Movement Disorders
CLINICAL PRACTICE

REVIEW

Eye Movement Disorders in Movement Disorders

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Oculomotor assessment is an essential element of the neurological clinical examination and is particularly important when evaluating patients with movements disorders. Most of the brain is involved in oculomotor control, and thus many neurological conditions present with oculomotor abnormalities. Each of the different classes of eye movements and their features can provide important information that can facilitate differential diagnosis. This educational review presents a clinical approach to eye movement abnormalities that are commonly seen in parkinsonism, ataxia, dystonia, myoclonus, tremor, and chorea. In parkinsonism, subtle signs such as prominent square wave jerks, impaired vertical optokinetic nystagmus, and/or the "round the houses" sign suggest early progressive supranuclear gaze palsy before vertical gaze is restricted. In ataxia, nystagmus is common, but other findings such as oculomotor apraxia, supranuclear gaze palsy, impaired fixation, or saccadic pursuit can contribute to diagnoses such as ataxia with oculomotor apraxia, Niemann-Pick type C, or ataxia telangiectasia. Opsoclonus myoclonus and oculopalatal myoclonus present with characteristic phenomenology and are usually easy to identify. The oculomotor exam is usually unremarkable in isolated dystonia, but oculogyric crisis is a medical emergency and should be recognized and treated in a timely manner. Gaze impersistence in a patient with chorea suggests Huntington's disease, but in a patient with dystonia or tremor, Wilson's disease is more likely. Finally, functional eye movements can reinforce the clinical impression of a functional movement disorder.

Extraocular movement assessment is an essential element of the neurological clinical examination as eye movement abnormalities can be of localizing and diagnostic value. During the past few decades, advances in our understanding of the anatomical structures and neuronal networks that control eye movements have provided valuable insights into the underlying neural mechanisms of eye movement—insights that have also been translated into the neural control of limb movements through shared pathophysiological mechanisms of disease. Consequently, the examination of eye movements is valuable in the evaluation of patients with movement disorders. Particularly, neurodegenerative conditions often present with abnormal eye movements with variable semiology.[1] As the diagnosis of the majority of these disorders is based on clinical observation, knowledge of their different eye movement abnormalities is essential.

In this educational review, we provide a brief physiological background on the role of the central nervous system (CNS) in the control of eye movements and summarize these clinical findings across common movement disorders.

Methods

This a nonsystematic educational review of articles extracted from PubMed with several search terms, such as "oculomotor," "saccades," "pursuit," "nystagmus," "parkinsonism," "ataxia," "dystonia," "myoclonus," and "tremor." Selection of the articles was based on their educational value.

Physiology and Anatomy

Eye movements are mainly divided in 2 classes: those that stabilize the image on the fovea—namely, fixation, smooth pursuit,

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and the vestibulocular and optokinetic reflexes—and those that shift the focus of the fovea toward another area/image of interest, namely, saccades.[1,2] The first group are predominantly automatic or reflexive, whereas saccades are usually active components of perception, action, and cognition that support a variety of behavioral functions. Smooth pursuit requires a visible moving target, whereas saccades can be performed with or without visible targets. Saccades are further divided into subcategories; for example, visually guided saccades shift the eyes toward a visual target (suddenly appearing or preexisting),[3] memory-guided saccades move the eye to a position that used to be occupied by a target, predictive saccades are generated in anticipation of or in search of the appearance of a target at a particular location, and antisaccades move the eye to a mirror location in the opposite direction to a suddenly appearing target. All of those categories of eye movements can be tested at the bedside.

Phenomenology

Saccades

During examination of visually guided saccades, the examiner provides 2 targets (eg, the index fingers of the examiner's 2 hands) within the visual field of the patient and requests the patient to alternate fixation from 1 target to the other. The nature of the elicited saccade depends on the nature of target and the instructions for the task. For example, if the target is suddenly presented, such as wiggling a finger, reflexive saccades are assessed/elicited. Alternatively, if the examiner provides a cue to refixate to stationary targets (eg, auditory, by calling the name of the target) then command voluntary saccades are tested, or if the patient is requested to repetitively refixate between the 2 constantly visible targets in their own time, without cues, then self-paced saccades are elicited. Memory-guided saccades are tested by requesting the subject to perform a saccadic movement toward a memorized target in the visual field (the examiner initially presents 2 targets: 1 fixation target and 1 memorized target). Then the memorized target disappears and the patient is asked to move the eyes to the location of the memorized target). The technique for testing saccades should be chosen appropriately each time; for example, in Parkinson's disease (PD), self-paced or memory-guided saccades are usually more affected than reflexive saccades, which can be normal (Table 1).[4] The evaluation includes the assessment of saccadic latency (how long it takes for the eyes to start moving following presentation of a cue or target), saccadic velocity (the speed of the eye movement), and saccadic accuracy (whether the eye overshoots or undershoots the target). A mild undershoot followed by a single small corrective saccade to the target may be normal, whereas sustained hypermetria that does not disappear after a few repetitions is always abnormal.[5]

Oculomotor Apraxia

Leigh and Zee describe acquired ocular motor apraxia as a loss of voluntary control of saccades, pursuit, and vergence, with preservation of reflex movements, especially slow and quick phases of the vestibulo-ocular reflex.[6,7] The term *oculomotor apraxia* should be used when there is evidence of loss of cerebral control of gaze. In a subgroup of patients, the abnormality is characterized by a spasm of fixation where the eyes cannot move away from a continuously present target but can move when that target disappears. In oculomotor apraxia, the saccadic latency is increased, but multiple factors can affect saccadic latency, such as the

TABLE 1 Clinical pearls

Oculomotor Findings	Clinical Exam
• In PD, the self-paced or memory-guided saccades are more likely to be abnormal compared WITH reflexive saccades.	• Chose self-paced or memory-guided saccades over reflexive saccades when testing saccades in suspected PD.
• In early stages of vertical supranuclear gaze paresis/palsy, before prominent gaze restriction, the disproportionally slowed vertical saccadic velocity (compared with horizontal) presents with the "round the houses" sign.	• Look for curvature in the trajectory of vertical or oblique saccades.
• OKN in PSP is more abnormal with upward visual stimuli, whereas OKN in PD is more abnormal with downward visual stimuli.	• Test OKN in both vertical directions in patients with parkinsonian syndromes.
• Oculomotor apraxia can be identified during spontaneous gaze shifts if the head moves first and the eyes follow.	• Observe spontaneous gaze shift during history taking.
• Convergence (functional) spasm is associated with miosis in contrast to CN VI lesion.	• Look for myosis when abduction is restricted and there is suspicion of functional etiology.
• Voluntary (functional) eye oscillations cannot be maintained for more than 25 seconds.	• Test abnormal eye movements for more than 25 seconds.

Abbreviations: PD, Parkinson's disease; OKN, optokinetic nystagmus; PSP, progressive supranuclear palsy; CN VI, Cranial Nerve VI.

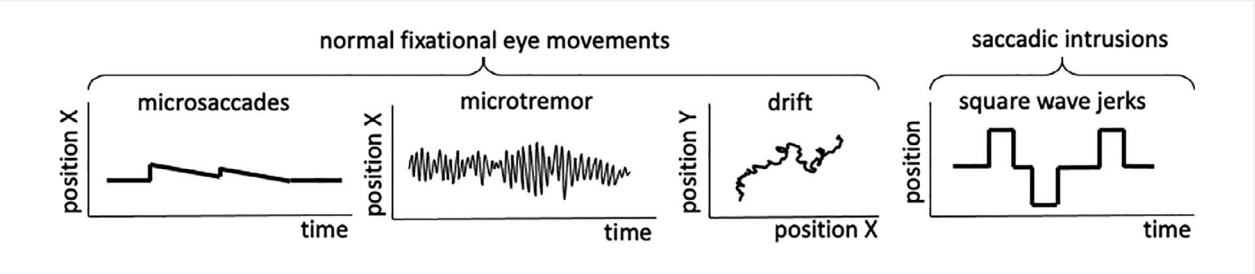

FIG. 1. Qualitative representation of eye movements during fixation.

salience of the target, the specific instructions to the subject, attention, and the subject's age.[2,8,9] Therefore, when tested at the bedside, these factors should be taken into account, and increased latency should be reproducible in a large proportion of saccades to be clinically relevant. Disruption of the descending cortical inputs from the frontal and parietal regions to the superior colliculus and then to the brainstem and cerebellum is usually the primary cause of increased saccadic latency in acquired oculomotor apraxia. In patients with prominent oculomotor apraxia, compensatory maneuvers are engaged (such as a head thrust or blink) to assist with breakage of fixation that allows initiation of the saccadic eye movement. If a patient moves the head first and then the eyes during spontaneous gaze, this is usually attributed to oculomotor apraxia, as normally the eyes move first and the head follows.

Fixation Eye Movements

Fixation can be tested at the bedside by providing a stationary target (eg, the examiner's finger). The examiner evaluates the ocular alignment in different positions and looks for abnormal eye movements such as saccadic intrusions or gaze-evoked nystagmus. There are several classes of normal fixation-related eye movements, but square wave jerks (SWJs) have been the most studied (Fig. 1). SWJs are normal with a frequency of less than 9 per minute and an amplitude of less than 5 degrees (usually less than 2 degrees).[10–13] They comprise a small horizontal saccade away from fixation followed by a corrective saccade back to fixation after an intersaccadic interval of about 200 milliseconds.[10] Presence of the intersaccadic interval, the lack of a slow phase (both movements to and from the target are saccadic), and the fact that the eyes do not cross the midline are characteristics that differentiate SWJs from other eye movements such as nystagmus or flutter (busts of horizontal bidirectional back-to-back saccades without an intersaccadic interval).

Another abnormality of fixation is gaze distractibility or impersistence, which is the inability to maintain fixation by suppressing reflexive saccades to stimuli that appear in the visual field.[14] It is characteristic of Huntington's disease but can also be seen in other conditions such as Wilson's disease.[15]

Pursuit Eye Movements

During the assessment of pursuit movements, the eyes follow a smoothly moving target. The examiner assesses how well the eyes match the movement of the target smoothly without the need for corrective movements. When the ocular velocity is lower than the target velocity (reduced pursuit gain), the eyes fall behind, and "catch-up" saccades are necessary to maintain the eyes on the target.

Optokinetic Nystagmus

Optokinetic nystagmus (OKN) contributes to stabilization of the images on the fovea during head rotations or during tracking of a moving field. It is a normal examination finding, and its absence or a lateralized deficit is abnormal. For testing at the bedside, a rotating drum or a moving tape with stripes or even a bedside heavily illustrated magazine is usually adequate. The slow phase of the OKN is a smooth pursuit movement, and the fast phase is a restorative saccade in the anticompensatory direction—the direction of the inferred head motion—bringing the eyes back to the original position.[16] Depending on the instructions, different types of OKN can be tested. Typically, at the bedside, the "stare" OKN is tested by asking the patient to observe the stripes (or pictures) as they pass in front of him/her. Note that OKN gain (ratio of fast phase velocity to target velocity) depends on many factors including attention, the luminance contrast of the targets, and age of the patient.[17–19]

OKN can be particularly useful in identifying subtle impairment of the saccadic or pursuit movements, for example, when asymmetry between left and right horizontal OKN is identified. Vertical OKN has normally lower gain than the horizontal OKN,[2] but marked asymmetry between the horizontal and vertical OKN can be suggestive of vertical eye movement abnormality. For example, in early progressive supranuclear palsy (PSP), the vertical OKN lacks a quick phase and the eyes tend to drift toward the direction of the presented stimuli.[20] In particular, downward saccades are affected first, therefore OKN with upward moving stimuli is mostly affected at the earliest stages of PSP. In contrast, in PD, the gain of OKN induced by

downward-moving stimuli is reduced compared with the OKN with upward-moving stimuli.[21]

Nystagmus

The presence of nystagmus during oculomotor examination is usually abnormal. Nystagmus is classified as either jerk nystagmus or pendular nystagmus. Jerk nystagmus has a slow phase and a fast phase. The slow phase, which takes the eye away from fixation, is the abnormality, with the fast phase being a restorative saccade back toward the intended fixation point. The direction of the nystagmus is traditionally determined by the direction of the fast phase. Pendular nystagmus consists of just slow phases, and the amplitude of the 2 phases is approximately equal. In the movement disorder clinic, pendular nystagmus is seen in Whipple disease or oculopalatal myoclonus, whereas jerk nystagmus can be seen in cerebellar syndromes (Table 2), and many brainstem and peripheral lesions.

Vestibular Eye Movements

The vestibular system controls eye movements mainly through the vestibulo-ocular reflex (VOR). VOR is tested at the bedside by evaluating for a corrective saccade after a passive rapid movement of the head during fixation (head impulse test). Another way is by evaluating nystagmus after head shaking (passive rotational oscillatory shaking of the head while in a 30-degee neck flexion position, at 2–3 Hz frequency and 10-degee amplitude, for 10–20 seconds with eyes closed). Dynamic visual acuity is tested by comparing visual acuity while the head is stationary to visual acuity measured during head rotations of approximately 10-degee amplitude and 2 Hz frequency. Impaired VOR leads to a significant drop of visual acuity during head rotations (1 line loss can be normal, 2–3 lines lost can be seen in unilateral vestibular loss, and 4 or more is typically seen with bilateral vestibular loss). During slow head movements (<1 Hz) with eyes opened, the VOR and optokinetic reflex both stabilize the eyes. However, in cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS), VORs, optokinetic reflexes, and smooth

TABLE 2 Cerebellar syndromes, clinical syndromes, and exam

Localization	Syndrome	Exam Findings
Flocculus/paraflocculus	Eye fixation impairment	Gaze-evoked nystagmus, rebound nystagmus and downbeat nystagmus, postsaccadic drift, saccadic pursuit
Nodulus/ventral uvula	Vestibulo-ocular response impairment	Loss of tilt suppression of postrotational nystagmus (after rapid shaking or rotation), periodic alternating nystagmus
Dorsal vermis/posterior fastigial nucleus	Saccadic eye movement impairment	Saccadic hypometria (bilateral vermis), saccadic hypermetria (bilateral fastigial nucleus), impairment in the initiation of pursuit

TABLE 3 Patterns of eye movement abnormalities in parkinsonian disorders; some features are shared, whereas others are specific to particular disorders

Oculomotor abnormalities	PD	MSA	PSP	CBS
Progressive gaze limitation			+++	
Saccadic hypometria	+	++	+++	++
Slow saccades			+++	
Saccadic apraxia				++
Impaired SP		+++	++	++
Impaired OKN		++	+++	++
Increased SWJs	+	++	+++	+
Impaired VORS		++	+	
Gaze-evoked nystagmus		+++	+	
pDBN and ccHSN		+++		

+, mild; ++, moderate; +++, severe.
Abbreviations: PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; SP, smooth pursuit; OKN, optokinetic nystagmus; SWJs, square wave jerks; VORS, vestibulo-ocular reflex suppression (modified from Anderson and MacAskill[1]); pDBN, positional downbeat nystagmus; ccHSN, cross-coupled head-shaking nystagmus.

pursuit are deficient; therefore, multiple corrective saccades are evident during low-frequency head movements (of approximately 0.5 Hz) while the eyes are fixated to a stationary target.[22,23] Suppression of the VOR can be tested by evaluating fixation to a head-fixed target (usually the patient's own thumb with the arm extended) during head (and simultaneous arm) rotation. Abnormalities of the vestibulo-ocular reflex can cause disequilibrium and oscillopsia. Intact VOR in a patient with gaze palsy points to a supranuclear origin of the gaze palsy.

Eye Movements in Parkinsonism

Oculomotor examination can be helpful in differentiating parkinsonian syndromes (Table 3). In the initial stages of PD, there are no major eye abnormalities on clinical exam in contrast with other parkinsonian syndromes that present with early oculomotor deficits.

Saccades are affected in PD and ascribed to abnormal output of the substantia nigra pars reticulata projections to the superior colliculus.[24] Typically, the initial oculomotor abnormality in PD is hypometria of voluntary saccadic eye movement, more in the vertical than the horizontal plane.[25,26] One clinical correlate of this abnormality is that hypometric saccades during visual scanning leads to a smaller scanned area, which then leads to an increased risk of falls in patients with PD, especially during turns.[1,27,28] Self-paced saccades are usually more affected than reflexive saccades, which appear to be relatively normal, at least for targets close to the center of the visual field.[29–32] Similar to limb bradykinesia, saccadic bradykinesia with a decrement in saccadic velocity and amplitude over time has also recently been described.[33]

If vertical saccadic velocity and amplitude are impaired at the early stages of a parkinsonian syndrome, classical presentation of PSP known as Richardson syndrome (PSP-RS) should be considered.[34–37] Normal aging causes restriction of vertical gaze, especially upward,[38] but in PSP-RS the impairment is more prominent in the downward direction. The earliest sign of PSP-RS, before gaze restriction occurs, is decreased vertical saccadic velocity. At that stage of the disease, the disproportional slowing of the vertical component compared with the horizontal component causes a curved trajectory during oblique or vertical saccades, classically described as the "round the houses" sign.[39] Later on, there is limitation of voluntary gaze first vertically and then horizontally. Eventually, patients with advanced disease develop complete ophthalmoplegia.[36] OKN testing can help identify early subtle saccadic abnormalities. In PSP-RS, the fast phase (saccadic phase) of OKN is impaired so that the eyes drift in the direction of the slow phase (pursuit phase). Importantly, other parkinsonian syndromes can cause supranuclear palsy but not as early as PSP-RS. For example, in corticobasal syndrome with PSP pathology (CBS-PSP) vertical supranuclear gaze palsy is present in 20% of patients early in the disease and up to 50% overall.[40] In CBS with corticobasal degeneration pathology, vertical supranuclear gaze palsy has been reported between 18% and 59% of late-stage cases, and it is less common than CBS-PSP in early stages.[41–46] For a broader differential diagnosis of supranuclear gaze palsy, see Table 4.

TABLE 4 Differential diagnosis of supranuclear gaze palsy

• Vascular
• Posterior thalamo-subthalamic paramedian artery occlusion
• Artery of Percheron occlusion
• Neurodegenerative
• Progressive supranuclear palsy
• Corticobasal degeneration
• Multiple system atrophy
• Parkinson's disease
• Neurodegeneration with brain iron accumulation
• Amyotrophic lateral sclerosis
• Metabolic/genetic
• Niemann-Pick type C
• Gaucher (usually horizontal)
• Spinocerebellar ataxias (1, 2, 3, 6)
• Abetalipoproteinemia
• Tay-Sachs disease
• Maple syrup urine disease
• Wilson's disease
• Glutaric aciduria type 1
• Neoplastic
• Pineal gland tumors
• Paraneoplastic, autoimmune, inflammatory
• Anti-Ma2 encephalitis
• Anti-glutamic acid decarboxylase antibody
• Anti-glycine receptor antibody
• Anti-IgLON5 antibody
• Infectious
• Prion disease
• Whipple disease

Markedly increased saccadic latency can differentiate CBS from other parkinsonian syndromes such as idiopathic PD, multiple system atrophy (MSA), and PSP.[29] This abnormality in CBS also correlates with limb apraxia scores.[29] Notably, the saccadic velocity is not greatly impaired in CBS, and once saccades are launched, the velocity is usually normal. In contrast, in PD the saccadic latency is generally preserved, at least in the early stages of the disease. However, patients with PD and dementia exhibit prolonged latency compared with those with normal cognition and controls, suggesting that saccadic latency may correlate with cognitive status in PD.[47,48]

Abnormal fixation is usually nonspecific but can be helpful in differentiating parkinsonian syndromes. SWJs are more frequent in all parkinsonian syndromes, with PSP at the most impaired end of the spectrum (increased SWJ frequency and amplitude[49]) and PD at the less impaired end.[50,51] MSA can also present with more frequent and sometimes large amplitude SWJs (macro-SWJs).[29,52]

Smooth pursuit eye movements are generally preserved in early-stage PD, but abnormal saccadic intrusions appear as the disease progresses. There is evidence that the abnormal saccades during pursuit are not truly "catch up" saccades (as a result of decreased pursuit velocity) but, rather, anticipatory saccades that take the eyes ahead of the moving target, probably reflecting deficits in saccadic inhibition.[32] In PSP, vertical pursuit eye movements are impaired early in the disease, and because of simultaneous impairment of the saccadic system, no catch up saccades can be initiated to compensate for the deficit.[53] Notably, the low-frequency pursuit movements are initially preserved and only the high-frequency movements fail.[53]

Subtle cerebellar signs, such as presence of nystagmus or saccadic dysmetria, can differentiate MSA from other parkinsonian syndromes. In a series of 25 MSA cases, downbeat nystagmus with Dix-Hallpike positioning (positional nystagmus) was found in 10 cases, even in patients with no other cerebellar signs on examination.[54,55] Because downbeat nystagmus (positional or induced by head shaking) is uncommon in PD, this sign can be useful in differentiating MSA and PD.[54,56] In MSA, the saccadic hypometria is mild–moderate, and it is not associated with low velocity (velocity is usually normal).[29,54]

Finally, convergence insufficiency is common in PD, especially in patients with cognitive impairment (https://collections.lib.utah.edu/ark:/87278/s6p29vr1).[57–59] It can cause blurred near vision, which can significantly impact the quality of life. Convergence training is a treatment option.[60]

Eye Movements in Some Ataxia Syndromes

Ataxia Telangiectasia

Ataxia telangiectasia is a multisystem autosomal recessive disorder attributed to mutation of the *ATM* gene.[61,62] The neurological manifestations in ataxia telangiectasia include a cerebellar syndrome (ataxia, impaired coordination, speech disturbance, gait impairment). Other movement disorders such as dystonia, chorea, tremor, and myoclonus can also occur later in the disease.[63] An eye exam is particularly important for recognition of telangiectasias on the sclera and for the characteristic eye movement abnormalities, which are mainly impaired fixation caused by pathologic torsional and downbeat nystagmus and impaired saccades caused by increased latency and dysmetria. In addition, pursuit movements are saccadic, and OKN is abnormal as a result of eye deviation toward the direction of the slow component.[64,65] The presence of nystagmus and prominent saccadic intrusions lead to impaired visual fixation, which is hypothesized to be the cause of poor quality of vision in ataxia telangiectasia.[66]

Ataxia with Oculomotor Apraxia

There are multiple types of ataxia with oculomotor apraxia, but type I and type II are the most common.[67–69] Both types are autosomal recessive conditions attributed to mutations in the *APTX* and *SETX* genes, respectively,[67–69] and onset is earlier in type I (early childhood) compared with type II (teenage years). As the name reveals, oculomotor apraxia is the most prominent oculomotor disorder as reflected in prolonged saccadic latencies.[70] However, this feature is present only in 50% to 60% of the patients.[67–69] Other oculomotor abnormalities include saccadic pursuit and dysmetric saccades (hypometric and hypermetric) as well as increased antisaccade error rates.[70] Cerebellar ataxia is the most common movement disorder in these patients, but other hyperkinetic and hypokinetic movement disorders can occur. Severe peripheral neuropathy and characteristic blood abnormalities can aid diagnosis.[68–72]

Niemann-Pick Type C

Niemann-Pick type C (NPC) is a lysosomal storage disorder with autosomal recessive pattern of inheritance. The symptoms vary and can include psychiatric symptoms, cognitive decline, dysarthria, dysphagia, gelastic cataplexy, hypotonia, seizures, and movement disorders.[73–75] Most common movement disorders are ataxia and dystonia, but myoclonus, chorea, and tremor can also be present.[76,77] Supranuclear gaze palsy, especially in the vertical plane, is the most characteristic abnormality in NPC.[78] In particular, downward saccades are affected first (controlled unilaterally) followed by upward saccades (controlled bilaterally). Supranuclear gaze palsy carries high clinical significance for the diagnosis of NPC as it occurs early in the disease[79] and can lead to disease-specific treatment.[80,81]

Spinocerebellar Ataxia

Overall the oculomotor abnormalities in spinocerebellar ataxia (SCA) reflect cerebellar pathology with or without involvement of other brain regions and can be useful for differentiating the different genotypes.[1] In SCA 2, the most significant oculomotor sign is reduced saccadic velocity, which correlates with the number of CAG repeats and is thought to be attributed to brainstem involvement.[82–85] SCA 2 also presents frequently with supranuclear gaze palsy.[86] SCA 3 can present with vertical supranuclear ophthalmoplegia with normal horizontal saccades at least at the initial stages of the disease.[86,87] Furthermore, bulging eyes are characteristic of SCA 3.[88,89] Besides nystagmus, SCA 6 can present with impaired smooth pursuit even in the presymptomatic stage.[90] Gaze-evoked and rebound nystagmus are present in many SCA subtypes, but they appear to be particularly common in SCA 3 and SCA 6, with positioning downbeat nystagmus being a specific feature of SCA 6 (https://collections.lib.utah.edu/ark:/87278/s6vx45m7 and https://collections.lib.utah.

edu/ark:/87278/s60k7jb4).[91–95] In SCA 7, the retinal manifestations can be preceded by oculomotor abnormalities mainly affecting saccadic accuracy and velocity.[96–98]

Eye Movements in Myoclonus

Opsoclonus Myoclonus

Opsoclonus was initially described by Orzechowski in 1927[99] and later Kinsbourne, who introduced the term "dancing eyes."[100] Opsoclonus is classically described as conjugate, involuntary, rapid, nonrhythmic, and chaotic movements of the eyes (https://collections.lib.utah.edu/ark:/87278/s6cw0k1c).[101] It comprises back-to-back multidirectional saccades without an intersaccadic interval. Typically it presents in childhood with acute or subacute onset, and it is commonly associated with encephalitis or posterior fossa tumors, mostly neuroblastoma.[102,103] In adults, it is associated with paraneoplastic syndromes.[104,105] The pathophysiology is presumed to be immune mediated, although the exact mechanism is unclear.[106,107] It is thought that opsoclonus is attributed to instability in the fine balance between the omnipause and burst neurons in the brainstem that normally generate the saccadic eye movements.[108] Opsoclonus can be associated with limb myoclonus. As it settles, opsoclonus may metamorphose into ocular flutter (bursts of horizontal bidirectional back-to-back saccades without an intersaccadic interval), and opsoclonus and ocular flutter can co-occur in many instances.

Oculopalatal Myoclonus

Guillain and Mollaret first described the syndrome of palatal myoclonus, and they pointed out that it can be caused by lesions along the dentato-rubro-olivary pathway (Guillain-Mollaret triangle).[109] Palatal myoclonus is usually rhythmical; therefore, the term *palatal tremor* is sometimes used. There are 2 forms of palatal myoclonus. The first form is essential palatal myoclonus, which is usually isolated with no associated symptoms except for an ear-clicking sound and has recently been identified to commonly have functional etiology.[110] The other form is symptomatic palatal myoclonus, which is secondary to a lesion in the Guillain-Mollaret triangle, and it can affect the oculomotor system and other body parts such as the diaphragm. The symptoms of symptomatic palatal myoclonus can occur weeks to months after the lesion.[111] When palatal myoclonus is associated with abnormal eye movements, the most common abnormality is pendular nystagmus. Usually the nystagmus presents in the vertical plane, but a horizontal or rotational component might be present.[112,113] Convergent–divergent nystagmus has also been reported.[114] Typically, the palatal and ocular movements have the same frequency and phase.[115] The amplitude of the abnormal eye movements has been reported as large as 8 degrees.[116] The most accepted pathophysiologic mechanism of symptomatic palatal myoclonus is that a CNS lesion along the dentato-rubro-olivary pathway causes denervation of the olivary nucleus. Once released from cerebellar inhibitory input, the olivary nucleus enlarges and develops sustained synchronized oscillations, which are fed back to the cerebellum for further modulation and eventually cause the abnormal movements.

Whipple Disease

Whipple disease is caused by an infection with *Tropheryma whipplei* and mainly causes gastrointestinal or other systemic symptoms. It can affect the CNS, and its neurological manifestations are variable. Insidious neuropsychiatric and cognitive symptoms are most commonly present with the second most common neurological finding being the oculomotor disturbance.[117–119] In particular, oculomasticatory myorhythmia is thought to be a pathognomonic sign for Whipple disease.[117,118] It is characterized by oscillatory convergent–divergent movements of the eyes with a frequency of approximately 1 Hz accompanied by synchronous oscillatory contractions of the muscles of mastication (https://collections.lib.utah.edu/ark:/87278/s6tq8z4m).[120] When these movements spread further to the face or the extremities, the term *oculofacial-skeletal myorhythmia* is more appropriate.[121,122] Supranuclear ophthalmoplegia mimicking PSP can also occur.[119] Usually a hyperkinetic movement disorder such as myoclonus, chorea, or dystonia is also part of the clinical picture.[123,124]

Prion Disease

Prions are abnormal misfolded proteins that can cause transmissible and genetic neurodegenerative diseases.[125] In humans, prions can cause Creutzfeldt-Jakob disease (CJD) and its variant, as well as Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia (FFI), and Kuru. Early ocular motor findings have been reported in patients with CJD.[126] Centripetal nystagmus (during eccentric gaze: fast phase toward primary gaze and slow phase toward eccentric position),[127] breakdown of saccades, and gaze deviation are the most prominent features.[126,128,129] Vertical supranuclear ophthalmoplegia in CJD can resemble PSP.[128,130] Although not commonly reported, ocular dipping can also be a characteristic ocular abnormality.[131,132] Disordered fixation with saccadic intrusions in the setting of severe insomnia can be a useful early diagnostic clue of FFI.[133] Gerstmann-Sträussler-Scheinker disease also presents with abnormal eye movements in the early stages such as pathologic nystagmus, impaired visual tracking, impaired VOR, and gaze-evoked nystagmus. At the late stages of the disease, almost all patients have a variety of ocular movement abnormalities.[134]

Eye Movements in Dystonia

Isolated Dystonia

Bedside examination of oculomotor function in isolated cervical dystonia is usually normal. However, there is evidence of

asymmetric vestibulo-ocular reflexes and other subtle abnormalities when tested in the laboratory.[135,136] Similarly, the eye movements in patients with blepharospasm are largely normal when tested at the bedside,[132] but more detailed testing in the laboratory has revealed impairment of saccadic initiation with longer saccadic latencies, although peak velocities and accuracy are normal.[138] In addition, SWJs and macro-SWJs, as well as vertical and horizontal involuntary deviations and convergence spasms, have been described in blepharospasm.[139]

Oculogyric Crisis

Oculogyric crisis (OGC) is a rare disorder characterized by dystonic conjugate eye deviation.[140–142] The etiology is usually attributed to medication adverse effects. The most common medication class associated with OGC is neuroleptics, although other classes have also been associated (for a comprehensive list of medications related to OGC see Barow et al[140]). Although OGC is typically described as a dystonic movement, it is not typically seen in primary dystonia, and rarely can be associated with blepharospasm.[139] It can be seen in other movement disorders, mainly parkinsonism (especially postencephalitic and disorders of dopamine synthesis), but also focal brain lesions (eg, striatal necrosis), immune encephalitides, and some pediatric genetic disorders (eg, *CACNA1A* mutations).

Stiff Person Syndrome

Stiff person syndrome (SPS) is characterized by progressive fluctuating muscle spasms usually affecting the axial muscles of the lower back and abdomen.[63] Antibodies directed against glutamic acid decarboxylase, anti-amphiphysin, anti-glycine receptor, anti-DPPX, and other antibodies, have been associated with SPS.[143,144] The pathophysiology is thought to be related to impairment of inhibitory GABAergic spinal networks,[145] but there is also evidence of cortical[146] and brainstem[147] involvement. Oculomotor impairment is not always part of the clinical picture, but there are reports that SPS can present with a variety of eye movement abnormalities such as strabismus causing diplopia attributed to horizontal gaze limitation, deficient gain of pursuit movements, increased saccadic latency, and gaze-evoked nystagmus.[148,149] In addition, "stiff eyes" can be part of the SPS phenomenology and represent restriction of the range of extraocular movements in the vertical or horizontal plane, leading to erroneous consideration of PSP.[150,151] Fatiguability of saccadic latency, velocity, and accuracy in SPS can differentiate it from PSP. The pathophysiology of "stiff eyes" is unclear, but intravenous immunoglobulin (IVIG) can be helpful therapeutically.[150,152]

Eye Movements in Tremor

Wilson's Disease

Wilson's disease is an autosomal recessive condition attributed to mutation in the *ATP7B* gene leading to excessive accumulation of copper in the liver and the brain. In a series of 34 patients, impairment of vertical pursuit was found in 85% of the patients and of horizontal pursuit in 41% of the patients. The next most common abnormality was impaired vertical OKN in 41% of the cohort.[153] Supranuclear upgaze palsy and reduced saccadic velocity have also been reported.[154] Gaze distractibility or impersistence, similar to Huntington's disease, has been described by Wilson himself[15] and more recently by Lennox and Jones.[155] Antisaccades can have increased error rate and latency.[156] The link between the ocular abnormalities and the pathology in Wilson's disease remains unclear. The eye exam is also important for the identification of Kayser-Fleischer rings.

Eye Movements in Chorea

Huntington's Disease

Huntington's disease is caused by an autosomal dominant CAG trinucleotide repeat expansion in chromosome 4. It manifests with chorea and other involuntary movements, gait disturbance, incoordination, and psychiatric and cognitive problems. The earliest oculomotor finding is prolonged voluntary saccadic latency attributed to oculomotor apraxia, requiring occasional blink or head thrust for saccadic initiation.[14,157,158] In addition, fixation is impaired because of a failure to inhibit saccades toward stimuli within the visual field.[14] Eccentric gaze holding is also impaired as the eyes tend to be brought back to the primary gaze by an inappropriate saccade.[14] Slow saccades can be seen early in the disease, especially in those with a high CAG repeat number, but usually after other generalized motor impairments.[159] Otherwise, saccades can be hypometric in both the vertical and horizontal planes.[158] Smooth pursuit movements can also be affected by reduced gain, but usually later in the disease.[160] Oculomotor exam is of high yield in Huntington's disease and can be proven essential when hyperkinetic movement disorder with early psychiatric or cognitive findings is encountered.

Functional Eye Movements

Functional eye movement disorders can present in isolation or in the setting of other functional syndromes.[161,162] Convergence spasm is likely the most common functional oculomotor disorder[163] and presents with persistence of convergence despite the absence or removal of a near fixation target. It can be confused with cranial nerve VI palsy, but it can be differentiated by observing normal abduction and the associated miosis during accommodation, which are not present with a sixth nerve palsy.[162,164–166] Functional limitation of gaze can be accompanied by eyelid fluttering on attempted eye movements, and patients commonly have effortful facial expressions.[162] Voluntary saccadic oscillations such as voluntary (or functional) nystagmus usually cannot be maintained for more than 25 seconds, a helpful feature in differentiating functional from nonfunctional

movements.[167,168] In addition, other functional movement disorders such as functional opsoclonus, OGC, and ocular flutter have been described.[169] The oculomotor abnormalities encountered in functional eye movement disorders are distractible and variable, similar to functional movements affecting other body parts.

Conclusions

Eye movement abnormalities are highly varied in movement disorders and affect many different mechanisms. A systematic approach to the examination is recommended to avoid missing crucial observations. Fixation should be assessed for at least 15 seconds to assess for SWJs. Horizontal and vertical pursuit and saccades should always be examined. OKN can be a useful supplement but needs careful interpretation if attention is a concern. Abnormal VOR points to vestibular or cerebellar abnormalities or both (such as in CANVAS).

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

P.K.: 1A, 1B, 1C, 2A

D.K.: 2B

T.A.: 2B

M.H.: 1A, 1B, 1C, 2B

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