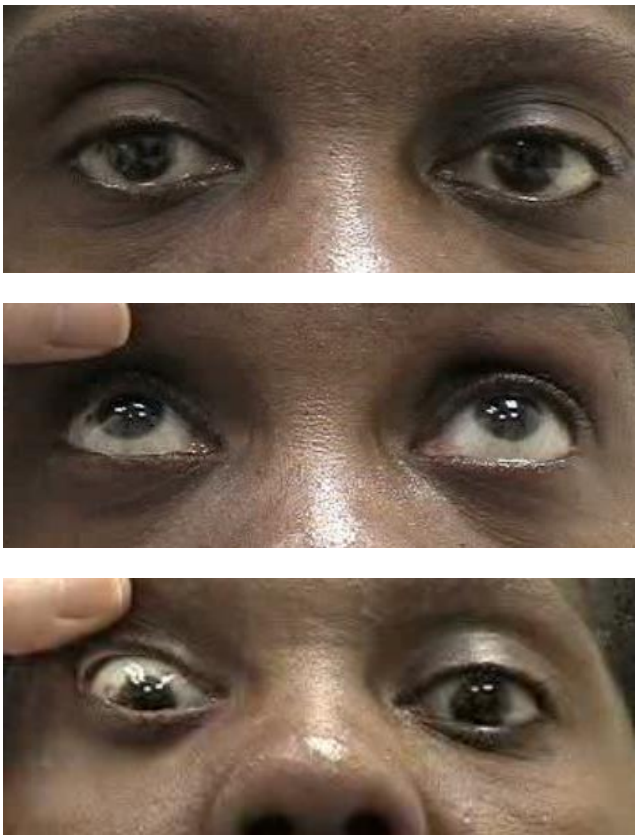

Figure 3. Supranuclear downgaze palsy. Top photo – During smooth pursuit testing, downgaze below midline cannot be achieved. Middle photo – During saccade testing, the eyes are not able to return to midline after an upward saccade. Bottom photo – With passive vertical movement of the head eliciting compensatory vestibular responses, the downgaze deficit is overcome.

Midbrain gaze palsies (dominant role = control of vertical eye movements)

Rostral interstitial medial longitudinal fasciculus and interstitial nucleus of Cajal

The rostral interstitial medial longitudinal fasciculus (riMLF) contains most of the burst neurons for vertical saccades. Lesions result in slowed or absent vertical saccades, especially when bilateral. Acute onset vertical gaze palsy is most often due to midbrain infarction. The riMLF is supplied by the thalamic-subthalamic paramedian artery, which originates from the posterior cerebral artery (PCA) at the bifurcation of the basilar artery and the PCAs. A single thalamic-subthalamic paramedian (the artery of Percheron[10]) artery supplies both riMLF in roughly 20% of patients[11], making bilateral riMLF lesions possible from a single vessel infarct.[12] Each riMLF projects bilaterally to the motoneurons for eye elevation, but only unilaterally to the motoneurons for eye depression.[1, 13, 14] As a result, riMLF lesions have a more profound effect on downgaze (Fig. 3). Bilateral lesions tend to cause either loss of downward saccades or of all vertical saccades. The effects of unilateral lesions are less well understood.[1] The riMLF controls torsional saccades also, although I do not discuss these further – as they are difficult to test at the bedside. In theory, a unilateral riMLF lesion should have effects only on torsional saccades and, perhaps, mild slowing of downward saccades. However, published case reports describe more extensive vertical gaze deficits.[15] In some of these cases, it is likely that other structures – such as INC which also contains vertical burst neurons[7] – may be involved simultaneously. Bilateral INC lesions have the potential to impair all vertical eye movements.[16] Deficits of both the riMLF and INC tend to affect the eyes conjugately, as each riMLF sends signals to vertical eye muscles for each eye. Unilateral (or monocular) vertical gaze palsies are

more difficult to understand, but are occasionally seen.[17] A specific condition – the double-elevator palsy – results in impairment of both elevator muscles (superior rectus and inferior oblique) in one eye. It is unclear if this is due to a lesion in supranuclear structures or in the oculomotor nucleus or fascicle. [18, 19]

Dorsal midbrain syndrome (Parinaud syndrome)

The dorsal midbrain syndrome is a constellation of signs including a supranuclear upgaze palsy, convergence-retraction nystagmus (often elicited by attempts at upgaze), Collier's sign (lid retraction), and pupillary-light near dissociation. Stroke, pineal gland tumors or hemorrhage, and hydrocephalus are common etiologies. The supranuclear gaze palsy is likely due to involvement of projecting fibers from the INC.

Pontine gaze palsies (dominant role = control of horizontal eye movements)

Paramedian pontine reticular formation

Lesions of the paramedian pontine reticular formation (PPRF) impair the supranuclear burst neurons for horizontal gaze. This often results in a complete ipsilateral horizontal gaze palsy for all functional classes of eye movements, but – as is more typical for most supranuclear problems – a selective impairment (absence or slowing) of horizontal saccades may occur, with preservation of smooth pursuit and vestibular eye movements.[20, 21] An example of lateralization with a PPRF lesion is impaired conjugate gaze to the right (right eye abduction and left eye adduction) with a right PPRF lesion (Fig. 4). Acutely, gaze may even be deviated contralaterally – to the left in the case example. Bilateral PPRF lesions result in absence of horizontal gaze (or selective loss of saccades) and slowed vertical saccades.[22-24]

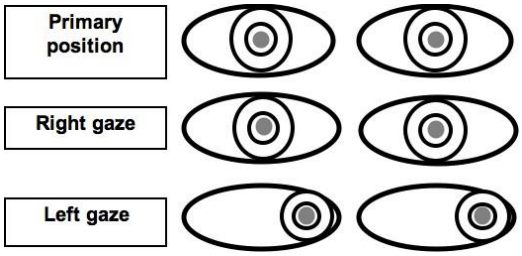

Figure 4. Right horizontal gaze palsy from a right paramedian pontine reticular formation (PPRF) lesion.

Unilateral PPRF and MLF (one-and-a half-syndrome)

When a lesion involves both the PPRF and the MLF (the already decussated MLF with fibers that originated in the contralateral abducens nucleus) on one side of the pons, the one-and-a-half syndrome results.[25-27] The PPRF lesion causes an ipsilateral horizontal gaze palsy and the MLF lesion causes an ipsilateral internuclear ophthalmoplegia (INO) with impaired ipsilateral adduction (see next section on INO). The only horizontal eye movement that remains intact is abduction of the eye contralateral to the lesion; thus "one and a half" of the horizontal eye movements are impaired. An exotropia (outward deviation of the eyes) is typically present.[28] An example of lateralization with the one-and-a-half syndrome is the complete absence of horizontal eye movements in the right eye (impaired abduction from the PPRF lesion, impaired adduction from the INO) and impaired adduction of the left eye (from the PPRF lesion) with a right combination PPRF and MLF lesion (Figs. 5 and 6).

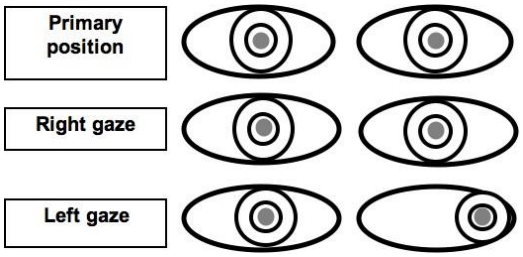

Figure 5. Right one-and-a-half syndrome from a lesion involving the right medial longitudinal fasciculus (causing the right adduction deficit) and either the right paramedian pontine reticular formation (PPRF) or right abducens nucleus (causing a right horizontal gaze palsy).

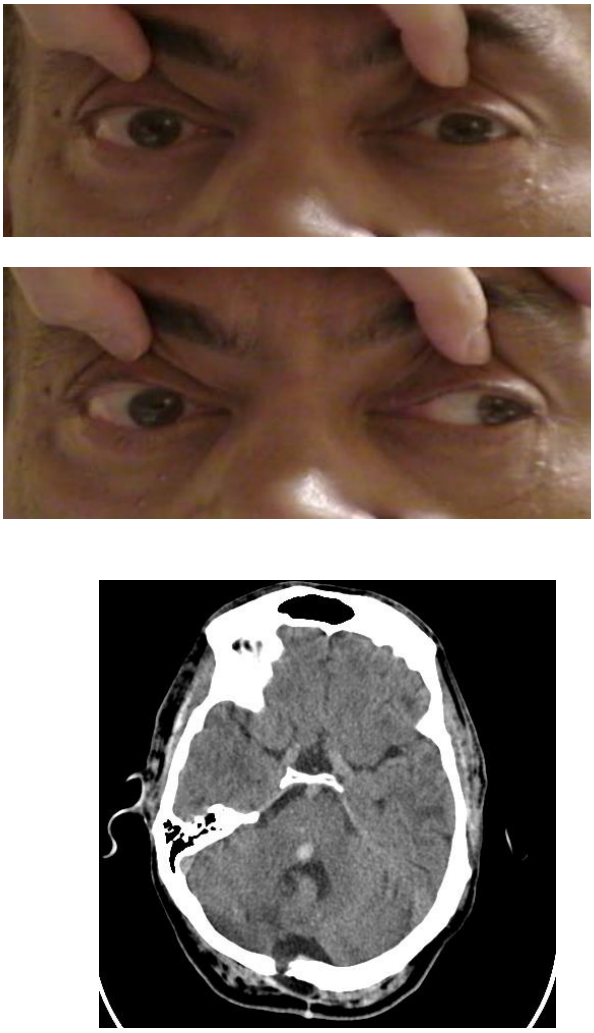

Figure 6. A patient with a right one-and-a-half syndrome from a right dorsal pontine hemorrhage (seen on MRI in bottom photo). Attempted right gaze (top photo) discloses a right horizontal gaze palsy. Attempted left gaze (middle photo) reveals impaired adduction of the right eye and intact abduction of the left eye.

III. INTERNUCLEAR OPHTHALMOPLEGIA

Medial longitudinal fasciculus

Internuclear ophthalmoplegia (INO) results from a lesion of the medial longitudinal fasciculus (MLF) either in the midbrain or pons. The MLF carries signals from the abducens nucleus to the contralateral medial rectus subnucleus of the oculomotor nucleus, thereby allowing conjugate horizontal eye movements with simultaneous contraction of the ipsilateral lateral rectus and contralateral medial rectus muscles. Lesions of the MLF virtually always occur after the immediate decussation of the fibers originating in the abducens nucleus, so the predominant clinical feature of impaired adduction is found ipsilateral to the MLF lesion. The classic signs of a unilateral INO are impaired adduction of the eye ipsilateral to the MLF lesion and dissociated nystagmus of the contralateral abducting eye (Fig. 7). Testing of horizontal saccades generally enhances the prominence of these deficits. With a subtle INO, eye movements may appear full with smooth pursuit testing and subtle slowing of the adducting eye compared to the abducting eye during horizontal saccade testing (adduction lag) may be the only clue to the presence of an INO.[29] Adduction of the eye ipsilateral to the MLF is often intact with convergence eye movements.[30] A skew deviation (vertical and torsional misalignment of the eyes secondary to asymmetric supranuclear vestibular signals) with the higher eye ipsilateral to the lesion may be present in combination with INO, since ascending vestibular signals also travel in the MLF.[31]

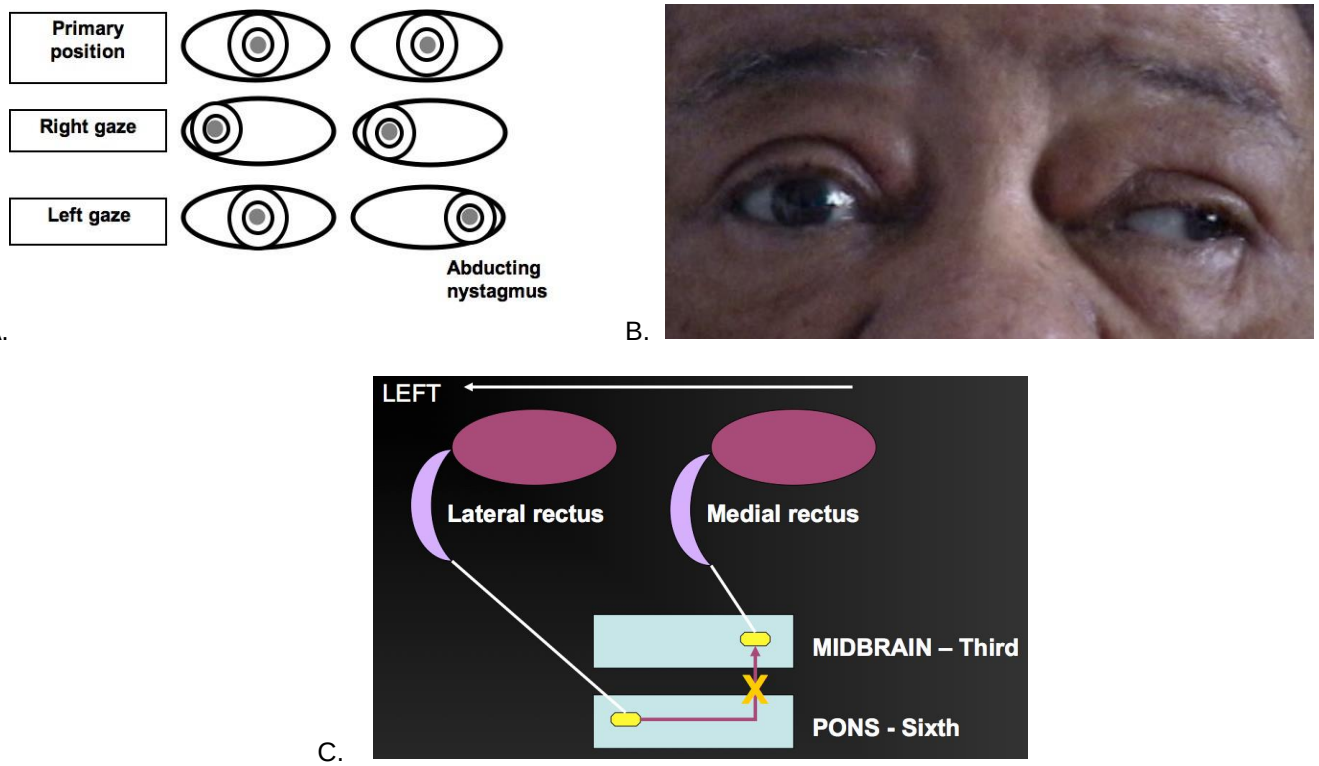

Figure 7. Right internuclear ophthalmoplegia (INO) from a right medial longitudinal fasciculus (MLF) lesion. A. Full right gaze. Limited adduction on left gaze with abducting nystagmus in the left eye upon left gaze. B. Impaired adduction of the right eye in a 67 year old woman with a right INO from a midbrain microvascular infarction. C. Schematic of the lesion (X) in the ascending portion of the MLF that originated from the left abducens nucleus.

TABLE: SUPRANUCLEAR AND INTERNUCLEAR LESIONS AND ASSOCIATED OCULAR MOTOR DEFICITS

LOCATION	EYE MOVEMENT ABNORMALITY
SKEW DEVIATION	
Brainstem ascending vestibular pathways	Ocular tilt reaction: skew deviation, head and eyes roll toward lower eye
SUPRANUCLEAR GAZE PALSIES	
riMLF	Supranuclear vertical gaze palsies Unilateral lesion - abnormal torsional saccades, minimal slowing of downward saccades Bilateral lesions - loss of downward eye movements or loss of all vertical saccades
Dorsal midbrain	Supranuclear upgaze palsy; convergence-retraction nystagmus; Collier's sign (lid retraction); and pupillary-light near dissociation
PPRF	Supranuclear horizontal gaze palsy – ipsilateral with unilateral lesion, complete with bilateral lesion
Unilateral PPRF and MLF	One-and-a-half syndrome – ipsilateral horizontal gaze palsy and impaired adduction
INTERNUCLEAR	
Medial longitudinal fasciculus	Ipsilateral impairment of adduction (restriction and adduction lag); contralateral abducting nystagmus

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