INTRODUCTION

With the exception of reflexive movements, such as vestibulo-ocular reflexes and fast phases of nystagmus, cerebral structures determine when and where the eyes move, while brainstem centers determine how they move. The premotor centers for conjugate gaze and vergence eye movements are in the brainstem. Those specifically for horizontal gaze are in the pons; while those for vertical gaze, vergence and ocular counter-rolling (torsional movements) are in the upper midbrain. The mechanisms for horizontal eye movements are better understood than those for vertical eye movements and are based on clinicopathological and radiological correlation, and animal and bioengineering experiments.

Vertical Gaze

The premotor substrate for vertical gaze lies in the midbrain reticular formation (MRF); however, some vertical saccades are programmed in the paramedian pontine reticular formation (PPRF) which projects to the MRF via a juxta-MLF pathway and coordinates horizontal, vertical, and oblique trajectories. The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) contains medium-lead (short-latency) excitatory burst neurons for both up and down gaze, although their exact location is controversial: The burst cells for upward saccades are probably caudal, ventral, and medial whereas those for downward saccades are more rostral, dorsal, and lateral. Burst-tonic and tonic neurons in the region of the interstitial nucleus of Cajal (INC) discharge in relation to vertical eye position and play a role in vertical pursuit and eye position. The burst neurons for upward saccades project dorsally and laterally from the riMLF and decussate in the posterior peduncle to decussate at the anterior limb of the internal capsule, and medial cerebral peduncle to decussate at the level of the trochlear nucleus, before continuing on to innervate the contralateral horizontal PPRF; the oblique misdirection is similar to torsipulsion seen with lateropulsion.

Saccades

Saccades are initiated mainly in the frontal lobes; horizontal saccades are initiated in the contralateral frontal lobe, while vertical saccades require bilateral activation. Saccades are divided into four broad groups: 1). Intentional (voluntary) saccades are internally triggered and include target searching, memory guided, predictive (where the target has not yet appeared), and visually guided volitional saccades to a known target; 2). Reflexive saccades are externally triggered by a new visual or auditory stimulus; 3). Spontaneous saccades are internally triggered by both the frontal eye fields (FEF) and the superior colliculus to repeatedly scan the environment at about 20 Hz per minute; they occur during other motor activities, at rest, and even during sleep; 4). The quick phases of nystagmus.

Four areas in the cerebral cortex are particularly important in controlling saccades: 1). The posterior parietal cortex (PPC), Brodmann's area 39, in the upper angular gyrus and 2). The frontal eye fields (FEF) Brodmann's area 8 are involved in triggering reflexive visually guided saccades. The PPC contains area 7a and the lateral intraparietal area (LIP) which has a projection to the superior colliculus (SC). The superior colliculus also has some role in reflexive and orienting saccades; 3). The prefrontal cortex (PFC), area 46, has a major role in suppressing unwanted reflexive saccades when visual attention is engaged by a specific target. Anterior frontal lobes lesions cause difficulty maintaining fixation and suppressing unwanted saccades to distracting stimuli. The generation of memory guided saccades is more complex but involves the visual cortex (area 17), the PPC for visuospatial integration, the PFC for spatial memory and sorting, and finally the FEF to trigger the saccade; 4). The supplementary eye fields (SEF), area 6, in the supplementary motor area as well as the basal ganglia are involved in sequencing complex memory guided saccades; the left side has a more dominant role.

Overall the frontal poles are responsible for internally guided or volitional saccades to explore the immediate past or future environment, while the parietal poles initiate reflexive and searching saccades to explore the current environment.

The major pathways for saccades descend predominantly in the pedunculotegmental tract through the corona radiata, anterior limb of the internal capsule, and medial cerebral peduncle to decussate at the level of the trochlear nucleus, before continuing on to innervate the contralateral horizontal
gaze center in the PPRF. The frontal eye fields also project via a transthalamic pathway to the pretectal nuclei and to the deeper layers of the superior colliculus, presumably for vertical gaze. Saccades of different amplitudes and directions are encoded in neurons in the frontal eye fields and superior colliculi in a retinotopic fashion; thus, the size and direction of saccades are determined by which neurons are stimulated.

The frontal eye fields (FEF) also project via the caudate nucleus to neurons in the substantia nigra pars reticulata, which in turn project to the intermediate and deeper layers of the superior colliculus and tonically suppress saccades by a GABA-ergic mechanism. Controlled disinhibition of this basal ganglial system is important for normal visually guided saccades and probably essential for saccades to remembered targets.

The superficial sensory division of the superior colliculus receives a direct orderly input from the retina via the accessory optic tract, bypassing the lateral geniculate body, such that the visual field may be mapped on its surface (retinotopic). The deep motor division receives visual input from the striate cortex (area 17) and projects to motor areas in the subthalamic region and brainstem. The deeper division also receives input from the contralateral FEF and posterior parietal cortex (PPC) directly, and indirectly via the basal ganglia, as well as a somatosensory and auditory input. Stimulation of the superior colliculus drives the eyes contralaterally to a point in the visual fields corresponding to the retinal projection to that site; it may also play a role in relaying excitatory information from part of the inferior parietal lobule, which influence initiation of saccades to some extent. Isolated lesions of the superior colliculus produce minimal, but specific, defects of saccades; when they are combined with experimental lesions of the frontal eye fields, however, significant contralateral saccadic defects result. Purely vertical saccades require bilateral simultaneous stimulation of corresponding points in the superior colliculi, or in the FEF.

Pursuit Eye Movements

Despite its complexity, the control of smooth pursuit eye movements can be broken down into three components: sensory, motor, and attentional-spatial. The stimulus for pursuit is movement of an image across the fovea at velocities greater than 3-5°/sec. The sensory component includes information from the retinal ganglion (M) cells via the magnocellular layer of the lateral geniculate nucleus and optic radiations and projects to the prestatre cortex (areas 18 and 19) and then to the superior temporal sulcus region (in rhesus monkeys), which contains cortical areas MT (middle temporal) and MST (middle superior temporal) equivalent to the parieto-temporo-occipital junction (PTO) in humans and encodes for location, direction and velocity of objects moving in the contralateral visual field; it is the major afferent input driving smooth pursuit. This sensory subsystem projects to the accessory optic tract and bilaterally to the pursuit motor subsystem, which is also located in the PTO region, as well as to the frontal (FEF) and supplementary eye fields (SEF). This indirect pursuit pathway focuses attention on small moving targets. A direct pathway, bypassing the attentional-spatial subsystem, enables large moving objects, such as full-field OKN stimuli, to generate smooth pursuit contralaterally even when the subject is inattentive. The superior colliculus also contributes to pursuit drive. The parieto-temporo-occipital junction (PTO) projects via the internal sagittal stratum and the posterior limb of the internal capsule to the ipsilateral dorsolateral and lateral pontine nuclei. The pursuit pathways control ipsilateral tracking and so must either remain on the same side, or undergo a double decussation, at least once. Retinal slip, the sensory stimulus for vertical pursuit, is encoded by the dorsolateral pontine nuclei and relayed to the flocculus and posterior vermis before converging, via the INC, on the midbrain. The floccular Purkinje cells, posterior vermis and lobules VI and VII encode neural signals for gaze velocity and coordinate vestibular and eye movement velocity signals for pursuit. Johnston's group suggested the pursuit pathways project from the pontine nuclei to the contralateral flocculus and medial vestibular nucleus and then back to the ipsilateral abducens nucleus. The commands for vertical pursuit relay to the brainstem and cerebellum before reaching the relevant ocular motor neurons in the midbrain. The INC is involved in integrating vertical velocity commands to position commands and may play a role as the final common integrator for all nonsaccadic vertical and torsional eye movements.

Because of the wealth of distracting visual stimuli in the environment, an attentional-spatial subsystem is necessary to focus on selected targets and generate smooth pursuit. Mesulam proposed a hypothetical integrated network to modulate directed attention within extrapersonal space: This network includes a posterior parietal component containing an internal sensory map for reference to extrapersonal space; a limbic component in the cingulate gyrus to provide motivational drive to respond to external stimuli on the basis of past experience and present needs; a frontal component coordinate motor responses or programs for exploration, scanning, reaching, and fixating; and a reticular component necessary for arousal and vigilance.

The Cerebellum

The cerebellum plays a major role in both saccade and pursuit eye movement control as well in vergence movements and fixation. It is richly supplied by afferent fibers conveying ocular information, such as velocity, position, and neural integration, from the vestibular system, afferent visual system, PPRF, and MRF and coordinates the ocular motor system to drive the eyes smoothly and
transmitted.

The dorsal vermis and fastigial nuclei determine the accuracy of saccades by modulating their amplitude; they also adjust the innervation to each eye selectively for precisely conjugate movements. The flocculus, part of the vestibulocerebellum, is responsible for matching the saccadic pulse and step appropriately and for stabilizing images on the fovea. It adjusts the output of the neural integrator and participates in long-term adaptive processing to ensure that eye movements remain appropriate to the stimulus; for example, the amplitude (gain) and even the direction of the slow phases of the VOR are adjusted by the flocculus. The nodulus, also part of the vestibulocerebellum, influences vestibular eye movements and vestibular optokinetic interaction.

**SUPRANUCLEAR GAZE DISORDERS**

Interruption of the saccadic and pursuit pathways from the cerebral hemispheres before they reach the ocular motor generators in the brainstem will result in loss of voluntary eye movements, but spare reflex movements such as vestibulo-ocular and optokinetic responses and, depending on the level of the lesion, Bell's phenomenon\(^1\). Such findings comprise a supranuclear gaze palsy and occurs classically in progressive supranuclear palsy (PSP), as well as in a variety of disorders discussed below (Table 1)\(^1\).\(^2\). Bilateral lesions of the fronto-mesencephalic pathways cause loss of horizontal saccades in both directions, impair vertical saccades (particularly upward), but spare pursuit, VORs and the slow phases of OKN (global saccadic palsy).

**METABOLIC DISORDERS**

Inborn errors of metabolism are a group of inherited diseases that cause abnormalities in cellular biochemistry. They are best considered in terms of the affected subcellular organelle - lysosomes, peroxisomes, and mitochondria - but this is not always known. Metabolic diseases that affect the nervous system usually cause one of four clinical syndromes: 1) acute neonatal encephalopathy, 2) recurrent encephalopathy of childhood, 3) mental retardation, or 4) progressive neurological impairment. In general, the mechanisms by which inborn errors of metabolism cause disease are by the abnormal synthesis or catabolism of metabolic substrates, the production of abnormal cell proteins, the excessive accumulation of material within cells, and disturbances of oxidative metabolism\(^3\).

Most enzyme defects are inherited as autosomal recessive or x-linked traits, while abnormalities of structural proteins are usually transmitted by autosomal dominant inheritance. Disorders of oxidative function, which have the highest frequency of extraocular motility disturbances, may be transmitted by maternal mitochondrial DNA or by Mendelian inheritance. The metabolic disorders that cause ophthalmoplegia are summarized in Table 1.

**LYSOSOMAL STORAGE DISORDERS**

**Gangliosidoses**

Tay Sachs disease (Infantile GM2 gangliosidosis) is an autosomal recessive disorder caused by hexosaminidase A deficiency. It is ten times more common in Ashkenazi Jews than gentiles\(^4\). The clinical features are progressive visual loss and psychomotor retardation, a macular cherry red spot, macrocephaly beginning during the second year, and seizures. Most children die by 5 years. Affected children may have horizontal ocular deviation as an early feature, and later lose "exploratory" saccades followed by loss of pursuit and optokinetic responses, then voluntary saccades and finally vestibulo-ocular reflexes. Late in the disease, the patients may have tonic downward ocular deviation. Vertical vestibulo-ocular reflexes are lost before horizontal vestibulo-ocular reflexes. Loss of pursuit and optokinetic responses before loss of saccades is unusual but occurs in these patients perhaps because of loss of visual feedback as a result of damage to the retinal ganglial cells\(^5\). The diagnosis is established by showing decreased hexosaminidas A activity in leukocytes.

Juvenile GM2 gangliosidosis, a rare variant of Tay Sachs that mimics juvenile spinal muscular atrophy, is caused by deficiency of N-acetyl-beta-hexosaminidase. Age at onset is between 2 to 6 years. Features include ataxia, neurogenic weakness, intellectual impairment, ocular dysmetria and horizontal supranuclear palsy, dysarthria and myoclonus, sensory neuropathy and internuclear ophthalmoplegia. No treatment is available but heterozygote detection and prenatal diagnosis is possible.

Adult-onset GM2 Gangliosidosis is caused by partial hexosaminidase A deficiency. The clinical syndrome is similar to spinocerebellar atrophy or multiple system atrophy. The clinical features are cerebellar disturbances, peripheral neuropathy, psychosis, supranuclear gaze palsies, and internuclear ophthalmoplegia\(^6\).\(^7\). Vertical gaze is affected more than horizontal gaze. The diagnosis is established by measurement of plasma, leukocyte, or fibroblast hexosaminidase activity.

**Sphingolipidoses**

Gaucher's Disease Type II (Glucosylceramide Lipidosis) is caused by a deficiency of the enzyme glucocerebrosidase and is transmitted by autosomal recessive inheritance. Type I, the most common form of Gaucher's disease, does not affect the nervous system. Infants with Gaucher's disease type II usually have symptoms of neurovisceral dysfunction before 6 months of age, and frequently before 3 months of age. The initial symptoms are motor regression and cranial nerve dysfunction. Children are first hypotonic and then spastic. Head retraction is an early and characteristic sign that probably is due to meningeal irritation. Strabismus and horizontal supranuclear gaze palsies are typical. Death usually occurs during the first year.
and always by the second. The presence of Gaucher cells in the reticuloendothelial system and and deficient glucocerebrosidase activity in hepatocytes or leukocytes establishes the diagnosis. Enzyme replacement therapy is available by the intravenous administration of macrophage-targeted human placental glucocerebrosidase but is limited by its high cost.

**Gaucher’s Disease Type III.** A late-onset variant also caused by deficiency of the enzyme glucocerebrosidase is transmitted by autosomal recessive inheritance. Age at onset ranges from early childhood to adult life. Hepatosplenomegaly usually precedes neurologic deterioration. The most common neurologic manifestations are seizures and mental retardation. Mental regression varies from mild memory loss to severe dementia. Myoclonus and myoclonic seizures develop in many patients. Some combination of spasticity, ataxia, and cranial nerve dysfunction may be present as well as a horizontal supranuclear gaze palsy which progresses to a global supranuclear gaze palsy. Splenectomy may improve the hematological abnormalities but may make the neurologic and skeletal disease worse.

**Niemann-Pick disease type C (NPC)** is one of the most well known metabolic disorders that causes a supranuclear gaze palsy. It is also known as the DAF syndrome (downgaze palsy, ataxia, athetosis and foamy macrophages) a term coined by Cogan's group in 1981. The gene defect, located on chromosome 18 and transmitted by autosomal recessive inheritance, causes a flaw in lipid metabolism resulting in accumulation of unesterified cholesterol in lysosomes. Some now classify NPC as a Cholesterol storage disease. NPC differs biochemically and genetically from the primary sphingomyelinosis Niemann-Pick disease, types A and B. Three phenotypes are distinguished by age at onset and predominant symptoms: (1) The early-onset form is characterized by organomegaly and rapidly progressive hepatic dysfunction during the first year, often in the first 6 months. Developmental delay is noted during the first year, and neurologic deterioration (ataxia, vertical gaze palsy, dementia) occurs between 1 and 3 years of age. (2) The delayed-onset form is more common than the other two and has the most stereotyped clinical features. Early development is normal. Cerebellar ataxia or dystonia develop at 3 years, and vertical gaze palsy and cognitive difficulties follow at 6 years. Vertical gaze palsies are particularly uncommon in children and always suggests Niemann-Pick disease type C. Progressive neurologic degeneration is relentless, dementia, seizures, spasticity and cause severe disability during the second decade. Organomegaly is seldom prominent early in the course. (3) The late-onset form begins in adolescence or adult life and is similar to the delayed-onset form except that the progression is considerably slower. Occasionally have retinal crystalloid opacities may be seen forming a halo around the macula.

The diagnosis is made by demonstrating decreased cholesterol esterification in skin fibroblasts, as well as by demonstrating two types of unusual storage cells in the bone marrow (one is large and vacuolated and the other small; both contain dark granular material). Unlike Niemann-Pick disease, types A and B, the activity of sphingomyelinase in leukocytes and fibroblasts is normal or slightly decreased. Treatment is mainly supportive: A regimen of lovastatin, cholestyramine, and niacin lower plasma and hepatic lipid concentrations but its effect on neurologic progression is not known.

**Pelizaeus-Merzbacher’s disease** is an X-linked recessive dysmyelination disorder caused by defective biosynthesis of myelin proteolipid protein. The clinical picture is that nystagmus, titubation, ataxia, involuntary movements, spasticity and psychomotor retardation. Optic atrophy and seizures are late findings. When the onset is in the neonatal period death usually occurs by 5-7 years; when the onset is after one month, survival to adulthood is common. Early on the nystagmus may be misdiagnosed as spasms nutans and the neurological syndrome as cerebral palsy. Elliptical pendular nystagmus with a larger vertical component, and superimposed or interposed upbeat nystagmus, is said to be characteristic of Pelizaeus-Merzbacher disease. Such nystagmus may be difficult to see with the naked eye, but detected more easily with an ophthalmoscope. Both horizontal and vertical saccades and pursuit are impaired, and some patients appear to have ocular motor apraxia.

2. **THE AMINOACIDOPATHIES**

**Maple Syrup Urine Disease (MSUD)** is a branched-chain aminoaciduria caused by deficiency of a specific ketoacid dehydrogenase and is transmitted by autosomal recessive inheritance. Three phenotypes are recognized: 1) the classic form is characterized by neonatal seizures and encephalopathy; 2) the intermediate causes progressive mental retardation, and 3) the intermittent form has episodes of ataxia, irritability and lethargy provoked by intercurrent illness or stress. The neonatal form is associated with complete absence of enzyme and the other forms with partial deficiency.

Affected newborns with the classic form may have mild ptosis, ophthalmoplegia with predominant loss of upgaze, and bilateral internuclear ophthalmoplegia. Ocular flutter may also occur. The ocular motor findings are believed to be caused by upper brainstem (nuclear and paranuclear) rather than supranuclear involvement. One newborn with clinical features of classic MSUD developed bilateral internuclear ophthalmoplegia, limited upgaze, and ocular flutter at part of the initial presentation. The vestibulo-ocular reflexes did not overcome the horizontal ocular motility disturbance.
High levels of leucine were identified in the serum but valine and isoleucine were normal. This may suggest that hyperleucinemia is responsible for the neurological disturbances of MSUD.

Definitive diagnosis requires the identification of branched chain keto acids and amino acids in blood and urine. Treatment is dietary with the addition of thiamine.

Glycine Encephalopathy (Nonketotic Hyperglycinemia) is caused by deficiency of the glycine cleaving enzyme and transmitted by autosomal recessive inheritance. Onset is usually in the first week. The clinical features are progressive lethargy, seizures and episodic hiccuping. Posis, bilateral internuclear ophthalmoplegia, and severe limitation of upgaze may occur during the first week and complete bilateral external ophthalmoplegia by the second week. Ocular motor involvement is believed to be in the brainstem. The diagnosis of glycine encephalopathy should be suspected in newborns with encephalopathy, seizures, hiccups, apneic spells, and incomplete development of the corpus callosum. Diagnosis is confirmed by showing higher concentrations of glycine in the cerebrospinal fluid than the blood (may be normal if the child is not feeding). Treatment is not satisfactory and includes the use of sodium benzoate and dextromethorphan to lower blood glycine concentrations.

3. DISORDERS OF LIPOPROTEIN METABOLISM

Abetalipoproteinemia (Bassen-Kornzweig's syndrome-1951), a low density lipoprotein deficiency, is transmitted by autosomal recessive inheritance. The main clinical features are abetalipoproteinemia, acanthocytosis, ataxia and retinitis pigmentosa. Affected individuals may develop a progressive ophthalmoplegia with bilateral internuclear ophthalmoplegia and restriction of upgaze. Peripheral neuropathy may also occur. Treatment is with DL-alpha-tocopherol and vitamins A and E.

Tangier Disease (High Density Lipoprotein Deficiency) is transmitted by autosomal recessive inheritance. The main features are large yellow tonsils, peripheral neuropathy, alaphalipoprotein deficiency, hepatosplenomegaly, and lymphadenopathy. Posis and ophthalmoplegia may also occur. Treatment is not available.

4. DISORDERS OF METAL METABOLISM

Hepatolenticular Degeneration (Wilson's Disease) is caused by a disturbance in the biliary excretion of copper and its incorporation into ceruloplasmin. Symptoms result from the accumulation of copper in liver and brain. A Kayser-Fleischer ring in the cornea, caused by accumulation of copper in Descemet's membrane, is virtually always present in patients with neurologic complications.

Eye movement abnormalities are unusual in Wilson's disease but saccades may be lost while smooth pursuit is preserved. A patient was reported with slow voluntary horizontal saccades, a supranuclear upgaze palsy and limited downgaze. The clinical features of Wilson's disease may suggest a psychiatric disorder or multiple sclerosis.

5. PEROXISOMAL DISORDERS

Peroxisomal disorders, which are mainly characterized by the abnormal metabolism of very-long chain fatty acids, are not known to cause gaze palsies; however, some cases of Joubert's syndrome may result from peroxisomal dysfunction.

Joubert's syndrome is an autosomal recessive disorder of cerebral malformations characterized by cerebellar vermal agenesis, severe developmental delay, episodic tachypnea and apnea, nystagmus, congenital retinopathy and supranuclear horizontal and vertical gaze palsies.

6. MITOCHONDRIAL CYTOPATHIES

Mitochondrial disorders, with the exception of some patients with Leigh's disease, rarely affect vertical gaze selectively. Mitochondrial disorders that affect ocular motility include Kearns syndrome, Pearson's syndrome, some forms of Leigh's disease, the CPEOs and Dominantly Inherited Mitochondrial Myopathy with Multiple Mitochondrial-DNA Deletions (nuclear mitochondrial-DNA signalling defects).

These disorders are discussed in the section on "Ocular Muscle Disease".

7. MISCELLANEOUS

Kernicterus: The triad of athetosis, sensory neural deafness and impaired upgaze should suggest CNS damage as a result of neonatal jaundice. The upgaze palsy is usually supranuclear and can be overcome by the vertical vestibulo-ocular reflex and Bell's phenomenon in most patients. Horizontal saccades may also be pathologically slow.

Deficiency disorders: Vitamin B12 deficiency may cause a supranuclear upgaze palsy which responds to treatment. Jejunooileal bypass may cause a reversible vertical gaze palsy. Wernicke's encephalopathy and infantile beri beri can cause gaze palsies. Vitamin E deficiency caused by malabsorption may be associated with spinocerebellar degeneration and ophthalmoplegia.

Drug intoxication: Anticonvulsant toxicity and anesthesia commonly cause gaze palsies and internuclear ophthalmoplegia but are usually associated with impaired consciousness. Edis and Mastalgia described a patient with a vertical gaze palsy as a result of barbiturate intoxication. The patient was drowsy, had a full range of horizontal eye movements with gaze evoked nystagmus, absent upgaze, absent convergence and normal downgaze. Upward vestibulo-ocular reflex and Bell's phenomenon were absent. The patient recovered spontaneously within a few days.

Congenital Vertical Ocular Motor Apraxia is rare condition and must be distinguished from metabolic and...
degenerative disorders, such as the neurovisceral lipidosis which cause progressive neurological dysfunction, and from stable disorders such as birth injury, perinatal hypoxia, and Leber's congenital amaurosis.

**Ataxia telangiectasia**, an autosomal recessive disorder characterized by multiple pulmonary infections, progressive ataxia and oculo-cutaneous telangiectasia\(^{15}\), may be associated with loss of voluntary eye movements and the fast phases of vestibular nystagmus. Both horizontal and vertical eye movements may be affected, pursuit may be affected later but the vestibulo-ocular reflexes usually persist. Choreoathetosis and myoclonus are also late features. Similar ocular motor disorders occur in children with Pelizaeus-Merzbacher disease, ataxia telangiectasia, Cockayne's syndrome and succinimide semialdehyde dehydrogenase deficiency\(^{40,41}\) and an autosomal recessive disorder "ataxia-ocular apraxia" which mimics ataxia telangiectasia\(^{42,43}\).

**Tonic Upward Deviation of Gaze** (forced upgaze), a rare sign, is seen in unconscious patients and must be distinguished from oculogyric crises, petit mal seizures, and psychogenic coma. Sustained upgaze may follow diffuse brain injury caused by hypotension, cardiac arrest, or heatstroke: some of these patients later develop myoclonic jerks and large-amplitude downbeat nystagmus; their prognosis is extremely poor. Autopsy evidence usually demonstrates cerebral and cerebellar hypoxic damage, with relative sparing of the brainstem\(^{44}\). Rarely, tonic upward gaze deviation may be psychogenic but can be overcome, in fact cured, by cold caloric stimulation of the external auditory meatus.

**Benign paroxysmal tonic upward gaze** may occur in young children in association with ataxia and downbeat nystagmus on attempted downgaze\(^{35}\) the duration of deviation is variable (seconds to hours) occurring frequently throughout the day. It has been associated with cystic fibrosis\(^{46}\). This disorder, which usually starts in the first year of life and lasts about two years, has no known cause; there is no evidence to support that the episodes are seizures or oculogyric crises. The condition is reminiscent of the intermittent or "periodic ataxias" which may respond to the appropriate therapy or medication such as acetazolamide and valproic acid\(^{47}\). Tonic upgaze may be seen in normal infants during the first months of life\(^{48}\).

**Tonic Downward Deviation of Gaze** (forced downgaze) is usually associated with impaired consciousness in patients with medial thalamic hemorrhage, acute obstructive hydrocephalus, severe metabolic or hypoxic encephalopathy, or massive subarachnoid hemorrhage. The eyes may also be converged as if looking at the nose. Tonic downward gaze deviation may also occur in psychogenic illness, especially feigned coma but also can be overcome by caloric stimulation.

In otherwise healthy neonates, downward deviation of the eyes while awake, but with preserved VORs, may occur as a transient phenomenon. Tonic vertical deviation as a result of ictal activity is rare.

**Paroxysmal ocular downward deviation** which lasts seconds and occurs in neurologically impaired infants with poor vision\(^{48}\) may also be seen in preterm infants with bronchopulmonary dysplasia but subsequent normal development\(^{49}\).

**Oculogyric Crisis** are spasmodic conjugate ocular deviations, usually in an upward, sometimes lateral, and occasionally downward direction. They occurred in the late stages of postencephalitic Parkinson's disease, following the 1918 influenza epidemic, but now are most frequently caused by neuroleptic medication, particularly haloperidol. They may also occur in patients with neurosyphilis, carbamazepine or lithium carbonate toxicity, head injury and in the early stages of autosomal dominant "rapid onset dystonia-parkinsonism"\(^{50}\). A typical attack or crisis lasts about two hours, during which the eyes are tonically deviated upward, repetitively, for periods of seconds to minutes. The spasms may be preceded or accompanied by disturbing emotional symptoms, including anxiety, restlessness, compulsive thinking, and sensations of increased brightness or distortions of visual background. The patient may be able to force the eyes back to the primary position temporarily using voluntary saccades, optokinetic tracking, head rotation, or blinks. Electroencephalograph (EEG) recordings during the attacks show no epileptiform activity\(^{51}\). The eyelids are usually open, although they may rhythmically jerk sometimes with twitching of the orbicularis oculi. In patients with Parkinson's disease, blepharospasm may also be present. The pupils are infrequently involved, with mydriasis or anisocoria. Attacks may be precipitated by excitement. They should be differentiated from benign paroxysmal tonic upward gaze. The emotional reaction preceding the crisis suggests a chemical imbalance in the limbic-vertical ocular motor connections\(^{51}\). Treatment for oculogyric crises includes L-dopa and high-dose trihexyphenidyl.

**WHIPPLE'S DISEASE**

Although Whipple's disease is caused by an infection, it include it here because of the importance of recognizing a treatable disease. The classic presentation is that of weight loss, gastrointestinal symptoms particular chronic diarrhea, arthralgias and lymphadenopathy. The most frequent central nervous system complications include progressive dementia, somnolence, supranuclear gaze palsies, ataxia and myoclonus. Occasionally intraocular complications may occur and include uveitis, vitreitis, vitreous hemorrhage, retinal hemorrhage, optic disc swelling and retinal vasculitis\(^{52}\). The diagnosis is made by identification of PAS positive "foamy" macrophages on small intestinal biopsy. More recently, molecular analysis of peripheral blood has
been helpful. Treatment is with antibiotics. It is important to be aware that there is a pure cerebral form of the disease. The combination of somnolence and unexplained supranuclear gaze palsies should arouse suspicion. To date the finding of "oculo-masticatory myorhythmia", a syndrome in which pendular ocular vergence oscillations coexist with rhythmic contraction of the masticatory muscles, is pathognomonic for Whipple's disease.

**SLOW SACCADES**

Disorders which cause slow saccades are listed in Table 2.

---

**TABLE 1**

**VERTICAL OCULAR MOTILITY DISORDERS MAY RESULT FROM DYSFUNCTION OF:**

1. **Ocular muscle**
   - Myopathies
     - Congenital myopathy
     - Dystrophy
     - Inflammation
     - Mitochondrial cytopathy
   - Mechanical restriction
     - Congenital familial fibrosis
     - High myopia (large globes - mechanical restriction)
   - Infiltrative disorders (thyroid, amyloid, metastases, cystinosis)
   - Metabolic and toxic (act at multiple sites, e.g. anticonvulsants, porphyria)
   - Trauma (orbital entrapment)
   - Vitamin E deficiency (associated with malabsorption)

2. **Neuromuscular Junction**
   - Myasthenia gravis
   - Toxins (e.g. botulism, organophosphates)
   - Eaton-Lambert syndrome (rarely affects eyes)

3. **Ocular motor nerves**
   - Porphyria (cutanea tarda?)

4. **Central nervous system disorders**
   - Nuclear and paranuclear centers in the brainstem
     - Brainstem injury (MS, vascular, encephalitis, neoplastic, paraneoplastic, toxins)
     - Familial congenital gaze palsy
     - Joseph's disease
     - Leigh's disease
     - Maple syrup urine disease
     - Mobius and Duane's syndromes
     - Spinocerebellar degeneration
     - Vitamin E deficiency
     - Internuclear ophthalmoplegia
     - One-and-a-half syndrome
   - Prenuclear:
     - Monocular 'supranuclear' elevator palsy
     - Ocular tilt reaction
     - Skew deviation
   - Supranuclear (predominantly horizontal)
     - Congenital ocular motor apraxia
     - Acutely, following hemispheric stroke
     - Gaucher's disease (type 2 and 3)
     - Ictal (transient, adverse)
     - Post-ictal (transient, ipsiversive)
     - Paraneoplastic (prostatic adenocarcinoma)
   - Supranuclear (predominantly vertical)
     - Congenital ocular motor apraxia (rare)
     - ALS (rare, V-H)
     - Autosomal dominant Parkinsonian-dementia complex with pallidopontonigral degeneration (dementia, dytonia, frontal and pyramidal signs, urinary incontinence)
     - B-12 deficiency (U-D)
     - Cerebral amyloid angiopathy with leukoencephalopathy
Dentatorubral-pallidolysian atrophy (autosomal dominant, dementia, ataxia, myoclonus, choreoathetosis)
Diffuse Lewy body disease (ophthalmoplegia may be global)
Dorsal midbrain syndrome
Familial Creutzfeld-Jakob disease (U>D)
Familial paralysis of vertical gaze
Fisher's syndrome
Gerstmann-Straussler-Scheinker disease (U=D, dysmetria, nystagmus)
Guamanian Parkinson's disease-dementia complex (Lytico-Bodig disease)
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration)
Hydrocephalus (decompensated shunt, untreated)
Joseph's disease
Kernicterus (U>D)
Late onset cerebello-pontomesencephalic degeneration (D>U)
Neurovisceral lipidosis; synonyms: DAF syndrome (downgaze palsy-ataxia-foamy macrophages), cysticlipidosis, Niemann-Pick disease type C (initially loss of downgaze, may become global)
Non-Guamanian (Dominant familial) Parkinson's disease-dementia complex (autosomal recessive)
OPCA (U>D, also slow horizontal saccades)
Pallidoluysian atrophy (dysarthria, dystonia, bradykinesia)
Paraneoplastic
Progressive supranuclear palsy (D>U)
Subcortical gliosis (U>D)
Wilson's disease (also slow horizontal saccades)
Supranuclear (global)
Abetalipoproteinemia
AIDS encephalopathy
Alzheimer's disease
Cerebral adrenoleukodystrophy
Corticobasal ganglionic degeneration
Fahr's disease (idiopathic striato-pallido-dentate calcification)
Gaucher's disease
Hexosaminidase A deficiency
Huntington's disease
Leber's amaurosis
Leigh's disease
Methylmalanohomocysteinuria
Malignant neuroleptic syndrome (personal observation)
Neurosphylis
Opportunistic infections
Paraneoplastic disorders
Parkinson's disease (transient gaze palsy with intercurrent infection)
Pick's disease (impaired saccades)
Progressive encephalomyelitis
Progressive multifocal leucoencephalopathy
Tay-Sachs disease (V>H)
Wernicke's encephalopathy
Whipple's disease (V>H)

EOM = extraocular movements; D = loss of downgaze; U = loss of upgaze; V = loss of vertical gaze;
H = loss of horizontal gaze; Global = loss of horizontal and vertical gaze. (adapted from Lavin and Weissman)
TABLE 2
SLOW SACCADES

AIDS-dementia complex
ALS
Anticonvulsant toxicity (consciousness usually impaired)
Ataxia-telangiectasia
Hexosaminidase A deficiency
Huntington’s disease
Internuclear ophthalmoplegia
Joseph's disease
Lesions of the paramedian pontine reticular formation
Lipid storage diseases
Lytic-Bodig disease
Myotonic dystrophy
Nephropathic cystinosis
Ocular motor apraxia
Ocular motor nerve or muscle weakness
Oliveopontocerebellar degeneration
Progressive supranuclear palsy
Whipple’s disease
Wilson’s disease

(adapted from Lavin and Weissman)
35 Sandik R. Paralysis of gaze as a presenting symptom of vitamin B12 deficiency. Euro Neurol. 23:198-200, 1984