Neural Control and Clinical Disorders of Supranuclear Eye Movements

Extensive knowledge exists about anatomic and pathophysiologic mechanisms governing eye movements. The shared goal of all eye movements is stable, clear vision via placement of an object of visual interest on the fovea, the retinal region with the best visual acuity. Several types of eye movements exist to achieve this shared goal, including smooth pursuit, vergence, vestibulo-ocular reflexes, optokinetic nystagmus, and saccades. Separate anatomic supranuclear neural networks exist for each eye movement type and converge upon a ‘final common pathway’ that includes the motoneuron originating in cranial nerve nuclei, the neuromuscular junction, and the extraocular muscle. Systematic exam of each type of eye movement, including range and dynamic aspects of motion, is essential for accurate localisation of supranuclear eye movement abnormalities.

Eye movement types and brainstem anatomy

Smooth pursuit maintains the image of a small, slowly moving target on the fovea. Vernon has shown that horizontal saccades are a conjugate eye movement by which a single foveal image is maintained with gaze shifts from near to far (vergence) or from far to near (convergence). Vestibulo-ocular reflexes generate compensatory eye movements during brief head movements that are essential for seeing clearly while walking or when the head is in motion. Optokinetic responses (OKN) are reflexive and generated by movement of a large visual scene and during sustained head rotation. OKN consists of slow eye movements in the direction of a moving stimulus, followed by quick movements to reset the eyes in the opposite direction.

Saccades are conjugate, extremely rapid eye movements with which we shift gaze and explore the visual world. Several factors, including sufficient force to overcome the elastic inertia of the extraocular orbital tissues, high saccadic velocity; and the need for a high degree of accuracy to place the small fovea on target, make saccades a demanding task for the brain. These demands result in the requirement of a high-frequency neural discharge from brainstem excitatory burst neurons (EBN) to stimulate the motoneuron to generate a saccade of a specific size and in a specific direction. EBN for horizontal saccades are located in the paramedian pontine reticular formation (PPRF) in the pons rostral to the abducens nucleus and, for vertical and torsional saccades, in the rostral interstitial medial longitudinal fasciculus (rMLF) rostral to the oculomotor nucleus (Figure 1). A few EBN for vertical saccades lie in the interstitial nucleus of Cajal (INC) (Figure 1). For horizontal saccades, EBN project to ipsilateral motoneurons to generate an ipsilateral saccade (for a rightward saccade, the premotor signal originates in the right PPRF EBN and projects to the right abducens nucleus). For vertical saccades, single EBN project to yoked muscle pairs (for example, superior rectus and inferior oblique for upward saccades and inferior rectus and superior oblique for downward saccades). Vertical EBN project to motoneurons for the elevator muscles bilaterally, but unilaterally to depressor muscles.
Inhibition of EBN, required at all times other than during a saccade, is mediated by tonically discharging omnipause neurons (OPN) in the nucleus raphe interpositus (RIP) in the PPRF (Figure 1). OPN firing ceases just before EBN firing and resumes at saccade end, however it is unclear if the OPN or the cerebellar caudal fastigial nucleus terminates the saccade.

Clinical supranuclear and internuclear disorders

Supranuclear eye movement abnormalities may result from dysfunction of cerebral, cerebellar, and brainstem connections to the ocular motor nuclei. The focus here is on brainstem supranuclear disorders (Table). Clinical hallmarks of a brainstem supranuclear gaze palsy include disproportionate impairment in the range or velocity of saccades and impairment of OKN, with VOR retention (Figure 2). Smooth pursuit may be affected, but usually to a lesser extent than saccades. If limitation in the range of vertical eye movement is present, vertical VOR should overcome the limitation, as the patient fixates on a target while the examiner moves the head vertically (Figure 2). Because vertical EBN projecting to motoneurons for the elevator muscles project bilaterally and to motoneurons for depressor muscles unilaterally, unilateral rMLF lesions may preferentially impair downward saccades. Bilateral rMLF lesions may abolish all vertical saccades. Individual case reports in humans do not always match these anatomical expectations, but it is probable that the lesions extend beyond the rMLF to other structures involved in vertical eye movement control.

An acute onset vertical gaze palsy is most often due to midbrain infarction. If in isolation, the infarct is typically due to microvascular ischaemia in the territory of the thalamic-subthalamic paramedian artery, which originates from the posterior cerebral artery. Bilateral rMLF lesions may occur from a single vessel occlusion because a single thalamic-subthalamocorticidal nervous system (a single thalamic vessel) supplies both rMLF in 20% of patients. An acute onset vertical supranuclear gaze palsy in combination with other neurological symptoms such as somnolence, delirium, homonymous hemianopia, and cortical blindness may represent a ‘top of the basilar’ stroke with rMLF thalamic, occipital lobe, and temporal lobe involvement. An acute onset supranuclear upgaze palsy in combination with eyelid retraction (Collier’s sign), convergence-retraction nystagmus, and pupillary light-near dissociation is the dorsal midbrain syndrome (also called Parinaud’s syndrome). The rMLF is not the location of the lesion, but rather the upgaze paresis is

Many vertical brainstem supranuclear gaze palsies affect the range of each eye movement symmetrically. As a result, visual symptoms may be minimised by the symmetry of the process. Supranuclear gaze palsies may be incidentally noted and diagnostically helpful in a visually asymptomatic patient with multifocal neurological disease. On the other hand, vague visual complaints such as visual blurring may occur, but are non-localising. Binocular diplopia will occur only when the two eyes are affected differently, causing an ocular misalignment. Diplopia may also be more common when the deficits have an acute catastrophic onset, such as with brainstem stroke.

The eye movement abnormalities discussed may be caused by any lesion affecting the structure specified. The eye movements themselves are exquisitely localising, but not indicative of underlying etiology. In the acute setting, brainstem ischaemia, hemorrhage, and demyelination are the most common causes. In the chronic setting, neurodegenerative and metabolic disease are most common. The eye movement disorders discussed may occur in isolation or in combination with other neurological findings, such as hemiparesis, ataxia, or extrapyramidal signs. When in isolation, it is possible for the lesion to be radiographically occult on MRI.

Vertical gaze palsies

Lesions of EBN in the rMLF result in slowing of vertical saccades and/or limitation in the range of vertical saccades. Vertical OKN may be absent or only slow phases generated, with no resetting fast phases. Smooth pursuit may be affected, but usually to a lesser extent than saccades. If limitation in the range of vertical eye movement is present, vertical VOR should overcome the limitation, as the patient fixates on a target while the examiner moves the head vertically (Figure 2). Because vertical EBN projecting to motoneurons for the elevator muscles project bilaterally and to motoneurons for depressor muscles unilaterally, unilateral rMLF lesions may preferentially impair downward saccades. Bilateral rMLF lesions may abolish all vertical saccades. Individual case reports in humans do not always match these anatomical expectations, but it is probable that the lesions extend beyond the rMLF to other structures involved in vertical eye movement control.

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**Table.** Localisation of supranuclear, nuclear, and internuclear saccadic gaze disorders.

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<th>LESION / SYNDROME</th>
<th>GAZE DISORDER</th>
<th>AETIOLOGIC EXAMPLES</th>
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| rMLF* – midbrain  | Supranuclear vertical gaze palsy | Acute – stroke  
Chronic – progressive supranuclear palsy |
| Dorsal midbrain syndrome | Supranuclear upgaze paresis, convergence-retraction nystagmus | Stroke, hydrocephalus, pineal pathology |
| PPRF** | If unilateral – ipsilateral supranuclear horizontal gaze palsy  
If bilateral – bilateral supranuclear horizontal gaze palsy | Acute – stroke, demyelination, Wernicke’s encephalopathy  
Chronic – Spinocerebellar ataxia type 2 |
| Abdüccens nucleus | Ipsilateral horizontal gaze palsy with saccades, pursuit, vestibulo-ocular reflexes affected | Stroke, Wernicke’s encephalopathy |
| MLF*** | Internuclear ophthalomplegia | Demyelination, stroke |
| PPRF or abducens nucleus and MLF | One-and-a-half syndrome | Stroke |

* rMLF – rostral interstitial medial longitudinal fasciculus  
** PPRF – paramedian pontine reticular formation  
***MLF – medial longitudinal fasciculus
due to projecting fibres from the vertical supranuclear control centres to the rostral dorsal midbrain. It is most commonly due to infarct, hydrocephalus, or pineal pathology; given the proximity of the pineal gland to the rostral dorsal midbrain. Werner's encephalopathy (WE), due to thiamine deficiency, consists of the classic triad of ophthalmoplegia, progressive ataxia, and dementia. Characteristic MRI findings in acute WE are T2 hyperintensity in the periaqueductal gray and dienochephalic periaqueductal regions. WE is more likely to cause prominent horizontal gaze paresis than vertical gaze paresis.

The most common chronic brainstem supranuclear vertical gaze palsy is the neurodegenerative condition progressive supranuclear palsy: The gaze palsy may be one of elevation, depression, or both. Accompanying features are parkinsonism with excessive early falls, a frontal lobe syndrome, axial rigidity, and dysphagia. A characteristic additional eye movement finding is excessive square wave jerks (small involuntary saccades that intrude upon fixation, taking the eye quickly away from centre followed after a brief interval by a small saccade that returns the eye to central fixation). Whipple's disease, due to Tropheryma whippeli infection, may cause a syndrome that mimics PSP with a vertical supranuclear gaze palsy and parkinsonism. The pathognomonic eye movement abnormality in Whipple's disease is ocularnystagmatory myorhythmia (OMM), although it may not always be present. OMM consists of acquired pendular nystagmus (e.g. there are no nystagm us quick phases, only oscillating slow phases) with a convergent-divergent trajectory with accompanying rhythmic movements of masticatory structures. The metabolic disorder Niemann-Pick Type C characteristically causes vertical brainstem supranuclear gaze palsy in addition to dystonia, dementia, seizures, ataxia, and hepatosplenomegaly.

**Horizontal gaze palsy**

Lesions of EBN in the PPRF result in slowing of horizontal saccades and/or limitation in the range of horizontal saccades in the direction ipsilateral to the lesion. For example, a right PPRF lesion affecting EBN will result in slowing and/or range limitation of rightward saccades. Horizontal OKN may be absent or only the slow phases generated, with no resetting fast phases. Smooth pursuit may be affected, but usually to a lesser extent than saccades. If limitation in the range of horizontal eye movement is present, passive horizontal VOR should overcome the limitation as the patient fixates on a target while the examiner moves the head horizontally: Bilateral PPRF lesions affecting bilateral EBN will result in a complete absence of all horizontal saccades and slowing of vertical saccades. Although not supranuclear gaze disorders, a discussion of supranuclear EBN PPRF is not complete without mention of abducens nuclear lesions and internuclear ophthalmoplegia (INO). Paired abducens nuclei lie in the floor of the fourth ventricle in the dorsal pons. Each nucleus is comprised of two intermixed neuronal populations: abducens motoneurons that project to the ipsilateral lateral rectus via the abducens nerve and interneurons that decussate in the pons and project to the contralateral medial rectus oculomotor subnucleus via the medial longitudinal fasciculus (MLF) (Figure 1). An abducens nuclear lesion will result in an ipsilateral horizontal gaze palsy; however saccades, smooth pursuit, and vestibulo-ocular reflexes will all be affected with the nuclear lesion. Abducens nuclear lesions are often accompanied by ipsilateral facial weakness, since the facial nerve fascicle wraps around the abducens nucleus. A lesion of the MLF in the pons or in the midbrain will result in an INO. The lesion most often occurs in the fibres projecting to the medial rectus subnucleus after their pontine decussation. The hallmark features of INO are impaired adduction in the eye ipsilateral to the MLF lesion and abducting nystagmus in the contralateral eye. When an INO occurs in combination with a PPRF EBN or abducens nuclear lesion, the one-and-a-half syndrome results. As an example, a right PPRF EBN or abducens nuclear lesion also affecting the MLF that originated on the left and decussated already will cause a right horizontal gaze palsy (limited abduction of the right eye and adduction of the left eye) and a right INO (limited adduction of the right eye with abducting nystagmus of the left eye) (Figure 3).

An acute onset horizontal gaze palsy or one-and-a-half syndrome is most often due to pontine ischaemic or hemorrhagic stroke, although haemorrhage into a vascular lesion or demyelination may also be causes. In addition to the impairment of saccades in the ipsilateral direction, gaze may be acutely deviated contralaterally past the midline. INO is most often demyelinating, but may occur acutely due to stroke. Horizontal gaze deficits in combination with nystagmus (upbeating or gaze-evoked most often) are the hallmark eye findings of Werner's encephalopathy. The finding of slow horizontal saccades in chronic progressive ataxia may suggest spinocerebellar ataxia type 2.

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**REFERENCES**