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REVIEW ARTICLE

Internuclear and supranuclear disorders of eye movements: clinical features and causes

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Eye movements bring visual stimuli to the fovea and also maintain foveal fixation on a moving target and during head movements. These movements are performed by the ocular motor system that consists of ocular motor nerves and nuclei in the brainstem originating in the cerebral cortex, cerebellum, vestibular structures, and the extraocular muscles. The ocular motor system is divided according to anatomic location into infranuclear, nuclear, internuclear, and supranuclear components. It is important to distinguish supranuclear and internuclear from nuclear and infranuclear disturbances affecting cranial nerves III, IV, and VI, because the disturbances are of highly varied causes and present different clinical pictures. Internuclear ophthalmoplegia is due to a lesion of the medial longitudinal fasciculus, caused by multiple sclerosis in younger patients, particularly when the ophthalmoplegia is bilateral, and usually of vascular origin in the elderly. Eye movement abnormalities of supranuclear origin are characterized by gaze palsies, tonic gaze deviation, saccadic and smooth pursuit disorders, vergence abnormalities, nystagmus, and ocular oscillations. Supranuclear disorders result from lesions above the level of the ocular motor nerve nuclei. If oculocephalic maneuvers move the eyes appropriately, the lesion causing the gaze palsy is supranuclear. Supranuclear disorders account for almost 10% of all patients with disorders of eye movements.

Introduction

As man depends on his visual sense more than on his other senses, a sophisticated ocular motor system exists to collect visual input that ultimately results in visual perception. Eye movements bring visual stimuli to the fovea and also maintain foveal fixation on a moving object and during head movements [1]. Eye movements are the result of activity in discrete systems. These movements are controlled by ocular motor nerves and nuclei in the brainstem originating in the cerebral cortex, cerebellum, vestibular structures, and the extraocular muscles [2]. The ocular motor system is divided according to anatomic location into infranuclear, nuclear, internuclear, and supranuclear components. The internuclear component refers to connections between the ocular motor nuclei such as the oculomotor, trochlear, abducens, and vestibular nuclei; the medial longitudinal fasciculus (MLF) is the name most often given to these connections. The supranuclear component refers to cortical structures and pathways that descend into the brainstem and are proximal to the ocular motor nuclei [1,3]. In this review, internuclear ophthalmoplegia, supranuclear control of eye movements, and eye movement abnormalities of supranuclear origin describing the clinical features and the pathophysiology of the diseases are presented.

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Methods

The articles and abstracts for this review were found by searching in Medline/Pubmed. A Medline literature search was conducted with the terms 'internuclear ophthalmoplegia', 'supranuclear ophthalmoplegia', 'eye movements', 'clinical features', and 'causes'. Additional articles were obtained from the reference lists of retrieved articles.

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) is caused by damage to the internuclear neurons that exit from the abducens nucleus, cross to the other side, arise in the MLF, and terminate in the subnucleus of the medial rectus in the nuclear complex of the third cranial nerve (Fig. 1). The clinical picture of INO consists of the

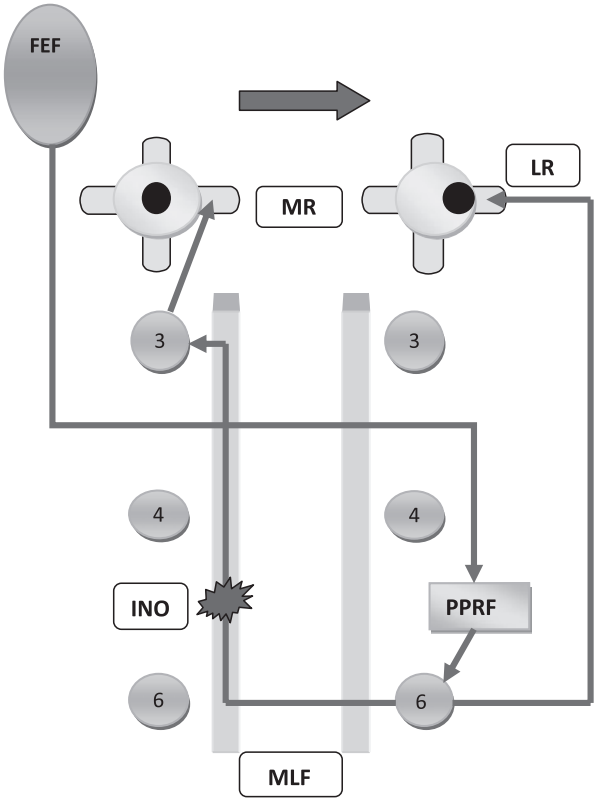

Figure 1 Volitional horizontal saccadic pathway with a lesion in the right medial longitudinal fasciculus (MLF) that results in an internuclear ophthalmoplegia (INO). FEF, frontal eye field; PPRF, paramedian pontine reticular formation; MR, medial rectus; LR, lateral rectus.

slowing, limitation or inability to adduct one eye, combined with nystagmus of the other abducting eye. The lesion is on the same side as the eye with the adduction weakness. The adduction limitation in INO is the same for pursuit and saccades, and can not be enhanced by caloric stimulation. Adduction with convergence movements is intact in the majority of patients. This finding can help distinguish an INO from partial third nerve palsy. In addition to accommodative convergence, fusional vergence can be retained, so that the patient shows no manifest strabismus. Often, INO is accompanied by gaze-evoked dissociated nystagmus on abduction of the contralateral eye. The basis for this is that structures responsible for the maintenance of eccentric gaze positions are located near the MLF [3,4]. Another hypothesis to explain abduction nystagmus implicates an adaptive response to overcome the weakness of the contralateral medial rectus (Hering's law) [5]. As the MLF contains pathways involved in the regulation of vertical eye movements, patients with INO often exhibit abnormalities with vertical eye movements, including diminished vertical gaze holding, abnormal optokinetic and pursuit responses, decreased vertical vestibulo-ocular reflex (VOR) gain, vertical gaze-evoked nystagmus, convergence-retraction nystagmus, decreased vertical smooth pursuit, and skew deviation [1,2]. In vertical skew deviation due to disruption of the otolithic-ocular connections; the higher eye is usually on the side of the lesion. Unilateral INO is associated with ocular tilt reaction characterized by ocular torsion and head tilt as a specific form of skew deviation in pontomesencephalic lesions [6]. Bilateral INO is usually accompanied by vertical gaze deviation nystagmus. Not all patients with INO complain of vertical and horizontal diplopia and oscillopsia [5,7,8].

Cogan separated INO into two groups based on involvement of adduction with the near reflex (pupillary constriction with a near vision effort, with ocular convergence, or with accommodation). Because the near reflex pathways do not go below the oculomotor complex, if convergence is normal, the MLF lesion is below the oculomotor nuclei; if convergence is not normal, the lesion is in the MLF at the level of the oculomotor nuclei. Cogan called these *posterior* and *anterior* INO, respectively [1,8,9].

The INO of multiple sclerosis is frequently bilateral and is found primarily in younger patients. A particularly frequent pattern is the subacute onset of INO in a patient with multiple sclerosis. The paralysis begins more or less abruptly, and subsequently improves during a course lasting weeks or months. Unilateral INO occurs more frequently in the elderly or in patients with vascular disorder. The mechanism is an infarction in the distribution of a small paramedian artery that supplies the region containing the MLF. Vessels in this region tend to respect the sagittal plane, supplying areas that do not cross the midline. Such lesions are very small and difficult to detect on MRI scanning. Rarely, bilateral INO may result from occlusion of a unilateral pontine branch artery [10]. INO can be persuasively mimicked by ocular myasthenia. If the adduction deficit is variable, an edrophonium test can reveal a myasthenic cause [11]. Table 1 lists common causes of INO.

Table 1 Common causes of internuclear ophthalmoplegia

Multiple sclerosis (commonly bilateral)
Brainstem vascular disorders (commonly unilateral)
Brainstem and fourth ventricular tumors, remote effect
Arnold-Chiari malformation
Brainstem encephalitis, Whipple disease, syphilis
Hepatic and Wernicke encephalopathy, Fabry disease
Drug intoxications (phenothiazines, tricyclic antidepressants, beta-adrenergic blockers, lithium, barbiturates, or D-penicillamine) and toxins (toluene)
Head trauma
Pseudo-internuclear ophthalmoplegia (myasthenia gravis or Fisher syndrome)

Internuclear ophthalmoplegia can be seen in clinical practice as isolated unilateral, bilateral, one-and-a-half syndrome, wall-eyed bilateral internuclear ophthalmoplegia (WEBINO), and 'INO and trochlear syndrome'. Isolated unilateral INO usually can be a unique and the sole manifestation of ischaemic stroke syndrome caused by small dorsal brainstem infarction, and generally has a good prognosis. Bilateral INO is usually due to multiple sclerosis [12–15].

One-and-a-half syndrome is present when the horizontal movement of one eye has been completely or partially lost, and it can neither adduct nor abduct (the 'one'), whilst the fellow eye has lost its adduction but retains normal abduction movements (the 'half'). Damage to the PPRF and/or the abducens nucleus causes paralysis of ipsilateral horizontal conjugate gaze. Simultaneous damage to the MLF produces INO characterized by paralysis of adduction of the ipsilateral eye, whilst the capacity for abduction of the contralateral eye is retained. Convergence is generally spared as oculomotor nerve is spared bilaterally. Some patients with one-and-a-half syndrome also have an associated facial nerve palsy, hemiparesis, and unilateral hemihypoanesthesia [9]. One-and-a-half syndrome is most often caused by multiple sclerosis, brainstem stroke, brainstem tumors, and arteriovenous malformations affecting the pontine tegmentum [7,16–18]. Ocular myasthenia can also mimic one-and-a-half syndrome [11].

Wall-eyed bilateral internuclear ophthalmoplegia is a rarely reported syndrome characterized by bilateral exotropia (wall-eyed) in primary position and bilateral INO. The cause of exotropia is uncertain. Convergence is impaired. There is dispute about whether WEBINO is caused by a pontine or midbrain lesion, and whether the medial rectus subnuclei are implicated. The most common causes of WEBINO are multiple sclerosis, vascular accidents, myasthenia gravis, post-infectious causes, chronic inflammatory demyelinating polyneuropathy, and rarely, progressive supranuclear palsy [19–21].

A highly rare syndrome characterized by INO and contralateral hypertropia secondary to a trochlear nerve palsy involves a unilateral MLF lesion at the caudal midbrain with extension into the trochlear nucleus on the same side. Because the trochlear nerve exits and decussates to innervate the opposite side superior oblique muscle, hypertropia is on the opposite side of the lesion. The concept of an INO combined with contralateral trochlear palsy due to mesencephalic lesion is illustrated with Fig. 2. However, in the case of INO; the higher eye is usually on the side of the lesion [4,22,23].

In a study of 65 patients from Mexico, INO was unilateral in 36 patients (55.4%) and bilateral in 22 patients (33.8%); one-and-a-half syndrome occurred in seven patients (10.8%). The most common causes were vascular in 24 patients (36.9%), multiple sclerosis in 21 patients (32.3%), and infectious diseases in nine patients (13.8%); the remaining 11 patients (17.0%) had other causes. Resolution of INO was seen in almost half of the patients during the first 9 months [24]. A recent study by Keane [25] presented a series of 410 patients with INO. The cause of INO was infarction in 157 patients (38%), multiple sclerosis in 139 (34%), and unusual causes in 114 (28%) in this study. Unusual causes included trauma (5%), tentorial herniation (5%), infection (4%), tumor (4%), iatrogenic injury (3%), hemorrhage (3%), vasculitis (2%), and miscellaneous (2%). Internuclear ophthalmoplegia was unilateral in 136 of the infarct cases (87%), 38 of those with multiple sclerosis (27%), and 48 of the unusual cases (42%) [25].

Supranuclear control of eye movements

In Ewald Hering's *Theory of Binocular Vision* published 140 years ago, he said: 'One and the same impulse of will drives both eyes simultaneously as we can direct a pair of horses with single reins.' He meant that the brain

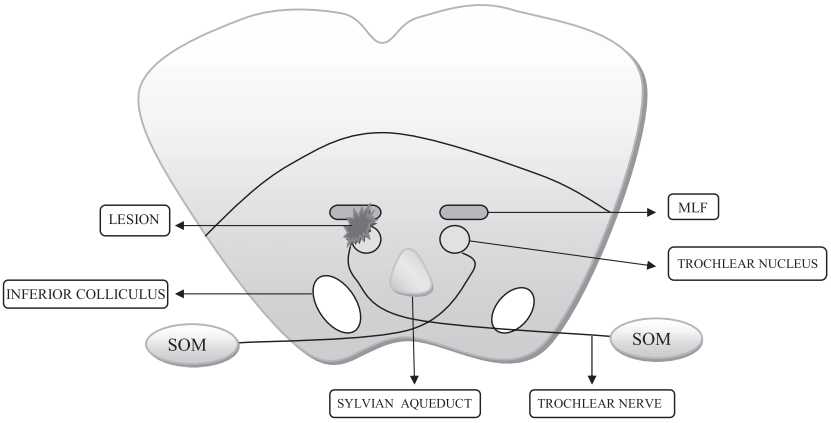

Figure 2 Anatomic drawing of the brainstem with axial cross section at the level of the trochlear nucleus and the medial longitudinal fasciculus. SOM, superior oblique muscle; MLF, medial longitudinal fasciculus. Note the close relationship of the MLF and the trochlear nucleus.

Table 2 The eye movement systems and their functions

Gaze shift	
Saccades	To bring images of objects of interest onto the fovea
Smooth pursuit	To keep the image of a moving target on the fovea
Vergence	To move the eyes in opposite directions
Gaze maintenance	
Optokinetic	To hold images on the retina during sustained head rotation
Vestibular	To hold images on the retina during brief head rotations
Fixation	To hold eyes conjugately in a particular position

controls the eyes as a single organ [12]. The eyes move to keep images on the foveas precisely as possible. There are the different types of eye movements to accomplish this task. If the eyes move conjugately, this is called *version movement*. Versional eye movements are divided into fast eye movements called *saccades,* slow eye movements called *smooth pursuits,* vestibulo-ocular, and optokinetic movements. Saccades are primarily directed toward stationary targets whereas smooth pursuit tracks moving targets. Compensatory movements of the head and body, or altered positions of the eyes to follow rotating targets, depend on the vestibular (*vestibulo-ocular reflex*) and optokinetic systems (*optokinetic reflex*). If the eyes move in opposite directions, this is called *vergence movement*, and it includes movements such as *divergence* and *convergence* [1,3,26]. Table 2 summarizes the six eye movement systems and their functions.

Saccadic eye movements

Saccades bring images of the objects of interest onto the fovea. They are fast eye movements (up to 1000 degrees per second) and their duration is very short (30–80 ms). Saccades can be voluntary, spontaneous, or reflexive in response to stimuli. The fast phases of vestibular and optokinetic nystagmus and the rapid eye movements of sleep are also saccades. Saccades are served by a cortical network consisting of the saccadic part of the frontal eye fields, the supplementary eye fields, the dorsolateral prefrontal cortex, the cingulate eye field, and the lateral intraparietal area (Fig. 3). The cortical eye fields project to the PPRF in the brainstem, to the superior colliculus, either directly or through the basal ganglia, and to pontine nuclei that relay the information to the saccadic region of the cerebellum [27]. It is well known that the frontal eye field is involved in the triggering of intentional saccades, the parietal eye field in that of reflexive saccades, the supplementary eye fields in the initiation of motor programs comprising saccades, the presupfplementary eye fields in learning of these programs, and the dorsolateral prefrontal cortex in saccade inhibition, prediction, and spatial working memory [27,28].

The PPRF is essential for horizontal eye movements [28]. It receives afferent impulses from the frontal eye field (Brodmann area 8) and from the posterior eye field by way of tracts that descend in the anterior limb of the internal capsule and the cerebral peduncle, and then cross the midline at midbrain level (Fig. 4). The critical structure for vertical eye movements is the rostral interstitial nucleus of the medial longitudinal fasciculus located in the rostral portion of the midbrain [29,30]. It receives some direct input from the frontal eye fields, but its activity is largely controlled by impulses from the PPRF [26,27,31–34].

Smooth pursuit eye movements

The smooth pursuit system allows foveal fixation on a moving target. These movements are much slower than saccades, with maximum frequency of 100 degrees per second. Each cerebral hemisphere controls ipsilateral pursuit. Smooth pursuit eye movements are served by a cortical network involving the visual system, the medial temporal area, the middle superior temporal area, and the pursuit subregion of the frontal eye fields. The middle superior temporal area and the adjacent areas project to the contralateral dorsolateral pontine nuclei that relay the information to the cerebellar cortex. The cerebellar nuclei project to the ipsilateral vestibular nuclei, which then project to the nuclei of cranial nerves III, IV, and VI via the MLF (Fig. 5). The pursuit gaze center drives pursuit movements to the ipsilateral side [3,7,26,27,30,35,36].

Vestibular and optokinetic eye movements

The vestibular system functions to stabilize gaze and maintain clear vision during head movements. Inputs from the semicircular canals related to angular accelerations during brief head rotations trigger the vestibulo-ocular reflex. The vestibulo-ocular reflex pathway passes from the vestibular ganglion to the vestibular nuclei that relay information to the cerebellum, primarily to the flocculonodular lobe. Impulses from this system travel to both sides of the brainstem to the ocular motor nuclei via the MLF. The horizontal vestibular fibers cross and synapse in the both the abducens nuclei and the PPRF. Therefore, stimulation of one horizontal semicircular canal causes contralateral horizontal eye movement (Fig. 4). The vertical vestibular fibers go to the contralateral oculomotor and trochlear nuclei [1,5]. The oculocephalic reflex is elicited by rotating the head sideways in comatose patients [3,12,29].

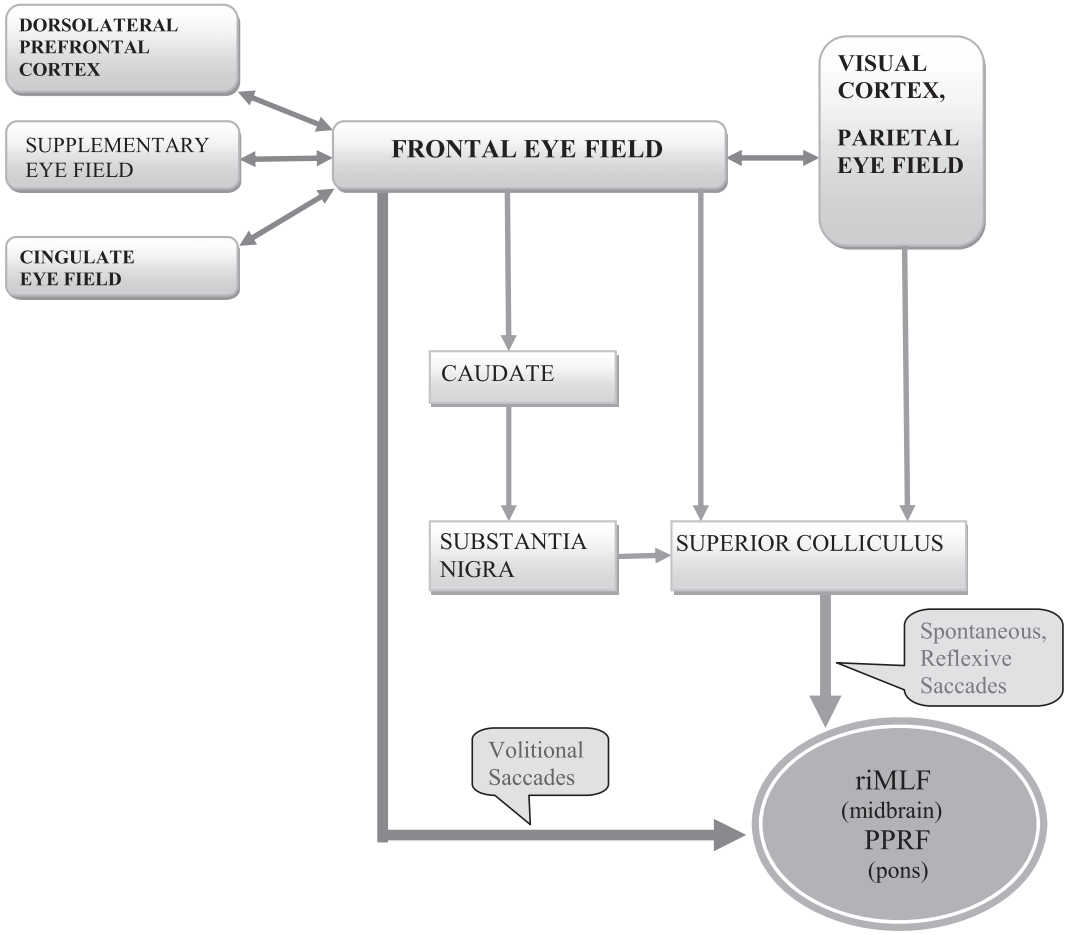

Figure 3 Main cortical areas and descending pathways involved in saccade control. riMLF, rostral interstitial medial longitudinal fasciculus; PPRF, paramedian pontine reticular formation.

The otoliths sense linear acceleration. Utricular and saccular fibers project to the vestibular nuclei, cerebellum, and the interstitial nucleus of Cajal. Sustained head tilting results in a static vestibular reflex [26]. The optokinetic system holds images of the seen world steady on the retina during sustained head rotation. A slow-phase eye movement (pursuit) is followed by a quick phase (saccade) to re-fixation. This sequence forms the pattern of optokinetic nystagmus. Optokinetic nystagmus is produced by fixation on an object that is moving relative to the observer. It depends on optic system, the striate cortex, the pontine, vestibular, and perihypoglossal nuclei, and the cerebellum. The vestibular and optokinetic systems work together to maintain clear vision during head rotation [12].

Vergence eye movements

Vergence eye movements move the eyes in opposite directions so that images of a single object are placed on both foveas. Convergence and divergence are active processes that depend on reciprocal activation and inhibition of the medial and lateral rectus muscles. Impulses pass from the medial to lateral rectus subnucleus motor neurons by way of the oculomotor internuclear complex and additional regions related to vergence areas 19 and 22 of the occipital lobes and the pontine tegmentum [1,3,12].

Neural integration

Gaze holding, which is sustaining the eyes conjugately in eccentric positions in the orbits, requires an appropriate tonic ocular motor activity called neural integration. A variety of structures may be important for its normal function, including the cerebellum, vestibular nuclei, pontine reticular formation, interstitial nucleus of Cajal (INC) and perihypoglossal nuclei. The perihypoglossal nuclei consist of the nucleus prepositus hypoglossi (NPH), the intercalates nucleus, and the

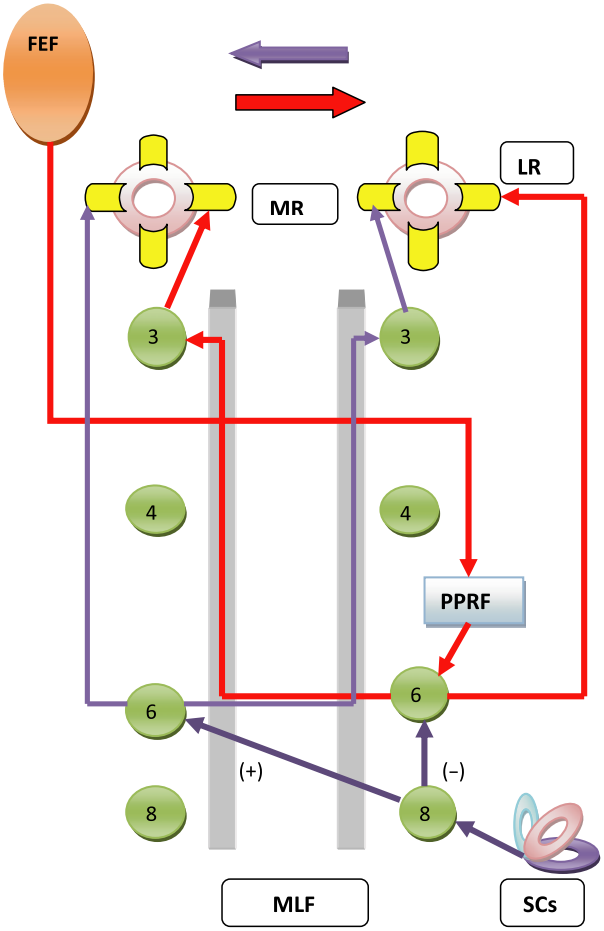

Figure 4 Details of the descending projection for horizontal saccadic eye movements (dark grey; red in online figure) and the ascending projections involved in the activation of the horizontal semicircular canal (light grey; blue in online figure). FEF, frontal eye field; PPRF, paramedian pontine reticular formation; MLF, medial longitudinal fasciculus; SCs, semicircular canals; MR, medial rectus; LR, lateral rectus.

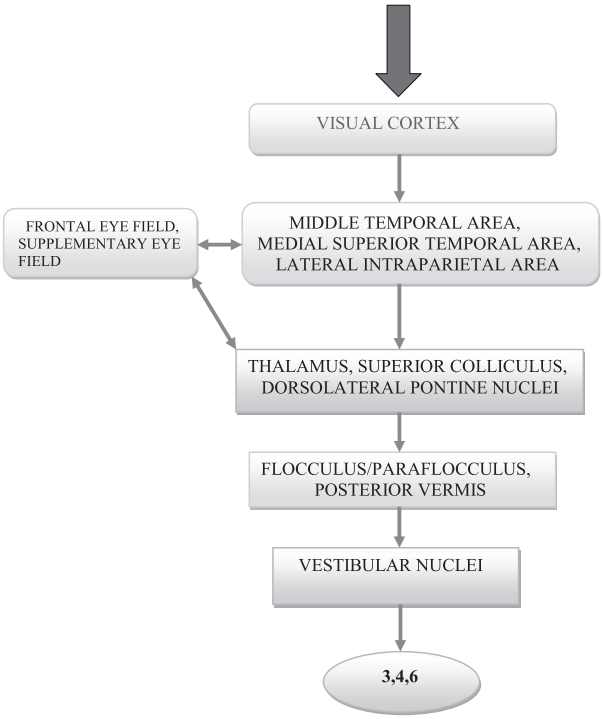

Figure 5 Schematic cortical areas and descending pathways of smooth pursuit system.

Table 3 Classification of supranuclear disorders of eye movements

Gaze palsies: horizontal, vertical (upward, downward), total
Tonic gaze deviation
Saccadic disorders
Smooth pursuit disorders
Vergence abnormalities
Nystagmus
Ocular oscillations

nucleus of Roller. Mainly, the INC is the neural integrator for vertical and torsional eye movements and the NPH and medial vestibular nucleus are the integrator for horizontal eye movements. However, the cerebral hemispheres, particularly the parietal lobes, also influence gaze holding by encoding the location of a target in space [3,8,12,26].

Supranuclear disorders of eye movements

In a Japanese study of ocular motility disturbances, supranuclear ocular motor disorders accounted for almost 10% of all patients with disorders of eye movements [36]. Supranuclear eye movement abnormalities can be classified as shown in Table 3. Patients with gaze palsy may be asymptomatic or may have blurry vision. Diplopia is present in vergence and disconjugate gaze abnormalities such as skew deviation and internuclear ophthalmoplegia. Vertigo is associated with involvement of the vestibular system.

The physician should observe the position of the eyes in primary position to evaluate for conjugate deviation, tropia, or phoria. The patient is asked to pursue a slow-moving target for observation of smooth pursuit eye movements, and to perform saccades by looking quickly from the primary position to an eccentric target. Oculocephalic maneuvers (doll's head maneuvers) are performed on an alert patient. If the oculocephalic maneuver moves the eyes appropriately into the weak field of gaze, the gaze palsy is supranuclear. If the oculocephalic maneuver does not move the eyes appropriately, the lesion may be internuclear, nuclear, or infranuclear. In addition, the near reflex should be examined for vergence eye movements [7,8].

Gaze palsy

Gaze palsy refers to weakness of the conjugate movement of the eyes in a particular direction. The types of gaze palsy include horizontal, vertical, and total [12].

Horizontal gaze palsy

Horizontal gaze palsy is due to a lesion in either the contralateral hemisphere, the frontopontine pathways, or the ipsilateral side of the pons [30].

Lesion of the frontal eye field
All saccades to the opposite side are initially abolished, usually in association with contralateral hemiparesis. Thus, there is conjugate eye deviation to the side of the lesion, called 'the patient looks toward the lesion.' Such gaze paresis resolves within a few days of stroke if there is no previous lesion in the contralateral frontal lobe [8,34].

Lesion of the paramedian pontine reticular formation
Unlike a hemispheric lesion, a lesion of the PPRF causes long-lasting saccadic gaze palsy to the ipsilateral side of the lesion. The patient with a pontine lesion looks away from the lesion. Because the PPRF lesions spare the vestibulo-ocular connections by way of the MLF, the vestibulo-ocular reflex and response to caloric stimulation are normal [8].

Lesion of the abducens nucleus
Because the abducens nucleus contains motor neurons that innervate the ipsilateral lateral rectus muscle and the axons of the PPRF neurons go to the MLF, a lesion of the abducens nucleus leads to ipsilateral gaze palsy of all eye movements including saccades, pursuit and VOR. The gaze paresis due to a lesion of the abducens nucleus can not be overcome by vestibular stimulation; however, vergence movements of the eyes are spared so adduction is possible with near stimulus [5,8].

Locked-in syndrome
Lesions in isolated bilateral corticospinal tracts, the PPRF, or the abducens nucleus in the pons cause bilateral horizontal gaze palsy, quadriplegia, and swallowing palsy, with normal vertical eye movements. This is called *the locked-in syndrome*, and it is usually the result of pontine infarction due to basilar artery thrombosis [8,12].

Vertical gaze palsy

If an isolated vertical gaze palsy is present, the lesion is in the midbrain, bilateral pons, or cerebral hemispheres. Elderly people may have difficulty with upward gaze in a non-specific manner. Vertical gaze palsy usually affects both upward and downward gazes [26,29,30,37–39].

Upward gaze palsy
Lesions of the dorsal midbrain or the pretectal area produce only an upward gaze palsy. An upward gaze palsy can be present due to aging, Parinaud syndrome, Parkinson's disease (PD), lipidosis, or Whipple disease [8].

Parinaud syndrome is associated with poor to absent upward gaze, lid retraction (Collier sign), convergence-retraction nystagmus, and light-near dissociation of midposition pupils [7,40]. The causes of Parinaud syndrome are listed in Table 4.

Patients with PD commonly complain of impaired visual function and difficulty reading, despite normal visual acuity. PD is associated with defects in saccadic and smooth pursuit movements, the blink reflex, and pupil reactivity. Upward gaze is moderately restricted, affecting saccades first and pursuit later. Steady fixation is often disrupted by square wave jerks. Slower saccadic gaze, hypometric saccades, cogwheel pursuit, convergence insufficiency, typical parkinsonian stare, reduced blink reflex, and abnormal optokinetic nystagmus are common in PD. These ocular abnormalities frequently respond to treatment [8,41,42].

Whipple disease is a rare infectious disorder characterized by weight loss, diarrhea, arthritis, and fever. It can lead to supranuclear gaze palsy that initially affects vertical saccades and quick phases of nystagmus;

Table 4 Causes of Parinaud syndrome

Pineal tumors
Paraneoplastic
Hydrocephalus
Vascular disorders
Midbrain hemorrhage or infarction
Thalamic hemorrhage or infarction
Metabolic disorders
Lipid storage diseases
Wilson disease
Kernicterus
Drug-induced
Barbiturates
Carbamazepine
Neuroleptics
Degenerative disorders
Progressive supranuclear palsy
Huntington disease
Olivopontocerebellar atrophy
Diffuse Lewy body disease
Miscellaneous
Multiple sclerosis
Whipple disease
Trauma
Encephalitis

eventually, all eye movements may be lost. Oculomasticatory myorrhythmia is a highly characteristic finding with pendular vergence oscillations and concurrent contractions of masticatory muscles [1,8].

Monocular elevation paresis which is also known as double elevator palsy is characterized by the inability to elevate one eye without ocular deviation from the primary position. The lesion involves the connection of the rostral interstitial nucleus of the MLF to the oculomotor nuclei in the pretectum. The vestibulo-ocular reflex is intact. Monocular elevation paresis may be congenital or acquired, and it may be mimicked by thyroid ophthalmopathy, myasthenia gravis, or chronic progressive external ophthalmoplegia [1,43].

Downward gaze palsy

Isolated downward gaze palsy is seen rarely, and is produced by lesions in both rostral interstitial nuclei of the MLF in the ventral midbrain. The lesions may be due to the posterior thalamo-subthalamic paramedian artery infarction, progressive supranuclear palsy, or histiocytosis [26].

Initially, patients with progressive supranuclear palsy (PSP) have difficulty with downward gaze palsy; the disorder progresses to involve upward and horizontal gazes. Fixation instability and eyelid abnormalities, particularly lid retraction, blepharospasm, and apraxia of eyelid opening and closure, are important distinguishing signs of PSP (Table 5). The end-stage of PSP is characterized by global ophthalmoplegia. Vestibulo-ocular maneuvers and calorics can drive the eye movements normally, confirming the supranuclear origin [44]. The clinical features of PSP resemble those of PD, diffuse Lewy body disease, corticobasal degeneration, and multisystem atrophy [45,46]. Unstable gait, absence of tremor, and absence of a response to levodopa differentiates PSP from PD, which is usually characterized by upward gaze palsy and cogwheel pursuit. Supranuclear vertical gaze palsy, gait instability, and the absence of delusions distinguishes PSP from diffuse Lewy body disease. Gait abnormality, severe upward gaze palsy, bilateral bradykinesia, and absence of alien limb separates PSP from corticobasal degeneration. Supranuclear vertical gaze palsy and increased age at symptom onset distinguishes progressive supranuclear palsy from multiple system atrophy [42,45–47].

Table 5 Differential diagnosis of PSP, PD, DLBD, CBD and MSA

	PSP	PD	DLBD	CBD	MSA
Vertical supranuclear gaze palsy	+++	+	–	–/+	–
Onset of symptoms (age)	40–50	60–70	60–70	50–70	40–60
Postural/gait instability	+++	+	++	++	+++
Falls	+++	–/+	+	+	+
Tremor dominant disease	–	+++	+	+	++
Response to levodopa	–/+	+++	+	–/+	+
Delusions	–	–/+	+++	+	–
Alien limb syndrome	–	–	–	+++	–
Autonomic symptoms	–	–/+	–	–	+++

PSP, progressive supranuclear palsy; PD, Parkinson's disease; DLBD, diffuse Lewy body disease; CBD, corticobasal degeneration; MSA, multiple system atrophy.

Total ophthalmoplegia

It can be seen in PSP, systemic lupus erythematosus, Miller Fisher Syndrome, Whipple disease, Wernicke encephalopathy, and drug intoxications (such as phenytoin, carbamazepine, tricyclic antidepressants, lithium, and baclofen) [8].

Miller Fisher Syndrome (MFS) is the most frequent variant of the Guillain-Barré Syndrome. It is characterized by the classic triad of ophthalmoplegia, ataxia and areflexia. Pupillary abnormalities, blepharoptosis, and facial palsy are frequently seen in MFS. MFS is mostly an acute, self-limiting condition, and can be associated with infectious, autoimmune, and neoplastic disorders. The anti-GQ1b IgG antibody titer is most commonly elevated in MFS. Patients with MFS usually had good recovery and no residual deficits [48].

Wernicke encephalopathy is a metabolic disorder caused by thiamine deficiency, most commonly seen in alcoholic people, characterized by ophthalmoplegia, mental confusion, and gait ataxia. The ocular motor findings include weakness of abduction, gaze-evoked nystagmus, vertical nystagmus in primary position, impaired vestibular responses, INO, the one-and-a-half syndrome, and horizontal and vertical gaze palsies that may progress to total ophthalmoplegia [8,12].

Tonic gaze deviation

Tonic gaze deviation refers to sustained eye movement in a particular direction. The deviation may be horizontal or vertical [1,5].

Horizontal deviation

Ipsilateral, acute lesions of the cerebral hemisphere or contralateral lesions of the pons cause tonic horizontal conjugated deviation. Irritation of the frontal eye fields in epileptic patients causes contralateral deviation of the eyes [8].

Vertical deviation

Vertical deviation may be upward or downward. Upward deviation is seen in oculogyric crisis following post-encephalitic parkinsonism, cerebrovascular disorders, or

response to phenothiazine. Downward deviation can occur in hydrocephalus, metabolic encephalopathy, or thalamic hemorrhage [26].

Saccadic disorders

Saccadic palsy

An inability to generate saccades is termed *saccadic palsy*. Horizontal saccadic palsy may occur transiently in acute lesions of the contralateral frontal eye field or the ipsilateral PPRF. Complete loss of all saccades can also be seen after cardiac surgery [8,32,49].

Saccadic dysmetria

Saccadic dysmetria refers to saccades of inappropriate amplitude, which also may be slow. Saccadic dysmetria is found in cerebellar disease in which centripetal saccades are hypermetric and centrifugal saccades are hypometric. Saccades in PD may be hypometric and associated with increased latency. Mild to moderate hypometria of saccades also may be seen in multiple system atrophy [50].

Slow saccades

Slow saccades are present in spinocerebellar and olivopontocerebellar degeneration, PD, PSP, Huntington chorea, Wilson disease, large unilateral lesions of the cerebral hemispheres, lesions of the PPRF, paraneoplastic syndromes, and drug intoxications with drugs such as anticonvulsants or benzodiazepines Varying degrees of slowing of saccades in the vertical plane or both horizontal and vertical planes may also be seen after cardiac surgery [8,49].

Ocular motor apraxia

Ocular motor apraxia describes an eye movement disorder characterized by loss of or severely diminished volitional saccades with retention of the fast phases of vestibular nystagmus [7,8]. *Congenital ocular motor apraxia*, which was initially described by Cogan, manifests in newborn infants. An affected child has difficulty performing horizontal saccades to commands. Instead, the child uses a head thrust in the desired direction of gaze until the eyes reach the desired position to maintain fixation. Spontaneous and reflex saccades are normal [51–53]. Although congenital ocular motor apraxia affects only horizontal eye movements, rare *acquired ocular motor apraxia* (Balint syndrome) develops with unilateral dominant or bilateral lesions of the frontal and posterior eye fields. Patients have impairment of both horizontal and vertical saccadic movements [26]. Balint syndrome is characterized by visual disorientation or simultanagnosia; ocular apraxia, which is a deficit of visual scanning; or optic ataxia, an impairment of pointing and reaching under visual guidance. Bilateral border zone infarction in the occipitoparietal region is the most frequent cause of the complete Balint syndrome [12,32–34,54,55].

Smooth pursuit disorders

Unilateral smooth pursuit paresis

A unilateral lesion of the parieto-occipital junction may cause difficulty with the ability to track a target in the ipsilateral direction. The patient uses small saccades, called saccadic pursuit or cogwheel pursuit, to follow the target. A contralateral homonymous field defect is often present in these patients. Optokinetic nystagmus is absent ipsilateral to the lesion. Unilateral smooth pursuit paresis also can be seen in patients with unilateral cerebellar disorders [27].

Bilateral smooth pursuit paresis

A patient with bilateral smooth pursuit paresis is unable to pursue a target smoothly. Saccadic pursuit is a main clinical finding. This disorder is not anatomically specific and can be seen with diffuse disease of the cerebral hemispheres, cerebellum, or brainstem. Impaired attention or some drugs (such as sedatives, anticonvulsants, lithium, and methadone) can also cause bilateral smooth pursuit paresis [8,35].

Vergence abnormalities

Convergence paralysis

Convergence paralysis is characterized clinically by horizontal diplopia with near and normal medial rectus muscle function during ductions and versions, there is no convergence to a near target. A lack of near effort by the patient also can simulate convergence paralysis. Rostral midbrain lesions caused by infection, infarction, or demyelination can cause convergence paralysis, although it can also be seen in PD and PSP. Convergence insufficiency is a very common problem causing reading complaints in students. It can often be seen in otherwise normal cases [1,42].

Convergence spasm

In spasm of the near reflex, the patient has symptoms of diplopia and blurred vision; evaluation shows miosis

(contraction of the pupil) and episodic adduction of one or both eyes. Ductional eye movements are full. Normal function of the lateral rectus muscle can be demonstrated using optokinetic nystagmus testing, vestibulo-ocular reflex maneuvers, or calorics. In the absence of neurologic findings, convergence spasm is usually psychological. The patient is usually in a stressful situation or using the eyes to read a lot when the spasm occurs. It is rarely an organic condition related to dorsal midbrain disease [1,56].

Divergence paralysis

A patient with divergence paralysis has horizontal diplopia and esotropia (the form of strabismus in which the visual axes converge) at distance. If the lateral rectus muscle has normal function with version testing and the divergence paralysis exists in isolation, no further evaluation is necessary. If the lateral rectus muscle is weak, divergence paralysis may be due to increased intracranial pressure, multiple sclerosis, infection, cerebrovascular disease, or lumbar puncture [1,26].

Nystagmus

Jerky, pendular, rotatory, dissociated, or mixed forms of nystagmus may be seen in eye movement disorders of central origin. *Jerky nystagmus* refers to slow-phase drifts and fast-phase corrections. *Pendular nystagmus* is a symmetric nystagmus describing sinusoidal oscillations. Nystagmus of unequal extent in the eyes is termed *dissociated form*. *Mixed forms* of nystagmus can coexist. Other forms of nystagmus occur in central disorders of the ocular motor system, including *see-saw* and *convergence-retraction nystagmus* [1,8].

Jerky nystagmus

Horizontal nystagmus in the primary position
Horizontal nystagmus in the primary position arises from lesions of the labyrinthine and vestibular nuclei. The direction of nystagmus, which is fast-phase, is contralateral to the lesion. A rotatory component may be present in labyrinthine disease, but purely rotatory nystagmus is characteristic of a central lesion. Central horizontal nystagmus is not diminished by optic fixation. Skew deviation (ipsilateral hypotropia) may occur in lateral medullary infarction, but only rarely in labyrinthine lesions [8].

Upbeat nystagmus
Upbeat nystagmus is seen in the primary position with lesions of the dorsal cerebellar vermis, pons, and medulla, and as an adverse effect of certain drugs (such as barbiturates) and cigarettes [57].

Downbeat nystagmus
Downbeat nystagmus can be caused by a lesion at the craniocervical junction, such as Arnold-Chiari malformation, cerebellar disease, hydrocephalus, metabolic disorder, familial periodic ataxia, multiple sclerosis, or multiple system atrophy [49]. In addition, downbeat nystagmus can be caused by drugs such as carbamazepine, barbiturates, phenytoin, and lithium, and toxins such as toluene, especially in glue-sniffing addiction. Downbeat nystagmus is usually present in the primary position, and it becomes more prominent on looking down (Alexander's law) [8,57].

Periodic alternating nystagmus
Periodic alternating nystagmus (PAN) is spontaneous and horizontal, and it reverses direction approximately every 3–4 min. It may arise from spinocerebellar degeneration, posterior fossa tumors, head trauma, vascular diseases, encephalitis, or phenytoin intoxication PAN also may be associated with downbeat nystagmus in the primary position in craniocervical junction anomalies and multiple sclerosis [54,58,59].

Gaze-paretic nystagmus
In gaze-paretic nystagmus, nystagmus is not present in the primary gaze; it appears in the extremes of lateral or vertical gaze, due to a defective neural integrator. The horizontal form of gaze-paretic nystagmus may be physiological (end-point nystagmus) or caused by ipsilateral cerebellar lesions mainly affecting the flocculus, sedatives, anticonvulsants, or ethanol. Gaze-paretic nystagmus in the upward gaze may be caused by a cerebellar lesion, INO, drugs (for example, barbiturates), or tobacco [8].

Bruns nystagmus
Bruns nystagmus is characterized by a combination of slow, large-amplitude nystagmus when looking toward the side of lesion and fast, small-amplitude nystagmus when looking to the opposite side. The slow nystagmus is caused by dysfunction of the neural integrator in the cerebellum, and the fast nystagmus is caused by vestibular dysfunction in the brainstem. Bruns nystagmus is commonly seen with tumors located at the cerebellopontine angle, such as acoustic neuroma [5,8].

Rebound nystagmus
Rebound nystagmus refers to a primary position nystagmus that follows a sustained gaze-paretic nystagmus in the opposite direction. It is usually seen in cerebellar diseases [7].

Central positional nystagmus
Positional nystagmus is triggered by particular head positions. Central lesions, such as medullar and posterior cerebellar vermis, result in an immediate positional nystagmus that persists and may be purely vertical or rotator [7].

Pendular nystagmus

Pendular nystagmus may be congenital or acquired; if acquired, it can be caused by multiple sclerosis, brainstem infarction, cerebellar lesions, metabolic disorders, or prolonged exposure to toluene. It can be horizontal, vertical, or both [5,7].

Dissociated nystagmus

Nystagmus of unequal extent in two eyes is termed *dissociated nystagmus*. INO caused by a lesion of the MLF is associated with nystagmus in the abducting eye and paralysis in the adducting eye [7].

Other forms of nystagmus

See-saw nystagmus
See-saw nystagmus is characterized by alternating cycles of elevation and intorsion of one eye and synchronous depression and extorsion of the other eye, at a frequency of about one cycle per second. It may be congenital or acquired; when acquired, it is associated with parasellar tumors or midbrain diseases including disease affecting the interstitial nucleus of Cajal [7,8].

Convergence-retraction nystagmus
Convergence-retraction nystagmus, characterized by quick phases that converge or retract the eyes, is caused by a lesion of the mesencephalon. It is usually accompanied by impaired upward gaze and other dorsal midbrain signs. It is best elicited by using optokinetic drum or attempting upward saccades [5].

Ocular oscillations

Square wave jerks

Square wave jerks are a type of ocular oscillations with small-amplitude, conjugate, saccadic eye movements that move the eyes away from the target and, after approximately 200 ms, return them to the original position. Square wave jerks may occur in normal individuals and in a variety of neurological disorders, most commonly, cerebellar disease, PD, PSP, or multiple system atrophy [50].

Ocular bobbing

Ocular bobbing refers to rapid downward deviation of the eyes followed by slow upward drift. Inverse bobbing (ocular dipping) is slow downward deviation followed by rapid upward return. Reverse bobbing is rapid upward deviation with slow downward drift. Ocular bobbing is usually seen in pontine dysfunction or metabolic encephalopathy [8].

Ocular flutter

Ocular flutter is characterized by horizontal saccadic oscillations without an intersaccadic interval. It has been hypothesized that ocular flutter is caused by loss of pause neuronal inhibition of burst neuron function in the PPRF [12,60].

Opsoclonus

Opsoclonus consists of combined horizontal, vertical, and/or torsional, disconjugate saccadic oscillations (saccadomania). As with ocular flutter, the possible pathophysiology of opsoclonus may be related to disorders of the inhibitory control of saccadic burst neurons by pontine pause cells. Opsoclonus and ocular flutter can be caused by viral encephalitis, neuroblastoma, remote effect of tumor, hydrocephalus, thalamic hemorrhage, or certain drugs (such as lithium, diazepam, phenytoin, tricyclic antidepressants, cocaine, or thallium) [8,26,60,61].

Conclusions

Eye movements are performed by the ocular motor system and the extraocular muscles. The ocular motor system is divided according to anatomic location into infranuclear, nuclear, internuclear, and supranuclear components. It is important to distinguish supranuclear and internuclear from nuclear and infranuclear disturbances. INO is caused by a lesion of the MLF that results from multiple sclerosis in younger patients, particularly when the ophthalmoplegia is bilateral, and that usually results from vascular disorders in the elderly. Supranuclear disorders of eye movements are characterized by gaze palsies, tonic gaze deviation, saccadic and smooth pursuit disorders, vergence abnormalities, nystagmus, and ocular oscillations. Oculocephalic maneuvers help in the differential diagnosis of eye movement disorders. Supranuclear ocular motor disturbances account for almost 10% of all patients with disorders of ocular motility.

Notes

This manuscript has been partially published in Turkish in *Türk Nöroloji Dergisi* [62]. *European Journal of Neurology* has the permission of Turkish Neurological Society to publish this article. [Correction added on 12 October 2009, after first online publication: the Notes section was inserted.]

References

1. Breen LA. Gaze abnormalities. In: Walsh TJ, ed. *Neuro-ophthalmology: Clinical Signs and Symptoms*, 3rd edn. Philadelphia, PA: Lea and Febiger, 1992: 525–543.
2. Pierrot-Deseilligny C. The control of gaze (3) Neurological defects [in French]. *Med. Sci. (Paris)* 2004; **20:** 357–362.
3. Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Sciences*, 4th edn. New York, NY: McGraw-Hill Co, 2000.
4. Frohman TC, Galetta S, Fox R, *et al*. Pearls & Oysters: the medial longitudinal fasciculus in ocular motor physiology. *Neurology* 2008; **70:** e57–e67.
5. Kommerell G. Supranuclear disorders of ocular motility. In: Schiefer U, Wilhelm H, Hart WM, eds. *Clinical Neuro-ophthalmology – A Practical Guide*. Berlin: Springer, 2007: 155–170.
6. Zwergal A, Cnyrim C, Arbusow V, *et al*. Unilateral INO is associated with ocular tilt reaction in pontomesencephalic lesions: INO plus. *Neurology* 2008; **71:** 590–593.
7. Daroff RB, Troost BT, Leigh RJ. Supranuclear disorders of eye movements. In: Glaser JS, ed. *Neuro-ophthalmology*. Philadelphia, PA: Lippincott, 1990: 299–324.
8. Walsh FB, Hoyt WF, Miller NR. *Walsh and Hoyt*'s Clinical Neuro-ophthalmology: The Essentials, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.
9. Thömke F, Hopf HC. Abduction paresis with rostral pontine and/or mesencephalic lesions: Pseudoabducens palsy and its relation to the so-called posterior internuclear ophthalmoplegia of Lutz. *BMC Neurol* 2001; **1:** 4.
10. Fisher CM. Neuroanatomic evidence to explain why bilateral internuclear ophthalmoplegia may result from occlusion of a unilateral pontine branch artery. *J Neuro-ophthalmol* 2004; **24:** 39–41.
11. Bandini F, Faga D, Simonetti S. Ocular myasthenia mimicking a one-and-a-half syndrome. *J Neuroophthalmol* 2001; **21:** 210–211.
12. Leigh RJ, Zee DS. *The Neurology of Eye Movements*. Philadelphia, PA: Davis, 1987.
13. Deleu D, Sokrab T, Salim K, *et al*. Pure isolated unilateral internuclear ophthalmoplegia from ischemic origin: report of a case and literature review. *Acta Neurol Belg* 2005; **105:** 214–217.
14. de Andrade DC, Lucato LT, Yamamoto FI, *et al*. Isolated bilateral internuclear ophthalmoplegia after ischemic stroke. *J Neuroophthalmol* 2007; **27:** 125–126.
15. Kim JS. Internuclear ophthalmoplegia as an isolated or predominant symptom of brainstem infarction. *Neurology* 2004; **62:** 1491–1496.
16. de Seze J, Lucas C, Leclerc X, *et al*. One-and-a-half syndrome in pontine infarcts: MRI correlates. *Neuroradiology* 1999; **41:** 666–669.
17. Espinosa PS. Teaching NeuroImage: one-and-a-half syndrome. *Neurology* 2008; **70:** e20.
18. Bogousslavsky J, Miklossy J, Regli F, *et al*. One-and-a-half syndrome in ischaemic locked-in state: a clinico-pathological study. *J Neurol Neurosurg Psychiatry* 1984; **47:** 927–935.
19. Chen CM, Lin SH. Wall-eyed bilateral internuclear ophthalmoplegia from lesions at different levels in the brainstem. *J Neuroophthalmol* 2007; **27:** 9–15.
20. Korkmaz A, Topaloglu H, Kansu T. Wall eyed bilateral internuclear ophthalmoplegia in chronic inflammatory demyelinating polyneuropathy. *Eur J Neurol* 2002; **9:** 691–692.
21. Matsumoto H, Ohminami S, Goto J, *et al*. Progressive supranuclear palsy with walleyed bilateral internuclear ophthalmoplegia syndrome. *Arch Neurol* 2008; **65:** 827–829.
22. Frohman TC, Frohman EM, O'Suilleabhain P, *et al*. Accuracy of clinical detection of INO in MS: corroboration with quantitative infrared oculography. *Neurology* 2003; **61:** 848–850.
23. Vanooteghem P, Dehaene I, Van Zandycke M, Casselman J. Combined trochlear nerve palsy and internuclear ophthalmoplegia. *Arch Neurol* 1992; **49:** 108–109.
24. Bolaños I, Lozano D, Cantú C. Internuclear ophthalmoplegia: causes and long-term follow-up in 65 patients. *Acta Neurol Scand* 2004; **110:** 161–165.
25. Keane JR. Internuclear ophthalmoplegia: unusual causes in 114 of 410 patients. *Arch Neurol* 2005; **62:** 714–717.
26. Milder DG, Billson FA. Supranuclear disorders of eye movement. *Aust N Z J Ophthalmol* 1989; **17:** 15–21.
27. Orban de Xivry JJ, Lefèvre P. Saccades and pursuit: two outcomes of a single sensorimotor process. *J Physiol* 2007; **584**(Pt 1)**:** 11–23.
28. Pierrot-Deseilligny C, Müri RM, Ploner CJ, *et al*. Cortical control of ocular saccades in humans: a model for motricity. *Prog Brain Res* 2003; **142:** 3–17.
29. Kömpf D, Pasik T, Pasik P, *et al*. Downward gaze in monkeys: stimulation and lesion studies. *Brain* 1979; **102:** 527–558.
30. Bender MB. Brain control of conjugate horizontal and vertical eye movements: a survey of the structural and functional correlates. *Brain* 1980; **103:** 23–69.
31. Heinzle J, Hepp K, Martin KA. A microcircuit model of the frontal eye fields. *J Neurosci* 2007; **27:** 9341–9353.
32. Eggers SD, Moster ML, Cranmer K. Selective saccadic palsy after cardiac surgery. *Neurology* 2008; **70:** 318–320.
33. Ramat S, Leigh RJ, Zee DS, *et al*. What clinical disorders tell us about the neural control of saccadic eye movements. *Brain* 2007; **130**(Pt 1)**:** 10–35.
34. Rivaud S, Müri RM, Gaymard B, *et al*. Eye movement disorders after frontal eye field lesions in humans. *Exp Brain Res* 1994; **102:** 110–120.
35. Pierrot-Deseilligny C, Gaymard B. Smooth pursuit disorders. *Baillieres Clin Neurol* 1992; **1:** 435–454.
36. Kobashi R, Ohtsuki H, Hasebe S. Clinical studies of ocular motility disturbances Part 1. Ocular motility disturbances: causes and incidence. *Jpn J Ophthalmol* 1996; **40:** 502–510.
37. Rufa A, Cerase A, De Santi L, *et al*. Impairment of vertical saccades from an acute pontine lesion in multiple sclerosis. *J Neuroophthalmol* 2008; **28:** 305–307.
38. Bogousslavsky J, Miklossy J, Regli F, *et al*. Vertical gaze palsy and selective unilateral infarction of the rostral

interstitial nucleus of the medial longitudinal fasciculus (riMLF). *J Neurol Neurosurg Psychiatry* 1990; **53:** 67–71.
39. Ranalli PJ, Sharpe JA, Fletcher WA. Palsy of upward and downward saccadic, pursuit, and vestibular movements with a unilateral midbrain lesion: pathophysiologic correlations. *Neurology* 1988; **38:** 114–122.
40. Karatas M, Karakurum B, Tuncer I. A case of Parinaud's syndrome due to the remote effect of small cell carcinoma. *Int J Neurosci* 2004; **114:** 291–297.
41. Armstrong RA. Visual signs and symptoms of Parkinson's disease. *Clin Exp Optom* 2008; **91:** 129–138.
42. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. *Neurology* 2004; **62:** 177–180.
43. Muñoz M, Page LK. Acquired double elevator palsy in a child with a pineocytoma. *Am J Ophthalmol* 1994; **118:** 810–811.
44. Josephs KA, Ishizawa T, Tsuboi Y, *et al*. A clinicopathological study of vascular progressive supranuclear palsy: a multi-infarct disorder presenting as progressive supranuclear palsy. *Arch Neurol* 2002; **59:** 1597–1601.
45. Rehman HU. Progressive supranuclear palsy. *Postgrad Med J* 2000; **76:** 333–336.
46. Litvan I, Campbell G, Mangone CA, *et al*. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study. *Brain* 1997; **120**(Pt 1)**:** 65–74.
47. Friedman DI, Jankovic J, McCrary JA III. Neuro-ophthalmic findings in progressive supranuclear palsy. *J Clin Neuroophthalmol* 1992; **12:** 104–109.
48. Lo YL. Clinical and immunological spectrum of the Miller Fisher syndrome. *Muscle Nerve* 2007; **36:** 615–627.
49. Solomon D, Ramat S, Tomsak RL, *et al*. Saccadic palsy after cardiac surgery: characteristics and pathogenesis. *Ann Neurol* 2008; **63:** 355–365.
50. Anderson T, Luxon L, Quinn N, *et al*. Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients. *Mov Disord* 2008; **23:** 977–984.
51. PeBenito R, Cracco JB. Congenital ocular motor apraxia Case reports and literature review. *Clin Pediatr (Phila)* 1988; **27:** 27–31.
52. Gonçalves Carrasquinho S, Teixeira S, Cadete A, *et al*. Congenital ocular motor apraxia. *Eur J Ophthalmol* 2008; **18:** 282–284.
53. Orrison WW, Robertson WC Jr. Congenital ocular motor apraxia. A possible disconnection syndrome. *Arch Neurol* 1979; **36:** 29–31.
54. Rizzo M, Vecera SP. Psychoanatomical substrates of Bálint's syndrome. *J Neurol Neurosurg Psychiatry* 2002; **72:** 162–178.
55. Pierrot-Deseilligny C, Gautier JC, Loron P. Acquired ocular motor apraxia due to bilateral frontoparietal infarcts. *Ann Neurol* 1988; **23:** 199–202.
56. Sitole S, Jay WM. Spasm of the near reflex in a patient with multiple sclerosis. *Semin Ophthalmol* 2007; **22:** 29–31.
57. Pierrot-Deseilligny C, Milea D. Vertical nystagmus: clinical facts and hypotheses. *Brain* 2005; **128**(Pt 6)**:** 1237–1246.
58. Hashimoto T, Sasaki O, Yoshida K, *et al*. Periodic alternating nystagmus and rebound nystagmus in spinocerebellar ataxia type 6. *Mov Disord* 2003; **18:** 1201–1204.
59. Shallo-Hoffmann J, Riordan-Eva P. Recognizing periodic alternating nystagmus. *Strabismus* 2001; **9:** 203–215.
60. Schon F, Hodgson TL, Mort D, *et al*. Ocular flutter associated with a localized lesion in the paramedian pontine reticular formation. *Ann Neurol* 2001; **50:** 413–416.
61. Furman JM, Eidelman BH, Fromm GH. Spontaneous remission of paraneoplastic ocular flutter and saccadic intrusions. *Neurology* 1988; **38:** 499–501.
62. Karatas M. Internükleer ve Supranükleer Göz Hareket Bozukluklari. *Turk Norol Derg* 2009; **15:** 54–63.

