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Ocular Motility Disorders

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Normal individuals and most patients with common concomitant childhood strabismus have full ocular rotations (versions and ductions). This chapter is devoted to some of the more frequently encountered childhood disorders of the central and peripheral nervous systems, neuromuscular junction, and extraocular muscles that appear clinically to have incomitant ocular misalignments.

Analysis of ocular alignment, versions, ductions, forced ductions, and generated force allows the examiner to sort the causes of these limited eye movements into three general categories: (1) neuromuscular dysfunction, (2) restriction of the globe by orbital tissues, and (3) combined neuromuscular dysfunction and restriction (Fig. 5-1). Diagnosis in children is especially challenging because it is rarely possible to clinically test the force generated by extraocular muscle action. A general anesthetic is routinely required to perform forced ductions. It may therefore be necessary to base diagnostic and therapeutic decisions on incomplete clinical information, and the clinician must rely on familiarity with the epidemiologic and clinical characteristics of each disorder.

DISORDERS OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

Eye movement disorders arising from disturbance of the normal neurophysiology may be classified as supra-nuclear, internuclear, or infranuclear.

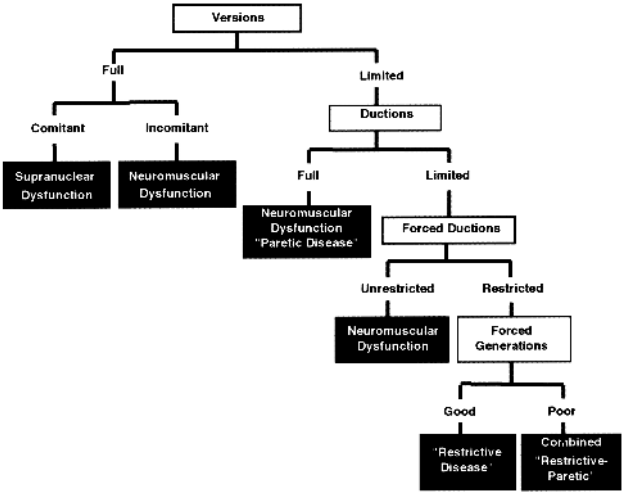


FIGURE 5-1. Clinical evaluation of range of eye movements. Versions and cover test measurements allow the examiner to decide whether the eye movements are normal (no limitation) or limited. Forced duction testing is used to differentiate a restriction (positive resistance to movement of the globe) from a "paresis" (no resistance to movement of the globe).

Supranuclear Eye Movements

Cranial nerves III, IV, and VI serve together with the extraocular muscles as a final mechanism that executes all eye movements. Supranuclear pathways initiate, control, and coordinate various types of eye movements. Several types of eye movements are briefly mentioned here (Table 5-1), but a detailed and lucid synthesis of current concepts of the neural control of eye movements can be found in many other sources.[288]

Physiology and Clinical Assessment

The *vestibular apparatus* drives reflex eye movements, which allow us to keep images of the world steady on the retinas as we move our heads during various activities. The eyes move in the opposite direction to the movement of the head so that they remain in a steady position in space. The semicircular canals are the end organs that provide the innervation to the vestibular

nuclei, which in turn drive cranial nerves III, IV, and VI to compensate for rotations of the head. In contrast, the otoliths respond to linear accelerations of the head and to gravity when the head is tilted. You can easily test the effectiveness of input from the semicircular canals by testing the vestibulo-ocular reflex (VOR). First, hold your head still and observe an object such as your index finger as you move it side to side at about 1 to 3 cycles/s. The image is a blur. However, if you hold your finger steady and rotate your head from side to side at the same frequency, you are able to maintain a clear image.

Several forms of *saccades*, fast eye movements, can be clinically observed. *Voluntary* saccades may be *predictive*, in anticipation of a target appearing in a specific location; *command-generated*, in response to a command such as "look to the right"; *memory-guided*; or *antisaccades*, in which a reflexive saccade to an abruptly appearing peripheral target is suppressed and, instead, a voluntary saccade is generated in the equidistant but opposite direction. *Involuntary* saccades consist of *the fast phase of nystagmus* due to vestibular and optokinetic stimuli; *spontaneous saccades*, providing repetitive scanning of the environment, although also occurring in the dark and in severely visually impaired children; and *reflex saccades*, occurring involuntarily in response to new visual, auditory, olfactory, or tactile cues, suppressable by antisaccades.[83]

TABLE 5-1. Types of Eye Movements.

Type of eye movement	*Function*	*Stimulus*	*Clinical tests*
Vestibular	Maintain steady fixation during head rotation	Head rotation	Fixate on object while moving head; calorics
Saccades	Rapid refixation to eccentric stimuli	Eccentric retinal image	Voluntary movement between two objects; fast phases of OKN or vestibular nystagmus
Smooth pursuit	Keep moving object on fovea	Retinal image slip	Voluntarily follow a moving target; OKN slow phases
Vergence	Disconjugate, slow movement to maintain binocular vision	Binasal or bitemporal disparity; retinal blur	Fusional amplitudes; near point of convergence

OKN, optokinetic nystagmus.

The pathway of saccades originates in the visual cortex and projects through the anterior limb of the internal capsule, through the diencephalon. It then divides into dorsal and ventral pathways, the dorsal limb going to the superior colliculi, and the ventral limb (which contains the ocular motor pathways for horizontal and vertical eye movements) to the pons and midbrain. The superior colliculus acts as an important relay for some of these projections (Fig. 5-2).

The neurons responsible for generating the burst, or discharge, for saccades are classified as excitatory burst neurons (EBN); inhibitory burst neurons (IBN) function to silence activ-

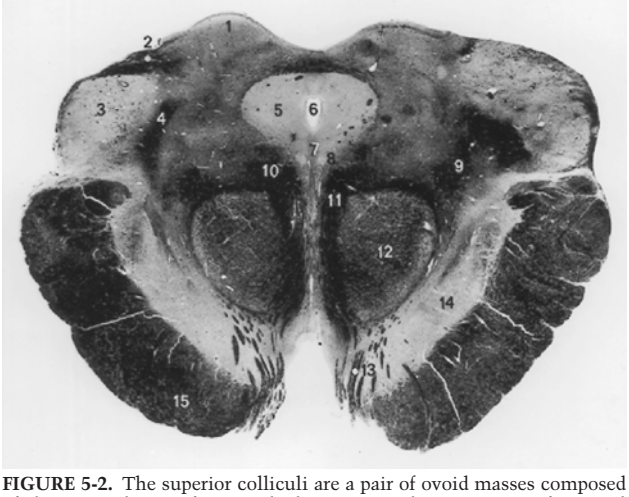


FIGURE 5-2. The superior colliculi are a pair of ovoid masses composed of alternating layers of gray and white matter; they are centers for visual reflexes and ocular movements, and their connections to other structures in the brain and spinal cord are varied and complex. Some of these other structures include the retina, visual and nonvisual cerebral cortex, inferior colliculus, paramedian pontine reticular formation, thalamus, basal ganglia, and spinal cord ventral gray horn. The fibers of the medial longitudinal fasciculus form a fringe on its ventrolateral side: *1*, superior (cranial) colliculus; *2*, brachium of superior (cranial) colliculus; *3*, medial geniculate nucleus; *4*, brachium of inferior (caudal) colliculus; *5*, central gray substance; *6*, cerebral aqueduct; *7*, visceral nucleus of oculomotor nerve (Edinger–Westphal nucleus); *8*, nucleus of oculomotor nerve; *9*, medial lemniscus; *10*, central tegmental tract; *11*, medial longitudinal fasciculus; *12*, red nucleus; *13*, fibers of oculomotor nerve; *14*, substantia nigra; *15*, basis pedunculi.

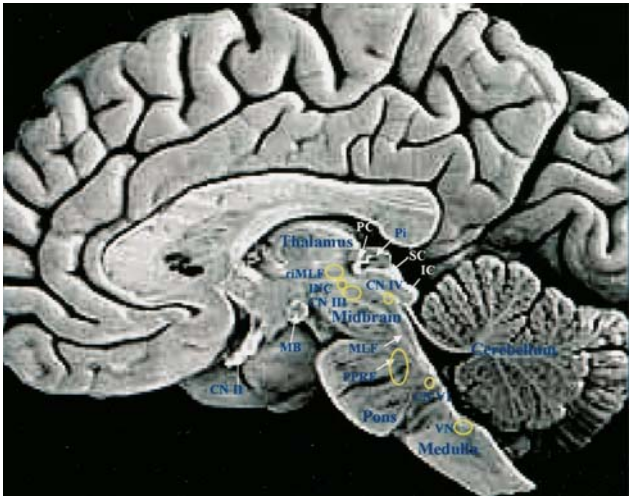


FIGURE 5-3. Brainstem structures controlling eye movements. Parasagittal section of the cerebrum and brainstem shows areas of the ocular motor nuclei and brainstem structures involved with internuclear and supranuclear pathways. *PC*, posterior commissure; *SC*, superior colliculus; *IC*, inferior colliculus; *Pi*, pineal; *riMLF*, rostral interstitial nucleus of the medial longitudinal fasciculus; *INC*, interstitial nucleus of Cajal; *CN III*, *IV*, *VI*, cranial nerve III, IV, VI; *MLF*, medial longitudinal fasciculus; *PPRF*, paramedian pontine reticular formation; *VN*, vestibular nuclei.

ity in the antagonist muscle during the saccade. In the brainstem, the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the pontine paramedian reticular formation (PPRF) provide the saccadic velocity commands, by generating the "pulse of innervation" immediately before the eye movement, to cranial nerves III, IV, and VI. Horizontal saccades are generated by EBN in the PPRF, which is found just ventral and lateral to the MLF in the pons (Figs. 5-3, 5-4, 5-5), and by IBN in the nucleus paragigantocellularis dorsalis just caudal to the abducens nucleus in the dorsomedial portion of the rostral medulla. Vertical and torsional components of saccades are generated by EBN and IBN in the riMLF, located in the midbrain.

Following a saccade, a "step of innervation" occurs during which a higher level of tonic innervation to ocular motoneurons keeps the eye in its new position, against orbital elastic forces

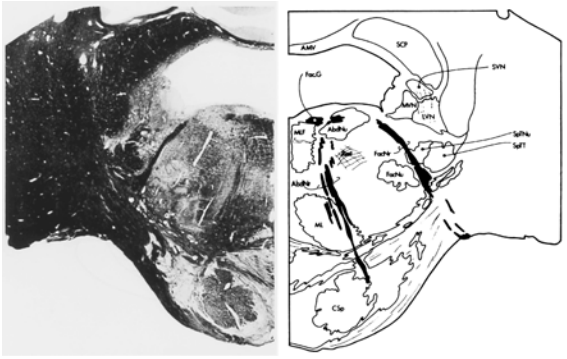


FIGURE 5-4. Transverse section of caudal pons. *AbdNu*, abducens nucleus; *AbdNr*, abducens nerve; *AMV*, anterior medullary velum; *CSp*, corticospinal tract; *FacG*, internal genu of facial nerve; *FacNr*, facial nerve; *FacNu*, facial nucleus; *LVN*, lateral vestibular nucleus; *ML*, medial lemniscus; *MLF*, medial longitudinal fasciculus; *MVN*, medial vestibular nucleus; *RetF*, paramedian pontine reticular formation; *SCP*, superior cerebellar peduncle; *SpTNu*, spinal trigeminal nucleus; *SpTT*, spinal trigeminal tract; *SVN*, superior vestibular nucleus. (Adapted from Haines DE. Neuroanatomy: an atlas of structures, sections, and systems. Baltimore: Urban & Schwarzenberg, 1983, with permission.)

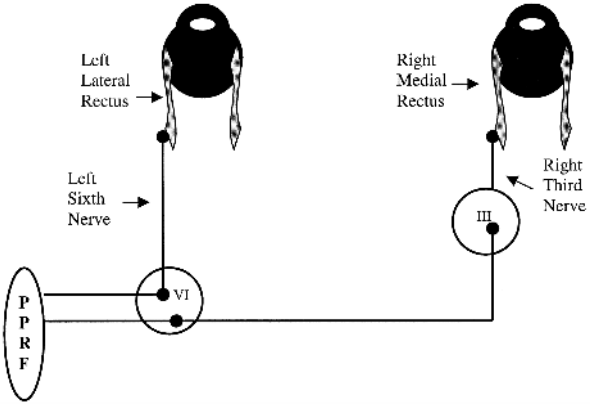


FIGURE 5-5. Schematic of brainstem pathways coordinating horizontal saccades. The PPRF, after receiving input from the ipsilateral cortical centers and superior colliculus, stimulates two sets of neurons in the abducens nucleus: (1) those that send axons to innervate the ipsilateral lateral rectus and (2) those whose axons join the MLF and subsequently activate the medial rectus subnuclei of the contralateral third nerve. *PPRF*, paramedian pontine reticular formation; *VI*, sixth cranial nerve nucleus; *III*, third cranial nerve nucleus.

that would restore the eye to an anatomically "neutral" position. For horizontal saccades, the step of innervation comes from the neural integrator (see following), primarily from the nucleus prepositus–medial vestibular nucleus complex. The eye is held steady at the end of vertical and torsional saccades by the step of innervation provided from the interstitial nucleus of Cajal in the midbrain.[288]

In addition to burst neurons, omnipause neurons, located in the nucleus raphe interpositus in the midline of the pons, between the rootlets of the abducens nerves, are essential for normal saccadic activity. Continuous discharge from omnipause neurons inhibits burst neurons, and this discharge only ceases immediately before and during saccades.[288]

Other burst neurons termed long-lead burst neurons (LLBN) have also been identified that discharge 40 ms before saccades, whereas the previously mentioned burst cells discharge 12 ms before saccades. Some LLBN lie in the midbrain, receiving projections from the superior colliculus and projecting to the pontine EBN, medullary IBN, and omnipause neurons. Other LLBN lie in the nucleus reticularis tegmenti pontis (NRTP), projecting mainly to the cerebellum but also to the PPRF. It appears that LLBN receiving input from the superior colliculus may play a crucial role in transforming spatially coded to temporally coded commands, whereas other LLBN may synchronize the onset and end of saccades.[288]

If an abnormality of saccadic eye movements is suspected, the quick phases of vestibular and optokinetic nystagmus (OKN) can be easily evaluated in infants and young children. To produce and observe vestibular nystagmus, hold the infant at arm's length, maintain eye contact, and spin first in one direction and then in the other. An OKN response can be elicited in the usual manner by passing a repetitive stimulus, such as stripes or an OKN drum, in front of the baby first in one direction and then in another. In addition, reflex saccades are induced in many young patients when toys or other interesting stimuli are introduced into the visual field. Older children are asked to fixate alternately upon two targets so that the examiner can closely observe the saccades for promptness of initiation, speed, and accuracy.

Smooth pursuit permits us to maintain a steady image of a moving object on our foveas and thereby to track moving targets with clear vision. The pathways for smooth pursuit have not been fully elucidated, but it appears that frontal and extrastriate

visual cortex transmits information about the motion of both the target and the eyes to the dorsolateral pontine nuclei (DLPN). This complex signal travels from the DLPN to the cerebellum (paraflocculus, flocculus, and dorsal vermis), and from the cerebellum via the vestibular and fastigial nuclei to its final destination, the ocular motor nerve nuclei III, IV, and VI. Unilateral lesions in the cortex and cerebellum affect smooth pursuit toward the side of the lesion.

Vergences are eye movements that turn the eyes in opposite directions so that images of objects will fall on corresponding retinal points. Two major stimuli are known to elicit vergences: (1) retinal disparity, which leads to fusional vergences, and (2) retinal blur, which evokes accommodative vergences. Convergence of the eyes, accommodation of the lens, and constriction of the pupils occur simultaneously when there is a shift in fixation from distance to near; together, these actions constitute the *near triad*.

The neural substrate for vergence lies in the mesencephalic reticular formation, dorsolateral to the oculomotor nucleus. Neurons in this region discharge in relation to vergence angle (vergence tonic cells), to vergence velocity (vergence burst cells), or to both vergence angle and velocity (vergence burst-tonic cells). Although most of these neurons also discharge with accommodation, experiments have shown that some do remain predominantly related to vergence.[32] Like versional movements, a velocity-to-position integration of vergence signals is necessary. The nucleus reticularis tegmenti pontis (NRTP) has been shown to be important in the neural integration, that is, velocity-to-position integration, of vergence signals. The cells in NRTP that mediate the near response appear to be separate from the cells which mediate the far response. Lesions of NRTP cause inability to hold a steady vergence angle. NRTP has reciprocal connection with the cerebellum (nucleus interpositus) and receives descending projections from several cortical and subcortical structures.[32,288]

The *cerebellum* plays an important role in eye movements. Together with several brainstem structures, including the nucleus prepositus and the medial vestibular nucleus, it appears to convert velocity signals to position signals for all conjugate eye movements through mathematical integration. Because of this, all the structures involved in this process are often referred to as the *neural integrator*. The role of the neural integrator in horizontal saccades was mentioned earlier.

To test the neural integrator clinically, observe fixation, fixation in eccentric gaze, saccades, pursuit, and OKN and also test for rebound nystagmus and VOR cancellation. To examine for rebound nystagmus, first ask the patient to fixate on a target from the primary position, then to refixate on an eccentric target for 30 s, and finally to return to the original primary position target. A patient with rebound nystagmus will show transient nystagmus with the slow phases toward the previous gaze position. To evaluate a child's VOR cancellation, it is easiest to place your hand on top of the patient's head to control both the head and a fixation target that will extend in front of the child's visual axis. You may use a Prince rule with a picture attached. Ask the child to fixate on the target as you passively rotate both the head and the target side to side. If the child is unable to cancel the VOR, you will observe nystagmus instead of the steady fixation expected in normal subjects.

Patients with faulty neural integration may show gaze-evoked nystagmus, impaired smooth pursuit, inability to cancel the vestibulo-ocular reflex during fixation, saccadic dysmetria, defective OKN response, or rebound nystagmus. Most frequently, gaze-evoked nystagmus is seen in conjunction with use of anticonvulsants or sedatives. However, because 60% to 70% of brain tumors in children are subtentorial, acquired eye movement abnormalities suggesting defective neural integration, whether isolated or associated with other neurological deficits, alert the examiner to investigate for a serious central nervous system abnormality.[39,110,132] Structural anomalies affecting the brainstem and cerebellum, for example, the Arnold–Chiari malformation, as well as metabolic, vascular, and neurodegenerative disorders, may also produce abnormalities of the neural integrator.

Reflex eye movements such as the vestibulo-ocular reflex and Bell's phenomenon are easy to elicit clinically and are very useful for gross localization of neural lesions. When both saccades and smooth pursuit in a certain direction are limited, the examiner tries to stimulate eye movements in that same direction with a doll's head (oculocephalic) maneuver, spin test, or forced lid closure. If any of the reflex eye movements are intact, the appropriate cranial nerve(s) and extraocular muscles(s) are clearly functioning, and the defect is necessarily supranuclear.

Disorders of Supranuclear Eye Movements

We focus here on a few disorders in which the normal physiology of supranuclear eye movements, such as saccade, smooth pursuit, vergence, and gaze holding, is disturbed.

Saccade Initiation Failure/Ocular Motor Apraxia

The term *saccade initiation failure* or *ocular motor apraxia* is used to specify impaired voluntary saccades and variable deficit of fast-phase saccades during vestibular or optokinetic nystagmus.[380,447] *Congenital ocular motor apraxia*, first described by Cogan,[96] is a congenital disorder that is characterized by defective horizontal saccades, but it does not represent a true apraxia because reflex saccades may also be impaired. The incidence of this condition is dependent upon the underlying etiology.

Etiology Patients with congenital saccade initiation failure show abnormal initiation and decreased amplitude of voluntary saccades; saccadic velocities in these patients are normal, and fast phases of nystagmus of large amplitude can occasionally be generated, suggesting that the brainstem burst neurons that generate saccades are intact.[288] Acquired saccade initiation failure may be caused by any number of conditions, as listed in Table 5-2. Some of these patients with the acquired type, such as those with Gaucher's disease (type 1 and some type 3 patients), do have abnormal saccadic velocities.[83,194] Although the exact cause or localization of the defect in congenital saccade initiation failure has not been determined, there is strong evidence suggesting that most disorders that cause saccade initiation failure can be localized subtentorially, particularly to the cerebellar vermis.[83,137,196,235,429,450]

Clinical Features The clinical presentation varies with the age and motor development of the child. Infants and children with poor head control who are affected are commonly thought to be cortically blind because the expected visually driven eye movements are not observed.[164,417] In such an infant, demonstration of vertical saccades, vertical pursuit, OKN response in any direction, or normal acuity on visual evoked response testing suggests the diagnosis of saccade initiation failure. However, lack of appropriate response to such testing does not exclude this diagnosis. Another suggestive clinical sign in young infants is an intermittent tonic deviation of the eyes in the direc-

TABLE 5-2. Congenital and Acquired Saccade Initiation Failure (SIF) (Ocular Motor Apraxia).

Classification by cause	*Specific etiologies*
Idiopathic[195]	
Perinatal problems	Cerebral palsy[195]; hypoxia[195]; hydrocephalus[195]; seizures[195]
Congenital malformations	Agenesis of corpus callosum[450]; fourth ventricle dilation and vermis hypoplasia[450]; Joubert's syndrome[282,332]; macrocerebellum[63]; dysgenesis of cerebellar vermis and midbrain[523]; Dandy–Walker malformation[195]; immature development of putamen[472]; heterotropia of gray matter[472]; porencephalic cyst[195,515]; hamartoma near foramen of Munro[515]; macrocephaly[195]; microcephaly[147,195]; posterior fossa cysts[375]; chondrodystrophic dwarfism and hydrocephalus[98]; encephalocele[375]; occipital meningocele[11]; COACH syndrome[162] (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, hepatic fibrocirrhosis)
Neurodegenerative conditions with infantile onset of SIF	Infantile Gaucher's disease (type 2, 3)[85,100,507]; Gaucher's disease type 2[56,497]; Pelizaeus–Merbacher disease[195]; Krabbe's leukodystrophy[195]; proprionic academia[195]; GM_1 gangliosidosis[195]; infantile Refsum's disease[195]; 4-hydroxybutyric aciduria[147,397]
Neurodegenerative conditions with later onset of SIF	Ataxia telangectasia[473,499,532]; spinocerebellar degenerations[7,21,36,228,270,369,512]; juvenile Gaucher's disease (type 3)[194]; Huntington's disease[31,471]; Hallervorden–Spatz disease[17]; Wilson's disease[265]
Acquired disease	Postimmunization encephalopathy[195,335]; herpes encephalitis[195]; posterior fossa tumors[195,298,477,536,540]
Other associations	Alagille's syndrome[12]; Bardet–Biedl syndrome[284]; carotid fibromuscular hypoplasia[195]; Cockayne's syndrome[147]; Cornelia de Lange syndrome[195]; juvenile nephronophthisis[129]; Lowe's syndrome[181]; neurofibromatosis type 1[168]; orofacial digital syndrome[305]; X-linked muscle atrophy with congenital contractures[524]

Source: Adapted from Cassidy L, Taylor D, Harris C. Abnormal supranuclear eye movements in the child: a practical guide to examination and interpretation. Surv Ophthalmol 2000;44:479–506, with permission.[83]

tion of slow-phase vestibular or optokinetic nystagmus; in these infants, fast-phase saccades may be impaired, again confounding our definition of oculomotor apraxia.[288]

Natural History With time, often by 4 to 8 months of age, the child develops a striking stereotypical "head-thrusting" behavior to refixate. First, the eyelids blink ("synkinetic blink")

and the head begins to rotate toward the object of interest. Next, the head continues to rotate past the intended target, allowing the tonically deviated eyes, which are now in an extreme contraversive position, to come into alignment with the target. Finally, as the eyes maintain fixation, the head rotates slowly back so that the eyes are in primary position. This apparent use of the VOR to refixate continues for several years, but with increasing age, patients demonstrate less prominent head thrusting and may even be able to generate some saccades although these are abnormal.[97,542]

In some infants, generalized hypotonia may be associated. This hypotonia seems to be more pronounced in boys and improves with increasing age. These babies later demonstrate the motor delay, incoordination, and clumsiness that have been noted in the literature.[153,395]

Clinical Assessment The parents of children are asked about any associated developmental abnormality. A complete ophthalmic examination is performed to rule out any strabismus or amblyopia, as strabismus has been reported in 22% of these patients in one series.[195] Vision, electroretinogram (ERG), and visual evoked potential (VEP) are normal in the congenital saccade initiation failure patients.[164,451] Any coexistent abnormal vision, nystagmus, or abnormal ERG or VEP suggests associated disease.[451] Neurological abnormalities or dysmorphic features are further investigated by the appropriate subspecialists. A brain MRI is necessary for any suspected neurological disorder, to look for any midline malformation, particularly around the fourth ventricle and cerebellar vermis.[83]

Systemic Associations Significant structural abnormalities of the central nervous system (CNS) may be associated, such as lipoma[477] or brainstem tumor.[540] Joubert's syndrome is associated with cerebellar hypoplasia and agenesis of the corpus callosum.[282] A neuroradiologic correlation has been made in children with saccade initiation failure, in which 61% of 62 children had abnormal scans, primarily the brainstem and cerebellar vermis; however, significant abnormalities in the cerebral cortex and basal ganglia were also found.[450]

Gaucher's disease,[185,197] ataxia telangiectasia[7,473] and its variants, and Niemann–Pick variants[100] may also present with the inability to generate saccades as well as blinking and head thrusting before refixation. Unlike congenital saccade initiation

failure, these disorders generally involve vertical as well as horizontal saccades and, of course, eventually manifest systemic signs.

Early-onset vertical saccade initiation failure has been observed in children with lesions at the mesencephalic–diencephalic junction, presumably infarcts resulting from perinatal hypoxia.[135,219]

Inheritance Occasional familial occurrence,[196,345,387,398,501] increased frequency in males, and occurrence in monozygotic twins[67] suggest a genetic process in some cases. Association with nephronophthisis has been described in two patients, each of whom exhibited deletions on chromosome 2q13.[55]

Treatment No treatment is available for congenital saccade initiation failure, but associated strabismus is treated accordingly.

Prognosis The visual and clinical prognosis of those patients with the congenital type is good. Many can adapt over time to allow gaze shifts with less head thrusting and can even generate some saccades, albeit still abnormal.[97,542]

Induced Convergence Retraction/Parinaud or Dorsal Midbrain Syndrome

Lesions of the posterior commissure in the dorsal rostral midbrain (see Fig. 5-2) may result from many disease processes and can affect a variety of supranuclear mechanisms, including those that control vertical gaze, eyelids, vergence, fixation, and pupils. Other terms such as *pretectal syndrome*, *Koerber–Salus–Elschnig syndrome*, *Sylvian aqueduct syndrome*, *posterior commissural syndrome*, and *collicular plate syndrome* all refer to this condition.

Incidence A report of 206 patients with pretectal syndrome in one neurologist's practice at a general hospital in southern California indicated the incidence to be 2.3% of all patients examined by this neurologist in an 18-year period.[255] Of these 206 patients, 71 exhibited induced convergence retraction.

Etiology and Systemic Associations The pretectum was confirmed as the critical structure that is affected in this disorder, investigated clinicopathologically in humans[91] and experimentally in monkeys.[371,372] Also, isolated interruption of the

TABLE 5-3. Causes of Childhood Dorsal Midbrain Syndrome.

Classification by cause	*Specific etiologies*
Tumor	Pineal germinoma, teratoma and glioma; pineoblastoma; others[386]
Hydrocephalus	Aqueductal stenosis with secondary dilation of third ventricle and aqueduct, or with secondary suprapineal recess compressing posterior commissure,[89,366] commonly caused by cysticercosis in endemic areas
Metabolic disease	Gaucher[100,492]; Tay–Sach; Niemann–Pick[154]; kernicterus[214]; Wilson's disease[265]; others
Midbrain/thalamic damage	Hemorrhage; infarction
Drugs	Barbiturates[138]; carbamazepine; neuroleptics
Miscellaneous	Benign transient vertical eye disturbance in infancy; trauma; neurosurgery[445]; hypoxia; encephalitis; tuberculoma; aneurysm[102]; multiple sclerosis

posterior commissure in humans produces the entire syndrome of upward gaze palsy, pupillary light–near dissociation, lid retraction, induced convergence retraction, skew deviation, and upbeat nystagmus.[251] Among the many underlying causes of this condition are hydrocephalus, stroke, and pinealomas. Table 5-3 lists other reported etiologies and systemic associations.

Clinical Features and Assessment The constellation of deficits are (1) vertical gaze palsy, (2) light–near dissociation of the pupils, (3) eyelid retraction (Collier's sign), (4) disturbance of vergence, (5) fixation instability, and (6) skew deviation.

Limitation of upward saccades is the most reliable sign of the convergence retraction. Upward pursuit, Bell's phenomenon, and the fast phases of vestibular and optokinetic nystagmus may also be affected either at presentation or with progression of the underlying process. It is rare for upgaze to be unaffected. Pathological lid retraction and lid lag are also common (Collier's sign).

When the patient attempts upward saccades, a striking phenomenon, convergence and globe retraction, frequently occurs; this is not true nystagmus, despite the common description of this clinical finding as convergence-retraction nystagmus, because there is no true slow phase. This action is best elicited with down-moving OKN targets because each fast phase is replaced by a convergence-retraction movement. Cocontraction of the extraocular muscles has been documented during this convergence-retraction jerk.[161]

Unlike the pathways from upward saccades, the pathways for downward saccades do not appear to pass through the posterior commissure (Figs. 5-3, 5-6). Perhaps because of this, disturbances of downgaze are not as predictable or uniform. Usually down-going saccades and pursuit are present, but they may be slow. Sometimes, especially in infants and children, there is a tonic downward deviation of the eyes that has been designated the "*setting sun*" sign, and down-beating nystagmus may also be observed. The "setting sun" sign may also be seen in children with hydrocephalus.

Convergence spasm may occur during horizontal saccades and produce a "pseudoabducens palsy" because the abducting eye moves more slowly than the adducting eye.[113] This phenomenon can cause reading difficulties early in the course of dorsal midbrain syndrome because it provides an obstacle to refixation toward the beginning of a new line of text. Indeed, older children may present with numerous pairs of corrective

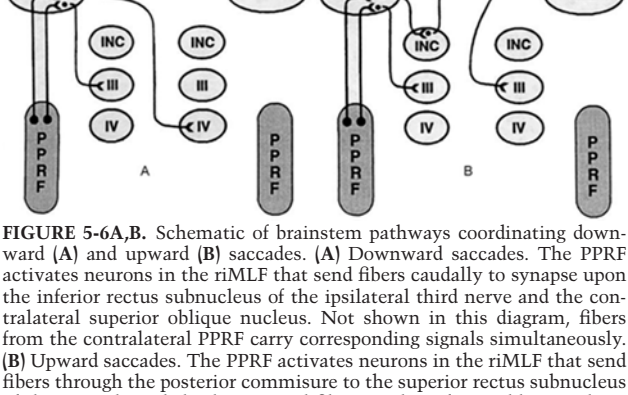


FIGURE 5-6A,B. Schematic of brainstem pathways coordinating downward **(A)** and upward **(B)** saccades. **(A)** Downward saccades. The PPRF activates neurons in the riMLF that send fibers caudally to synapse upon the inferior rectus subnucleus of the ipsilateral third nerve and the contralateral superior oblique nucleus. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. **(B)** Upward saccades. The PPRF activates neurons in the riMLF that send fibers through the posterior commisure to the superior rectus subnucleus of the contralateral third nerve and fibers to the inferior oblique subnucleus of the ipsilateral third nerve. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. *riMLF*, rostral interstitial nucleus of the medial longitudinal fasciculus; *INC*, interstitial nucleus of Cajal; *III*, third cranial nerve nucleus; *IV*, fourth cranial nerve nucleus; *PPRF*, paramedian pontine reticular formation.

spectacles that have been prescribed due to their "vague" complaints about reading and other near work. In other patients complaining of difficulties with near vision, convergence may be paralyzed. "Tectal" pupils are usually large and react more poorly to light than to near, and anisocoria is not uncommon.

All children with convergence retraction deserve thorough, prompt neurological and neuroradiologic evaluation because timely intervention may be decisive. The natural history of this disorder is dependent on the underlying etiology.

Treatment The underlying medical cause requires investigation and primary treatment. Once the condition is stable for a period of time, from 3 to 12 months, surgery has been performed with some success. In addition to treating the coexistent diplopia from skew deviation or horizontal strabismus, which may be surgically corrected, the anomalous head posture from defective vertical gaze may also be treated by inferior rectus recession or vertical transposition of horizontal recti during simultaneous horizontal strabismus correction.[74] Faden operation (posterior fixation suture, or retroequatorial myopexy) on both medial recti to control convergence spasms and bilateral superior rectus resection to alleviate the anomalous head posture have also been reported.[465]

Prognosis The medical prognosis is dependent upon the underlying etiology. In the aforementioned review of 206 patients, only 20 patients died: 11 of tumors, 7 after strokes, and 1 with transtentorial hernation with tuberculous abscess. The good prognosis in this series may have been skewed by the preponderance of patients with cysticercal hydrocephalus.[255]

The prognosis of strabismus surgery in all eviating anomalous head posture and diplopia was good in all three patients in one study after a minimum of 6 months follow-up.[74] In another report, head posture and ocular motility improved beyond expectation and remained satisfactory after a minimum of 1 year follow-up.[465]

Transient Vertical Gaze Disturbances in Infancy

Vertical gaze abnormalities may be benign and transient in infants. Four babies with episodic conjugate upgaze that became less frequent over time have been described.[6,113] During these episodes, normal horizontal and vertical vestibulo-ocular responses could be observed.

Tonic downgaze has been observed in 5 of 242 consecutively examined healthy newborn infants[215] as well as in other infants.[113,285] Again, the eyes can easily be driven above the primary position with the vestibulo-ocular reflex. Also, the eyes show normal upward movements during sleep. In contrast, infants with hydrocephalus who manifest the "setting sun" sign do not elevate the eyes during sleep or with an oculocephalic maneuver.

Premature infants with intraventricular hemorrhage may also develop tonic downgaze, usually in association with a large-angle esotropia.[480] These infants do not elevate the eyes with vestibular stimulation. Upgaze often returns during the first 2 years of life, but the esotropia does not resolve when upgaze returns.

Double Elevator Palsy/Monocular Elevation Deficiency

Monocular deficiency of elevation, that is, an apparent weakness of both the superior rectus and inferior oblique muscles, has been termed *double elevator palsy* or *monocular elevation deficiency*. This deficit may be caused by mechanical restriction of the globe or neural dysfunction at the supranuclear, nuclear, or infranuclear level. Congenital double elevator palsy of supranuclear origin is confirmed on clinical examination if the affected eye elevates during Bell's phenomenon or doll's head maneuver.[44,52]

Spasm of the Near Reflex

Spasm of the near reflex, also referred to as *convergence spasm*, is characterized by intermittent spasm of convergence, of miosis, and of accommodation.[95] Symptoms include headache, photophobia, eyestrain, blurred vision, and diplopia. Patients may appear to have bilateral sixth nerve palsies, but careful observation will reveal miosis and high myopia (8–10 D) on dry retinoscopy, accompanying the failure of abduction.[172] This key clinical clue prevents misdiagnosis and misdirected testing.[172,182,252,430]

Most commonly, spasm of the near reflex is psychogenic, and treatment may include simple reassurance, psychiatric counseling, or cycloplegia with bifocals. However, a number of cases of spasm of the near reflex associated with organic disease have been reported.[487] In a series of seven patients, two had

posterior fossa abnormalities (cerebellar tumor, Arnold–Chiari malformation), two had pituitary tumors, one had a vestibulopathy, and two had antecedent trauma.[112] None of these patients appeared to have a personality disorder, and none complained of significant disability. Nevertheless, no clear causal relationship or unified neuroanatomic localization has been established. It is prudent to keep in mind that just as any patient with organic disease may also have a functional disorder, disturbances that are clearly functional do not exclude coexisting organic disease.

Internuclear Opthalmoplegia

In the absence of peripheral lesions such as myasthenia gravis, *failure of adduction combined with nystagmus of the contralateral abducting eye* is termed *internuclear ophthalmoplegia* (INO) and localizes the lesion to the medial longitudinal fasciculus (MLF) unequivocally.

Etiology

The abducens nucleus consists of two populations of neurons that coordinate horizontal eye movements (see Fig. 5-5). Fibers from one group form the sixth nerve itself and innervate the ipsilateral lateral rectus muscle; fibers from the second group join the contralateral MLF and project to the subnucleus of the third nerve, which supplies the contralateral medial rectus muscle. In this way, the neurons of the sixth nerve nucleus yoke the lateral rectus with the contralateral medial rectus.

Clinical Features

Clearly, lesions of the abducens nucleus will cause an ipsilateral conjugate gaze palsy. Lesions of the MLF between the midpons and oculomotor nucleus, in turn, disconnect the ipsilateral medial rectus subnucleus from the contralateral sixth nerve nucleus and cause diminished adduction of the ipsilateral eye on attempted versions (see Fig. 5-3). The signs of INO may be accompanied by an ipsilateral hypertropia or skew deviation.

Clinical Assessment

A subtle adduction deficit is best appreciated when repetitive saccades are attempted; the adducting eye will demonstrate a slow, gliding, hypometric movement in conjunction with overshoot of the abducting eye. Usually, the ipsilateral eye can be

adducted with convergence, but convergence will also be impaired if the MLF lesion is rostral enough to involve the medial rectus subnucleus.

Systemic Associations

Similar to dorsal midbrain syndrome, INO is an anatomic rather than etiological diagnosis. A host of structural, metabolic, immunological, inflammatory, degenerative, and other processes can interfere with the function of the MLF and nearby structures. In young adults, multiple sclerosis is by far the most common cause of INO.[342] Multiple sclerosis also underlies most cases of bilateral INO. Although patients with bilateral INO generally remain orthotropic in primary position, they sometimes exhibit an exotropia in the *wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)* syndrome.[311] Additional causes of INO include Arnold–Chiari malformation,[23,99,118,533] hydrocephalus,[352] meningoencephalitis,[64,226] brainstem or fourth ventricular tumors,[99,439,482,496] head trauma,[49,84,254] metabolic disorders, drug intoxications, paraneoplastic effect, carcinomatous meningitis, and others. Peripheral processes, particularly myasthenia gravis and Miller Fisher syndrome, may closely mimic INO and should be considered in any patient with INO-like eye movements.

Treatment and Prognosis

The first goal is to treat the underlying etiology. For example, steroid therapy is necessary in multiple sclerosis, and blood pressure management is required for a hypertensive stroke. After this initial consideration, if the disorder persists and remains stable for at least 6 months, the accompanying exotropia may be corrected by surgery. In a series of three patients treated surgically for diplopia caused by bilateral INO (from brainstem vascular disease) with exotropia of 55 to 70 prism diopters, favorable results were achieved by bilateral medial rectus resections and bilateral lateral rectus recessions (with one lateral rectus on an adjustable suture in each of the three).[74] After a minimum of 6 months postoperative follow-up, all three patients achieved excellent cosmesis. In one of the three patients, binocularity was restored in the primary position, in the second diplopia was eliminated in primary and downgaze, and in the third diplopia was completely eliminated.

Ocular Motor Cranial Nerve Palsies

The processes that produce ocular motor nerve palsies in infants and children, as many neurological diseases in this age group, are commonly diffuse.

General Clinical Considerations

Muscle paralysis is diagnosed by the inability of the eye to move in the direction of action of the particular muscle voluntarily and reflexively, tested by the doll's head maneuver, spin test (looking for vestibular nystagmus), or forced lid closure (looking for Bell's phenomenon). Paresis of a muscle may be detected on testing of versions, at which time version in a particular direction may be limited but ductions may appear full. If the muscle is totally paralyzed, the ductions will be limited as well; in this case, if it is possible to perform a forced duction test, the test would reveal no restriction in the direction of action of a paretic muscle. However, after long-standing muscle paresis, the muscle may become tightened, and forced duction testing in the direction opposite to that of the muscle action would reveal restriction.

A subtle paresis is best appreciated when repetitive saccades are attempted; the eye will demonstrate a slow, gliding, hypometric movement in the direction of action of the particular muscle(s), in conjunction with overshoot of the other eye in that direction. The *primary deviation*, or the measured strabismus when fixing with the normal eye, is smaller than the *secondary deviation*, which is the strabismus measured when fixing with the restricted or paretic eye.

Significant factors in evaluating a child with ocular motor cranial palsies include (1) age of the child, (2) history of previous cranial nerve palsies or relevant systemic disease, (3) recent history of febrile illness, immunization, trauma, or exposure to toxins, (4) accompanying neurological symptoms or signs, and (5) the course under careful, regular observation.

Any child exhibiting an ocular motor nerve palsy accompanied by other neurological signs deserves a consultation with a neurologist and a thorough, timely workup. It is incumbent upon the ophthalmologist to detect and treat any amblyopia that may occur. Also, prevention of amblyopia, by alternate patching, for example, can be considered in severely amblyogenic conditions such as third nerve palsies.

The following discussion sets out an approach to the recognition and initial management of *isolated* third, fourth, and sixth nerve palsies and reviews some common childhood causes of combined ocular motor nerve palsies.

Sixth Nerve Palsies

Etiology and Systemic Associations

Acquired sixth nerve palsies, whether isolated or not, are usually caused by tumors (especially glioma and medulloblastoma) and trauma (47%–62%).[3,24,191,269,287,405] A significant number of cases are also due to inflammatory causes such as meningitis (including from Lyme disease), Gradenigo's syndrome,[117] cerebellitis, and postviral sixth nerve palsy. The clinician is also faced with numerous other possible etiologies (Table 5-4).

Clinical Features and Assessment

As previously mentioned, a lesion affecting the sixth nerve nucleus produces an ipsilateral horizontal gaze palsy. Injury to the nerve at any other location along its course results in absent or poor abduction of the ipsilateral eye (Fig. 5-7).

Of course, poor abduction is not specific to sixth nerve palsies and may also be caused by disorders of the neuromuscular junction (e.g., myasthenia gravis), restrictions (e.g., medial orbital wall fractures with tissue entrapment), and inflammation (e.g., orbital myositis). The examiner considers and excludes these possibilities before establishing the diagnosis of sixth nerve palsy. If a congenital anomaly of innervation, such as Duane's syndrome, is clearly identified as the cause of abduction deficit, no further investigation of the eye movement abnormality is necessary.

Acute comitant esotropia can also follow head trauma (usually minor), febrile illness, migraine, or occlusion of an eye or may not be related to any obvious inciting cause.[75,170,385,460] This condition is distinguishable on examination from a bilateral sixth nerve palsy. However, although an acute comitant esodeviation without accompanying signs is usually benign, it may in some cases be the harbinger of an intracranial tumor such as cerebellar astrocytoma or pontine glioma[29,526] or other pathology such as a Chiari 1 malformation.[517] Absence of symptoms or signs such as headaches, papilledema, or nystagmus may not rule out the possibility of an intracranial pathology. Therefore, a thorough ophthalmic examination is performed. MRI is

TABLE 5-4. Etiology of Infranuclear Sixth Nerve Palsy.

Location/signs	*Etiologies*
Fascicle Ipsilateral VIIth nerve palsy, facial analgesia, loss of taste from anterior two thirds of tongue; peripheral deafness; Horner's syndrome, contralateral hemiparesis	Tumor; demyelination; hemorrhage; infarction
Subarachnoid space Papilledema; other cranial nerve palsies	Meningitis; meningeal carcinomatosis; trauma; increased intracranial pressure causing downward pressure on brainstem; after lumbar puncture, shunt for hydrocephalus, spinal anesthesia, or halopelvic cervical traction; clivus tumor; cerebellopontine angle tumor; berry aneurysm; abducens neurinoma
Petrous apex Ipsilateral seventh nerve palsy; pain in eye or face; otitis media, leakage of blood or cerebrospinal fluid from ear; mastoid ecchymosis; papilledema	Mastoiditis; thrombosis of inferior petrosal sinus; trauma with transverse fracture of temporal bone; persistent trigeminal artery, aneurysm, or arteriovenous malformation
Cavernous sinus/superior orbital fissure Ipsilateral Horner's syndrome; ipsilateral IIIrd, IVth, Vth cranial nerve involvement; proptosis; disc edema; orbital pain; conjunctival injection	Cavernous sinus thrombosis; carotid-cavernous fistula; tumor; internal carotid aneurysm
Orbit Ipsilateral IIIrd, IVth, Vth cranial nerve involvement; proptosis; disc edema; orbital pain; conjunctival injection	Tumor; pseudotumor
Uncertain	Transient abducens palsy of newborn; after febrile illness or immunization; migraine; toxic; idiopathic

indicated if the esotropia is unresponsive to correction of refractive error, there is no history of flu-like illness, or no improvement is seen over the course of 1 to 4 weeks.

Natural History and Clinical Workup

Newborns may demonstrate a transient sixth nerve palsy that is frequently unilateral and occasionally accompanied by a temporary ipsilateral seventh nerve palsy.[53,267,291,400] Simple observa-

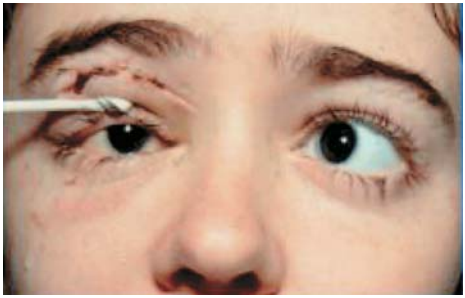


FIGURE 5-7. Right sixth cranial nerve palsy. These photos show the limitation of abduction on attempted right gaze typical of a sixth cranial nerve palsy. Forced duction testing of this patient's right eye showed no restriction to abduction.

tion is generally sufficient because resolution typically occurs within 4 to 10 weeks.

Older infants and children may develop transient isolated sixth nerve palsies 1 to 3 weeks after nonspecific febrile or respiratory illnesses,[267,405] after a specific viral illness such as varicella,[350] after immunization,[522] before mononucleosis,[273] or without any obvious precipitating factor.[435] Some of these palsies may recur, and the recurrences have no serious implications.[2,60,65,399,474,476] Again, aggressive investigation is not warranted, but two simple studies are advised: (1) a complete blood count with differential, which may show lymphocytosis as evidence of a recent viral infection, and (2) examination of the ears for otitis media. The parents are warned to observe for any new signs or symptoms. Careful reexamination at regular intervals is essential; deterioration or improvement in lateral rectus function provide important evidence for or against a progressive mass lesion. Most children in this group recover abducens function within 10 weeks, although a prolonged (9 months) palsy may rarely occur.[267]

Persistence, without improvement, or deterioration of an isolated sixth nerve palsy in a child beyond about 3 months requires an intensive neurological, neuroradiologic, and otolaryngologic evaluation. In adults, a substantial number of isolated sixth nerve palsies that last beyond 6 months are caused by potentially treatable, often slow-growing, tumors.[111,159,426] In a Mayo Clinic series of 133 children with acquired sixth nerve paresis, 15 presented with an isolated sixth nerve palsy due to tumor.[405] Of these, 12

developed additional neurological signs within a few weeks, whereas 3 patients took 2 to 3 months to develop additional signs. An additional problem is that a physician may not always be able to confirm that the sixth nerve palsy in a child is isolated. Therefore, if close follow-up to resolution of the palsy or paresis is not possible, neuroimaging is recommended.[24]

Treatment

Amblyopia prevention is always key in children younger than 7 to 9 years of age. Providing full hyperopic correction also relieves the demand for accommodation and thus decreases the chance of worsening esotropia.

Treatment options include botulinus toxin injection and surgery. One approach is to inject botulinus toxin into the antagonist medial rectus muscle to prevent tightening of the unopposed medial rectus,[442,444] sometimes allowing binocular vision in primary position, while the palsy is resolving.[218] Reducing medial rectus contracture with botulinus toxin injection may also improve a surgical result.[302]

Prognosis

Spontaneous recovery of abduction in childhood sixth nerve palsy or paresis is much less common than in adults. The rate of residual strabismus was found to be 66% in one study of any sixth nerve palsy or paresis in patients 7 years of age and younger, likely a result of permanent structural deficits without complete recovery in the setting of tumor and hydrocephalus-shunt malfunction as the most frequent etiologies. The rate of amblyopia in this study was 20%, thus highlighting the need for parent education and close follow-up.

The highest rates of spontaneous recovery have been reported in idiopathic (67%[24]), infectious (50%[24]), inflammatory (90%[191]), and traumatic (33%–50%[24,191]) cases.

Fourth Nerve Palsy

Etiology and Systemic Associations

Of the many causes of trochlear palsy in childhood (Table 5-5), "congenital" and traumatic are by far the most common.[191,209] The cause of most congenital trochlear palsies remains unknown, but aplasia of the trochlear nucleus has been reported to accompany the absence of other cranial nerve nuclei.[10,317,464] The superior oblique tendon or muscle is often the primary

TABLE 5-5. Etiology of Fourth Nerve Palsy.

Location/signs	*Etiologies*
Nucleus and fascicle Contralateral Horner's syndrome	Trauma; tumor; demyelination; after neurosurgery; nuclear aplasia; arteriovenous malformation; hemorrhage; infarction
Subarachnoid space Papilledema; other cranial nerve palsies	Trauma; tumor; increased intracranial pressure; after lumbar puncture or shunt for hydrocephalus; spinal anesthesia; meningitis; mastoiditis
Cavernous sinus/superior orbital fissure Ipsilateral Horner's syndrome, ipsilateral IIIrd, Vth, VIth nerve involvement; proptosis; disc edema; orbital pain	Tumor; internal carotid aneurysm; Tolosa–Hunt syndrome
Orbit Ipsilateral IIIrd, VIth nerve involvement; proptosis; enophthalmos; disc edema; orbital pain; conjunctival/episcleral injection	Tumor; trauma; inflammation
Uncertain location	Congenital; idiopathic

problem. Laxity of this tendon has been described on forced duction testing[381] and correlates well with the presence of attenuated superior oblique muscles on orbital MRI.[432] Therefore, congenital cases may be more correctly termed congenital superior oblique palsy/underaction instead of fourth nerve palsy. Absence of the superior oblique muscle altogether is also in the differential of an apparent congenital superior oblique palsy.[87]

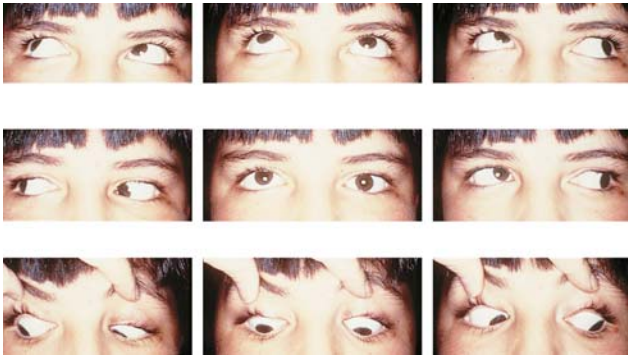
The trochlear nerves are particularly vulnerable to closed head trauma when there may be contrecoup of the tectum of the midbrain against the edge of the tentorium.[292] In this way, the nucleus or fascicle may be injured within the substance of the midbrain, or the nerve itself may be contused as it exits the brainstem dorsally and passes laterally around the midbrain (see Fig. 5-3). The proximity of the two trochlear nerves to each other at the site of their crossing in the anterior medullary velum (roof of the Sylvian aqueduct; see Fig. 5-4) explains the high incidence of bilateral involvement after coup-contrecoup, closed head trauma.[286]

Clinical Features and Assessment

Vertical deviations may also result from other processes, such as abnormal neuromuscular transmission, restriction, inflam-

mation, skew deviation, dissociated vertical divergence, small nonparalytic vertical deviations associated with horizontal strabismus, and paresis of other cyclovertical muscles. The clinical assessment of a vertical deviation is carefully executed to exclude these various possibilities.

It is important to ask about previous extraocular muscle surgery or orbital trauma and to obtain any history that suggests myasthenia gravis or skew deviation. The examiner notes any anomalous head position (Figs. 5-8, 5-9), versions, ductions, cover test measurements in cardinal fields of gaze, any secondary deviation, forced (Bielschowsky) head tilt test measurements, presence or absence of both subjective and objective torsion, and presence or absence of dissociated vertical deviation. Forced ductions, Tensilon testing, and other supplemental tests are performed as appropriate.



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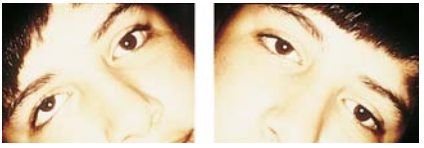

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FIGURE 5-8. (**A**) Unilateral congenital cranial nerve palsy, right eye. The photograpph demonstrates a right hypertropia that increases in left gaze. There is slight underaction of the right superior oblique nad significant overaction of the right inferior oblique muscle. (**B**) The photograph of head tilt test, with right hypertropia increasing on tilt right and diminishing on tilt left. Positive head tilt with the right hyper increasing in left gaze indicates a right superior oblique palsy.

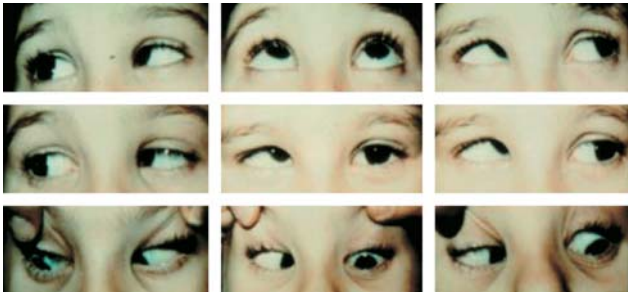


FIGURE 5-9. Bilateral asymmetric congenital fourth nerve palsy and esotropia. Note that the right superior oblique palsy is more severe than the left, and there is a right hypertropia in primary position. There is significant superior oblique underaction, right side more than left side. A significant V-pattern is present. There is a right hypertropia in right gaze and a left hypertropia in left gaze.

Several other comments regarding the clinical evaluation are crucial.

1. The familiar "Parks–Bielschowsky three-step" test helps to combine information from cover test measurements and the Bielschowsky head tilt phenomenon.[59,370] This test is only useful when there is a *palsy* of a *single* cyclovertical muscle and can therefore only be applied after the careful assessment just described.[281] A fourth nerve palsy would reveal hypertropia, worsening on horizontal gaze in the direction contralateral to the hypertropic eye, and worsening on head tilt ipsilateral to the hypertropic eye. Infants with congenital superior oblique palsies present with a head tilt, whereas older children and adults with decompensated congenital palsies complain of vertical and/or torsional diplopia.[323]

To diagnose a congenital superior oblique palsy, old photographs are helpful, often revealing a long-standing head tilt. Also, vertical fusional amplitudes frequently exceed the normal range of 3 to 4 prism diopters. The presence of a suppression scotoma when assessing diplopia or the presence of fusion also aids in establishing the chronicity of the condition as suppression is usually a childhood adaptation mechanism. Moreover, the presence of facial asymmetry may be associated with a long-standing head tilt from early childhood.[176,202,338,528] The presence of facial asymmetry may not be a specific sign for congenital superior oblique palsy, however, because patients with acquired

superior oblique palsy and heterotopic rectus muscles exhibited similar features of facial asymmetry.[502] The causal relationship of the head tilt due to an abnormal superior oblique is not established.[373] Hemifacial changes are often associated with plagiocephaly as a craniofacial anomaly, and craniofacial anomalies are commonly associated with anomalous extraocular muscles.[124]

2. The examiner also checks for bilateral and asymmetrical superior oblique palsies, because the larger paresis may "mask" the smaller until unilateral surgery is performed.[274,280] Bilateral involvement should particularly be suspected after closed head injury. Findings that suggest bilaterality include alternation of hypertropia with fixation, gaze, or head tilt: excyclotorsion of 10° or more: and V-pattern esotropia.[286]

3. Excyclodeviations usually occur with trochlear palsies, may accompany restrictions and myasthenia gravis, and are less commonly seen with skew deviations.[494] The triad of skew deviation, head tilt, and *incyclo*torsion of the hypertropic eye is termed the *ocular tilt reaction*, an entity that can mimic fourth nerve palsy on the traditional three-step test.[128] Therefore, examination for torsion, by double-maddox rod or simple fundoscopy, is essential in distinguishing a fourth nerve palsy from ocular tilt reaction.

Inheritance

Rarely, congenital superior oblique palsy may be familial.[28,198] The mode of inheritance in the described families has not been determined.

Natural History

Long-standing congenital superior oblique palsy may decompensate in adulthood for a variety of reasons, including trauma, with the presenting symptom of vertical diplopia. As for traumatic cases, most cases of unilateral injury do resolve (see following). Also, after long-standing fourth nerve palsy, a "spread of concomitance" may be observed where the deviation in rightgaze and leftgaze are nearly equal, although the differential deviation in right versus left head tilt persists. This spread of concomitance has been attributed to a "contraction" of the ipsilateral superior rectus muscle.[26]

Treatment

Most surgeons wait 6 to 12 months before deciding on strabismus surgery for traumatic cases, to await spontaneous resolu-

tion of the deviation or stability in measurements. For congenital cases presenting with head tilt in infancy, surgery may be performed as soon as possible to correct the head posture and thus to aid in normal development of the neck muscles and the alignment of cervical vertebrae. It is unknown, however, whether early strabismus surgery can prevent or reverse facial asymmetry. For the large head tilts in infancy, a superior oblique tuck may treat the head tilt quickly; the benefit of normalizing head posture with this procedure may outweigh the resultant iatrogenic Brown's syndrome.

For long-standing fourth nerve or superior oblique palsy, a variety of options exist. One approach is to operate on one muscle for vertical deviations of up to 15 prism diopters and to consider two-muscle surgery in deviations above 15 prism diopters. The first choice of procedure is often ipsilateral inferior oblique muscle weakening. The second procedure often performed when the deviation is greater than 15 prism diopters is either ipsilateral superior rectus recession,[26] when the vertical deviation is worse in upgaze, or contralateral inferior rectus recession, when the deviation is worse in downgaze.[202]

A fast and easy approach to deciding which muscle to weaken first is to perform a "modified Parks three-step test"[205] to determine which muscle is *overacting* and then to weaken that muscle first. This modified three-step test is performed in the same manner as the traditional one, except for the first step, in which the *overacting* vertical muscles are circled in each eye (instead of the traditional method of circling the presumed weak vertical muscles).

In the case of bilateral palsy, bilateral inferior rectus recession and Harada–Ito procedures are recommended, both able to treat excyclotorsional diplopia.

Prognosis

When a child presents with a postinfectious, isolated trochlear palsy that cannot be explained as congenital, traumatic, restrictive, myasthenic, or neoplastic, the prognosis is good and observation alone is sufficient.

Overall prognosis for recovery of isolated fourth nerve palsies in adults and children was reported to be 53.5% combined (1000 total patients from 2 months to 91 years of age, 90% of whom were over 19 years and 75% of whom were over 35 years of age).[424] Unilateral traumatic fourth nerve palsies in a series of 24 pediatric and adult patients (ages 7–78 years; mean, 35.4 years),

46% of whom sustained minor head trauma, resulted in 75% resolution.[483] Another series reported 65% resolution in unilateral but 25% in bilateral cases of traumatic fourth nerve palsy.[479]

Third Nerve Palsy

Etiology and Systemic Associations

In childhood, a third nerve palsy typically keeps company with other neurological findings, which aid in localization and diagnosis (Table 5-6), but isolated palsies do occur and are generally congenital, traumatic, infectious, or migrainous.[191,225,257,326,339,440] An acquired, isolated oculomotor nerve palsy in a child may also result from tumor, preceding viral illness, bacterial meningitis (most commonly pneumococcal, *Haemophilus influenzae* type b, or *Neisseria meningitidis*), or immunization.[76,77,86,191,225,257,309,326,339,347,430,440,446] Rarely, children may demonstrate gradually progressive paresis because of a slowly growing tumor[1] or a truly cryptogenic oculomotor palsy. Posterior communicating aneurysms, although extremely rare in children, should be considered as well.[313] Microvascular infarction due to atherosclero-

TABLE 5-6. Etiology of Infranuclear Third Nerve Palsy.

Location/signs	*Etiologies*
Fascicle Ipsilateral cerebellar ataxia; contralateral rubral tremor; contralateral hemiparesis; vertical gaze palsy	Demyelination; hemorrhage; infarction (rare in childhood)
Subarachnoid space Papilledema; other cranial nerve palsies	Meningitis; trauma or surgery; tumor; increased intracranial pressure; uncal herniation
Cavernous sinus/superior orbital fissure Ipsilateral Horner's syndrome; ipsilateral IVth, Vth, VIth nerve involvement; proptosis; disc edema; orbital pain; conjunctival/episcleral injection	Cavernous sinus thrombosis; tumor; internal carotid artery aneurysm; carotid–cavernous fistula; Tolosa–Hunt syndrome; pituitary apoplexy; sphenoid sinusitis, mucocele; mucormycosis
Orbit Ipsilateral IVth, Vth, VIth nerve involvement; proptosis; enophthalmos; disc edema; orbital pain; conjunctival/episcleral injection	Trauma; tumor; inflammation
Uncertain location	After febrile illness or immunization; migraine; idiopathic

sis, hypertension, or diabetes mellitus, a common cause of isolated third nerve palsy in adults, is extremely rare in children.

Clinical–Anatomic Correlation

The anatomic organization of the third nerve nucleus, like that of the sixth nerve nucleus, provides constraints that help differentiate the rare nuclear third nerve palsy from an infranuclear third nerve palsy. Because the superior rectus subnucleus supplies the contralateral superior rectus muscle, and the central caudal nucleus innervates both levator muscles, damage to a single oculomotor nerve nucleus gives rise to contralateral superior rectus weakness and bilateral ptosis. Also, because of the arrangement of the three medial rectus subnuclei and the visceral nuclei within the oculomotor nucleus, a nuclear third nerve palsy is not likely to produce isolated medial rectus involvement or unilateral pupillary involvement. In addition, other midbrain signs such as vertical gaze abnormalities are often associated with lesions of the oculomotor nucleus (see Fig. 5-6).

Because the oculomotor nerve innervates the levator palpebrae superioris, the sphincter of the pupil and ciliary body, as well as four extraocular muscles (the medial rectus, superior rectus, inferior rectus, and inferior oblique), it is easy to identify a complete infranuclear third nerve palsy by the presence of ptosis; a fixed, dilated pupil; and a "down-and-out" eye position resulting from the unopposed lateral rectus and superior oblique muscles (Fig. 5-10). However, third nerve palsies can be "partial"; any individual sign or combination of signs may be present and, if present, may be complete or incomplete. Numerous patterns can therefore arise.

Clinical Features and Assessment/Natural History

Oculomotor nerve palsies, like abducens and trochlear nerve palsies, should be distinguished from myasthenia and mechanical restrictions. Clinically observable involvement of the pupil or signs of *oculomotor synkinesis* (aberrant regeneration) establish involvement of the third nerve, assuming pharmacological and traumatic mydriasis can be excluded.

The manner through which neural impulses become misdirected is not always clear.[455] Misrouting of regenerating motor axons is firmly documented[152,392,456] and corroborates the frequent clinical observation of the appearance of synkinesis at about 8 to

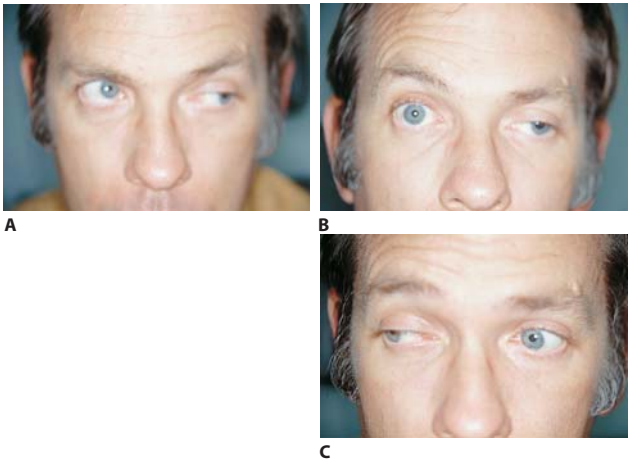


FIGURE 5-10. Patient with traumatic left third nerve palsy. The top photograph shows the classic appearance of a left third nerve palsy with ptosis and the eye in a down and out position. The left photograph shows full abduction, left eye. The bottom right photograph shows left eye with limited adduction. Note, there is lid retraction and miosis, left eye, on attempted adduction indicating aberrant innervation of the levator muscle and pupillary sphincter with part of the medial rectus nerve.

12 weeks after an acute palsy.[277] However, aberrant regeneration cannot comfortably account for transient oculomotor synkinesis[239,289,454] or spontaneous "primary" oculomotor synkinesis.[66,105,289,436,493] Ephaptic transmission, conduction of a nerve impulse across a point of lateral contact, and synaptic reorganization of the oculomotor nucleus are two proposed theories of synkinesis.[289,455] The presence of oculomotor synkinesis has not been reported with demyelination, but it does not otherwise narrow the differential diagnosis of third nerve palsy in the pediatric age group.

Congenital third nerve palsy is usually incomplete and unilateral and is frequently associated with oculomotor synkinesis and "miosis" of the pupil in the affected eye.[191,326,504] Although many children with congenital oculomotor nerve palsies have no associated neurological findings, some do,[41] and a thorough neurological evaluation of these infants is suggested. If there are additional neurological signs or bilateral third nerve palsies, MRI may also provide useful information.[175]

Rarely, paresis and spasm of the extraocular and intraocular muscles innervated by the third nerve may alternate, typically every few minutes, to produce *oculomotor palsy with cyclic spasms*.[295] With few exceptions, these cycles accompany congenital, rather than acquired, oculomotor palsies and continue throughout life. In some instances, several months to several years may elapse between the discovery of the paresis and the onset of the cyclic spasms. Investigation is not necessary unless the third nerve palsy is acquired or there is progressive neurological dysfunction. The pathogenesis of this phenomenon remains obscure.[272]

Ophthalmoplegic migraine generally begins in childhood[40] but may even be seen in infancy.[13,534] It is an uncommon disorder despite the fact that 2.5% of children experience a migraine attack by age 7 and 5% by age 15.[43] Symptoms of migraine in children include nausea, vomiting, abdominal pain, and relief after sleep in 90%.[419] The headaches, which may be accompanied by an aura, are often unilateral and throbbing in quality. Family history is positive in 70% to 90%. With ophthalmoplegic migraine, the patient characteristically experiences pain in and about the involved eye, nausea, and vomiting; often the third nerve palsy ensues as the pain resolves. Full recovery of third nerve function within 1 to 2 months is typical, but resolution may be incomplete and oculomotor sykinesis has been reported.[355] Multiple attacks may occur, and years may pass between episodes.[133] Most patients with ophthalmoplegic migraine have normal angiograms, but one 31-year-old with recurrent episodes of ophthalmoplegic migraine, which had begun at age 5, and partial third nerve palsy since age 7, demonstrated a small perimensencephalic vascular anomaly.[224]

Aneurysms have been reported to cause isolated third nerve palsies during the first and the second decades of life[71,135,157,158,313,383] and carry a high risk of mortality or significant morbidity if left undetected and untreated. On the other hand, aneurysms appear to be rare in children.[158,495] Angiography with general anesthesia can be risky in the childhood age group, and the gap between the sensitivity of angiography and MRI for detecting aneurysms continues to narrow. The clinician assesses all these variables along with the history and physical examination to decide on the appropriate workup for each patient. For example, in the child under age 10 with a family history of migraine who presents with nausea, vomiting, and headache, followed by third nerve palsy as these symptoms resolve, that

is, with typical ophthalmoplegic migraine, angiography may not be necessary.[166] However, when a third nerve palsy acquired in childhood cannot be explained on the basis of the clinical examination or noninvasive neuroimaging, the cerebrospinal fluid should be evaluated and angiography considered.

Treatment

After diagnosis and treatment of the underlying disorder, observation of any recovery of oculomotor nerve function is necessary before surgical intervention. When partial or full recovery occurs, it often does so within 3 to 6 months but it may take 1 year or more. Surgical treatment includes strabismus surgery and ptosis correction. The latter is approached with caution in an eye that lacks a functional Bell's phenomenon because of the risk of exposure keratopathy.

Prognosis

Two recent series have found fair to poor visual and sensorimotor outcome in oculomotor nerve palsy/paralysis of children with comparable mix of congenital, traumatic, and neoplastic cases.[339,440] The best ophthalmologic outcome with measurable stereopsis was in the resolved cases (3 of 20; 15%) in the first study, and in 4 of 31 patients with partial third nerve palsy in the second study, 2 of whom had spontaneous resolution. In the first series, amblyopia therapy was most effective with congenital causes, but treatment results were poor with other causes; young children with posttraumatic and postneoplastic oculomotor nerve injuries demonstrated the worst ophthalmologic outcomes.

Combined Ocular Motor Nerve Palsies

As the oculomotor, trochlear, and abducens nerves are in relatively close physical proximity from brainstem to orbit, it is not surprising that many diseases occurring at numerous locations can affect these nerves simultaneously.

Clinical Assessment

The evaluation begins by establishing that the eye movement abnormality is due to cranial nerve disease rather than supranuclear lesions, disorders of the neuromuscular junction, restrictive or inflammatory myopathies, or chronic progressive "neuromyopathies," for example, Kearns–Sayre syndrome. In the presence of a third nerve palsy, the fourth nerve function is

tested by observing for intorsion of the affected eye in downgaze. If multiple ocular motor nerve palsies are indeed present, a thorough history and examination, neuroimaging of the rostral brainstem, cavernous sinuses, and orbits, and examination of the cerebrospinal fluid (CSF) are typically necessary to distinguish between the myriad possible localizations and etiologies. Prompt diagnosis is particularly important for children with infections or pituitary apoplexy; the latter is often accompanied by severe headache, ophthalmoplegia caused by rapid expansion into the cavernous sinus, and rapid mental status deterioration.

ETIOLOGIES

Processes in the brainstem (tumor, encephalitis), subarachnoid space (meningitis, trauma, tumor), and of uncertain localization (postinfectious polyneuropathy) tend to *produce bilateral combined ocular motor nerve palsies* whereas processes in the cavernous sinus/superior orbital fissure (tumor, pituitary apoplexy, cavernous sinus thrombosis, carotid-cavernous fistula) and orbit (trauma, tumor, mucormycosis) usually cause *unilateral combined ocular motor nerve palsies*.

The ophthalmologist needs to be familiar with certain *generalized neuropathies* that may initially present with *acute ophthalmoplegia*. In a series of 60 patients with acute bilateral ophthalmoplegia, *Guillain–Barre* and *Miller Fisher syndromes* accounted for the diagnosis in 15 of 28 patients under age 45.[253] The bulbar variant of *Guillain–Barre syndrome (acute postinfectious polyneuritis)* frequently presents as a rapidly progressive, painless ophthalmoplegia. Early in the course, involvement of eye movements may be incomplete and mimic either unilateral or bilateral oculomotor nerve palsies, but complete ophthalmoplegia with or without involvement of the pupils and accommodation typically evolves within several days. Partial ptosis usually accompanies severe limitation of eye movements,[413] but levator function may be entirely normal or completely absent. Some degree of cranial nerve involvement occurs in about 50% of children with Guillain–Barre syndrome,[413] and in the setting of rapidly progressing bilateral ophthalmoplegia, dysfunction of other cranial nerves, particularly bilateral facial nerve involvement, strongly supports the diagnosis of acute postinfectious polyneuritis.

A variety of infections have been reported to precede Guillain–Barre syndrome in 50% to 70% of children; these include gastroenteritis, tonsillitis, measles, mumps, varicella, pertussis,

hepatitis, Epstein–Barr virus, *Campylobacter jejuni*, coxsackie virus, and nonspecific upper respiratory infections. Two of these, varicella[103,521] and acute Epstein–Barr virus infection,[184] precede or accompany the onset of Guillain–Barre syndrome with noteworthy frequency in children and young adults. Paresthesias, often painful, commonly appear early in the course, and signs of meningeal irritation may also appear early in children. Although a rise in CSF protein levels without pleocytosis is the rule, it generally does not occur for several days to weeks after the onset of symptoms and, in a small percentage of patients, is not observed at all. The patient should be referred to a neurologist for management in a hospital setting with materials for tracheostomy and mechanical ventilation readily available.

Ophthalmoplegia (external and sometimes internal), ataxia, and areflexia constitute *Miller Fisher syndrome*,[155] and diplopia is usually the first symptom. At least 20 children (under age 18 years) with Miller Fisher syndrome have been reported.[50] A preceding febrile or "viral" illness may be reported with many of the same infectious agents previously listed.

Although the eye movements often suggest unilateral or asymmetrical bilateral abducens pareses, many patterns have been reported including horizontal gaze palsy, upgaze palsy,[249] pupil-sparing oculomotor nerve palsy, and pseudointernuclear ophthalmoplegia.[30,125,478,520] All these eye movement patterns generally progress to severe bilateral ophthalmoplegia within 2 or 3 days. Ptosis and pupillary involvement may occur but are often absent.[78] Limb and gait ataxia typically appear 3 or 4 days after the ophthalmoparesis but are, at times, concurrent with it. Areflexia is almost invariably present by the end of a week.[141] An association with demyelinating optic neuropathy has also been reported.[368,488]

Miller Fisher syndrome is considered to be a variant of Guillain–Barre syndrome. However, there is some controversy as to the site of the lesion in Miller Fisher syndrome,[8,315,414,415,488] whereas Guillain–Barre is clearly a peripheral neuropathy. Clinical observations suggesting the possibility of CNS involvement in Miller Fisher syndrome have included apparently supranuclear eye movement abnormalities[314,459] and clouding of consciousness.[8,50] In some cases, evoked potentials[232] and MRI[416] have been normal; in others, CT images[121,541] and MRI[136,163] have displayed clear abnormalities in the brainstem as well as in the cerebral white matter and cerebellum. In yet another group, absent F waves and H reflexes on peripheral nerve testing and

markedly abnormal electroencephalograms suggested both peripheral and central involvement.[50] Two neuropathological studies demonstrated normal CNS in both,[119,378] and another showed inflammatory infiltration of peripheral and cranial nerve roots[25]; however, central chromatolysis in the nuclei of the third, fourth, fifth, and twelfth nerves and of the anterior horn cells has also been reported.[186] Additionally, anticerebellar antibody has been found to be reactive to a significantly greater number of bands on Western blotting of serum from Miller Fisher patients (6 of 7) compared to that of Guillain–Barre (3 of 6) or healthy controls (4 of 10).[227]

As with acute postinfectious polyneuritis, if the CSF is examined late enough in the course, the protein concentration is elevated in most cases.[141] A useful diagnostic tool is the presence of antiganglioside antibodies in serum of patients with Guillain–Barre and Miller Fisher syndromes. Patients with Guillain–Barre syndrome subsequent to *Campylobacter jejuni* enteritis frequently have IgG antibody to GM_1 ganglioside. Miller Fisher syndrome is associated with IgG antibody to GQ1b and GT1a ganglioside in 90% of cases.[527,539] Moreover, acute ophthalmoparesis without ataxia has also been found to be associated with anti-GQ1b antibody, suggesting that this is a milder variant of Miller Fisher syndrome.[539] These antibody findings are evidence for the molecular mimicry theory of postinfectious autoimmune pathology.

Despite its dramatic and alarming presentation, Miller Fisher syndrome generally has a benign prognosis. Careful observation is, however, recommended because ophthalmoplegia occurred early in one case of childhood Guillain–Barre syndrome that progressed to respiratory failure.[179] Occasionally, "relapsing Miller Fisher syndrome" appears to occur,[434,506] which should not be confused with recurrent ocular motor palsies that may accompany a rare familial syndrome of recurrent Bell's palsy.[9] Treatment of Guillain–Barre and Miller Fisher syndromes may, in severe cases, require plasmapheresis or intravenously administered immunoglobulin.[241,538]

Acute hemorrhagic conjunctivitis caused by enterovirus 70 can be accompanied by dysfunction of any of the cranial or spinal motor nerves,[220,246,513] resulting in a polio-like paralysis (radiculomyelitis) in approximately 1 in 10,000 patients infected with this virus.[535] Cranial nerve involvement occurred in 50% of the patients in one series.[246] Solitary seventh or fifth nerve palsies were most common, followed in frequency by combined fifth and

seventh nerve palsies. Prognosis correlates with severity and pattern of cranial nerve involvement; patients with mild weakness and involvement of cranial nerves VII, IX, and X tend to resolve fully, whereas those with severe weakness and involvement of cranial nerves III, IV, V, and VI often do not significantly improve. Optic atrophy may also occur. Treatment is only symptomatic.

Anomalies of Innervation

Some ocular motility disturbances, both congenital and acquired, arise when an inappropriate nerve or nerve branch innervates an extraocular muscle. Such "miswiring" immediately suspends the laws of extraocular motor physiology (e.g., Hering's and Sherrington's laws) and produces bizarre, intriguing eye movements. In certain cases, electromyographic (EMG) and pathological studies have confirmed the defective anatomy and physiology underlying the clinical presentation. Although miswiring can generate many types of abnormal eye movements, only the more common anomalous motility patterns are detailed here.

Sixth Nerve

Duane's Syndrome

Duane's syndrome is characterized by retraction of the globe and narrowing of the lid fissure on attempted adduction as well as limited eye movements. Three forms of abnormal motility have been classified[217]:

Type I: limited abduction with intact adduction (Fig. 5-11)
Type II: limited adduction with intact abduction
Type III: limited abduction and limited adduction

Incidence Duane's syndrome has been reported to account for 1% to 4% of all strabismus cases.[122]

Etiology Electromyographic data indicate that the medial and lateral recti contract simultaneously, that is, they "co-contract," and may thereby produce both the retraction of the globe into the orbit and the limitation of eye movement.[216,217,308] One can speculate as to how different distributions of inappropriate neural input from the oculomotor and abducens nerves to the lateral and medial recti could produce each of the three patterns of limited ocular motility seen in Duane's syndrome. This

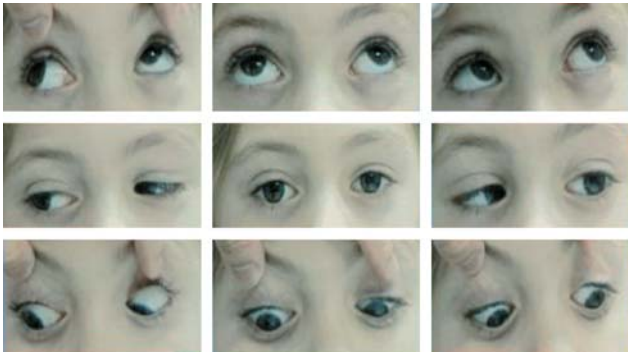
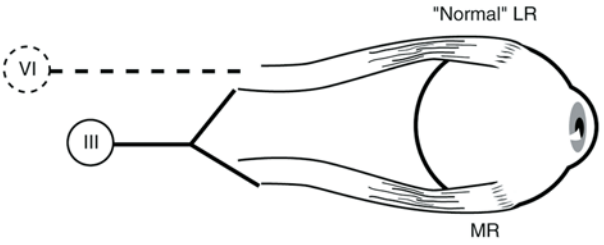


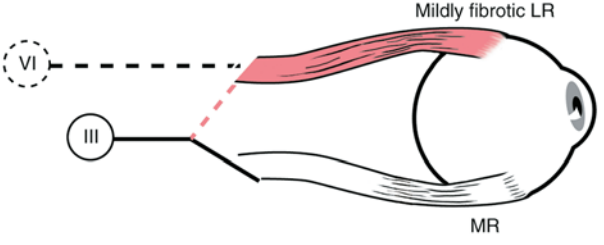
FIGURE 5-11. Duane's syndrome, left eye. This montage demonstrates the limitation of abduction (*middle, right photo*), palpebral lid fissure narrowing on adduction (*middle, left photo*), upshoot in adduction (*top, left photo*), and "Y" pattern (*middle, top photo*) seen with Duane's syndrome.

aberrant innervation is thought to be a result of congenitally deficient innervation of the VIth nucleus, leading to a fibrotic lateral rectus muscle (Fig. 5-12).

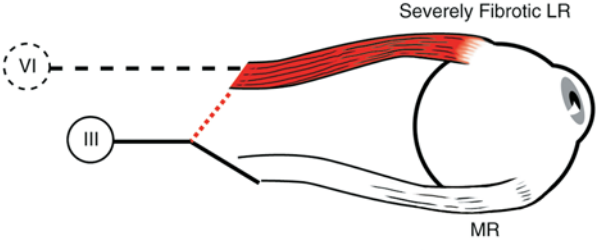
Neuropathological investigations of three patients with Duane's syndrome have all revealed aplasia or hypoplasia of the abducens nucleus and nerve, and in two of these cases, branches of the third nerve "substituted" for the defective sixth nerve by supplying some of its fibers to the lateral rectus. The first case was unilateral and demonstrated a hypoplastic lateral rectus muscle in addition to hypoplasia of the abducens nucleus and nerve.[310] In a second patient with bilateral type III Duane's syndrome, both abducens nuclei and nerves were absent; also, both lateral recti were found to be partially innervated by the inferior division of the oculomotor nerves and were histologically normal in innervated areas but fibrotic in areas not innervated.[213] The third patient had unilateral, left type I Duane's syndrome and showed, as did the previous case, absence of the sixth nerve, partial innervation of the lateral rectus by the inferior division of the oculomotor nerve, and fibrosis of the lateral rectus muscle in areas not innervated. However, although the left abducens nucleus was hypoplastic, containing less than half the number of neurons seen in the right nucleus, both medial longitudinal fasciculi were normal and the remaining cell bodies in the nucleus were interpreted to be internuclear neurons. This



"Early" onset embryonic aberrant CN III innervation



"Later" onset embryonic aberrant CN III innervation



"Late" onset embryonic aberrant CN III innervation

finding corroborates the clinical observation that, in unilateral type I Duane's syndrome, adducting saccades in the unaffected eye are usually normal.[177,322,333] This finding also indicates an exquisitely specific neural deficit. Electrophysiological techniques such as auditory evoked potentials[237] and eye movement recordings[351,537] have suggested that there may be other associated brainstem dysfunction, but these studies have not produced conclusive evidence or have not been reproducible.[403,481]

"Upshoots" and/or "downshoots" on attempted adduction are common motility findings. Theoretically, the cause of the upshoots and downshoots may be mechanical, innervational, or a combination of the two. In most cases, the mechanics of the lateral rectus seem to be largely responsible because weakening or eradicating the action of a tight lateral rectus results in significant reduction or elimination of upshoots and downshoots. The "bridle-effect theory" postulates that vertical sideslip of a tight lateral rectus across the adducting globe produces these movements[234,510]; however, neuroimaging has not confirmed vertical displacement of the lateral rectus during upshoots and downshoots.[62,511] In certain individuals, an innervational anomaly may account for upshoots and downshoots. For example, one of the authors (B.N.B.) has observed that continued severe upshoot on adduction in a patient whose lateral rectus was detached from the globe and allowed to retract far

FIGURE 5-12. Proposed embryonal etiopathogenesis of Duane's syndrome as a congenitally deficient innervation syndrome. The developing cranial nerves have a "trophic" function on the developing mesenchyme of the future extraocular muscles. If there is late or no innervation to the developing mesenchyme, the muscle becomes dysplastic, fibrotic, and inelastic. If there is early aberrant innervation of the developing mesenchyme by cranial nerve III, the lateral rectus has a "normal" architecture but abnormal innervation, leading to limited abduction only (type I). The later during embryogenesis the innervation, the more dysplastic the lateral rectus, leading to limited adduction as well (type III). The balance between the quantitative amount of aberrant innervation and the degree of lateral rectus fibrosis creates relatively different patterns of abduction and adduction, leading to the different "types" of Duane's syndrome. Type II Duane's syndrome (not depicted) may be caused by more innervation from the third cranial nerve to the lateral rectus compared to the medial rectus. *Dotted lines* represent absent or hypoplastic innervation; *dashed lines* represent later onset of innervation; *thickness of lines* represents quantitative amounts of innervation. *LR*, lateral rectus; *MR*, medial rectus; *III*, oculomotor nucleus; *VI*, abducens nucleus.

into the orbit before suture adjustment. In addition, there is EMG evidence for cocontraction of appropriate cyclovertical muscles and the lateral rectus during upshoots and downshoots[217,322,443]; such co-contraction could play a substantial role in some cases.

Clinical Features and Natural History Most large series indicate that females represent about two-thirds of cases and that the left eye is affected in about two-thirds of unilateral cases. Approximately 75% are type I; type III accounts for most of the rest, and type II is quite rare. Types I and II may occasionally coexist in the 10% to 20% of cases that are bilateral. Many Duane's syndrome patients are orthotropic in primary position or with a small head turn and have excellent binocular function.[229,391,402] Although amblyopia can occur in the involved eye, the reported incidence of amblyopia as well as anisometropia varies widely.[448,491] Most Duane's syndrome patients ignore or are unaware of sensory disturbances,[300] but occasionally an older child presents with "acute" awareness of diplopia in the appropriate fields of gaze.

As mentioned, upshoots and downshoots on attempted adduction may occur and may be accompanied by A, V, or X patterns, giving the appearance of oblique muscle dysfunction.

Clinical Assessment Other diseases should be considered in the differential diagnosis. Rarely, acquired orbital disease may produce limitations of abduction and retraction, thereby mimicking Duane's syndrome. This effect has been observed with medial orbital wall fractures, fixation of muscle by orbital metastases, orbital myositis, and a variety of other conditions.[165,266,367,469]

Systemic Associations Although Duane's syndrome is usually an isolated finding, it may accompany any of a multitude of other congenital anomalies in 5% to 57% of cases (Table 5-7).[307,363,377]

Inheritance Familial cases are not uncommon, and an autosomal dominant mode of inheritance best fits most, but not all, of the reported pedigrees.[126] Duane's syndrome, sensorineural deafness, upper limb defects, facio-auriculo-vertebral anomalies, and genitourinary and cardiac malformations appear as isolated findings or in combination throughout certain families and may all, perhaps, be ascribed to a highly pleiotropic autosomal dominant gene that is frequently nonpenetrant.[198a,361] Studies of

TABLE 5-7. Congenital Anomalies Associated with Duane's Syndrome.

Structure	*Associated anomalies*
Ocular/external	Microphthalmos; coloboma; heterochromia iridis; flocculi iridis; congenital cataract[33,34,363] Ptosis; nevus of Ota; hypertelorism; prominent epicanthus[33,34,210,377,448] Epibulbar dermoid[307,363,377,379]
Neural	Optic nerve anomalies[34,120,248,261,307,377]; DeMorsier syndrome[5] Sensorineural deafness[261–264,307,448] Seventh nerve palsy[106,307,377,428] Marcus Gunn jaw winking[230,307] Gusto-lacrimal reflex[58,307,393] Fourth nerve palsy[307] Möbius syndrome[307]
Musculoskeletal	Craniofacial anomalies; skeletal anomalies; Klippel–Feil syndrome; Goldenhar's syndrome; Marfanoid hypermotility syndrome; cleft lip/palate; muscular dystrophy[34,35,106,212,261–264,307,361,363,377,379,393,421,448]
Miscellaneous	Cardiac anomalies[35,307,377] Genitourinary anomalies[106,377] Noonan syndrome Fetal alcohol syndrome[211] Congenital panhypopituitarism[107] Oculocutaneous albinism[208]

monozygotic twins have revealed both concordance and discordance in more than one family.[207,247]

Two recent reports of large families with autosomal dominant Duane's syndrome, one in the U.K. and the other in Mexico, have both found linkage to chromosome 2q31.[20,148] Other reports have found deletions in chromosome 8q in patients with Duane's syndrome associated with other abnormalities such as mental retardation and hydrocephalus.[79,505]

Treatment A patient with unacceptable primary position deviation, head position, globe retraction, upshoot, or downshoot may require surgery. All these factors as well as the relative contributions of mechanical and innervational factors are considered during surgical planning. As a general recommendation, resections of the horizontal recti of an affected eye is usually avoided because this may increase globe retraction. Otherwise, the surgical approach is individualized.[275] Depending on the situation, a wide variety of techniques may prove helpful, including transposition of the vertical recti with or

without medial rectus recession,[169,331] Y-splitting of the lateral rectus,[410] adjustable sutures,[388] and posterior fixation sutures.[293,510]

Prognosis Recession of horizontal rectus muscle eliminates the face turn in 79% of cases and significantly reduces the face turn in most of the remaining patients.[276,388] Undercorrection of primary position esotropia may occur postoperatively as the amount of recession needs to be larger than indicated in the tradition tables for concomitant strabismus; rerecession is recommended for these cases if the initial recession was less than 8 mm or if forced duction testing still indicates restriction. The occasional overcorrections may be reversed by advancing the recessed muscle or recessing the antagonist horizontal rectus muscle if tight.[171,348,353]

Synergistic Divergence

Synergistic divergence is a striking motility pattern consisting of an adduction deficit with simultaneous bilateral abduction on attempted gaze into the field of action of the involved medial rectus.[109,514,525] As with Duane's syndrome, cocontraction of the lateral and medial recti has been demonstrated on EMG,[525] and it has therefore been suggested that synergistic divergence may be placed along the Duane's "spectrum" of congenital anomalous innervation. In this conceptual scheme, synergistic divergence is similar to type II Duane's syndrome, except that the larger part of the branch of the third nerve "intended" for the medial rectus is misdirected to the lateral rectus. The globe retraction characteristic of Duane's syndrome does not accompany synergistic divergence, presumably because there is so little innervation to the medial rectus. However, this hypothesis has not been verified by clinicopathological study, and saccadic velocity studies in two patients indicate that the abducens nerve may not necessarily be absent or severely hypoplastic.[188]

Synergistic divergence has been observed as early as 5 months of age,[108] may be bilateral,[187,188,486] and has been associated with other abnormalities including Marcus Gunn jaw-winking,[72,73,187] ipsilateral congenital Horner's syndrome,[238] arthrogryposis multiplex congenita,[109] congenital fibrosis syndrome, and oculocutaneous albinism.[72,73]

Surgical crippling of the ipsilateral lateral rectus has been combined with a variety of other procedures such as medial rectus resection and superior oblique tenotomy and inferior

oblique myectomy[330] to eliminate the simultaneous abduction as well as to correct the exotropia in primary position.[188]

Other types of anomalous innervation that may involve the sixth nerve include congenital or acquired synkinesis of the levator and lateral rectus during abduction,[242,343] acquired trigemino-abducens synkinesis with abduction accompanying jaw movements,[312,349,453] congenital twitch abduction on attempted upgaze,[271] or lateral gaze synkinesis on downward saccades.[503]

THIRD NERVE

OCULOMOTOR SYNKINESIS

Oculomotor synkinesis (aberrant regeneration of the third nerve) commonly accompanies third nerve palsies, usually those of congenital or traumatic origin, but also those caused by aneurysm, migraine, or tumor. This condition is discussed in detail in the section on third nerve palsies. Although oculomotor synkinesis is, perhaps, the most familiar form of anomalous innervation involving the oculomotor nerve, other patterns do occur.

VERTICAL RETRACTION SYNDROME

Vertical retraction syndrome is exceedingly rare with only several case reports in the literature.[258,376,389,433,518] Typically, elevation or depression of the globe is limited, and when attempted, it is associated with narrowing of the lid fissure and retraction. There may be an associated horizontal deviation that is greater with gaze in the direction of the limited vertical eye movements. Forced ductions are positive, although this does not preclude a central mechanism.

EMG study of one patient revealed lateral rectus muscle contraction on upgaze and downgaze. Eye movement recordings of this and two other patients in the same study showed a twitch abduction of the occluded eye on upward saccades, followed by a postsaccadic drift back and a slower abduction in downgaze; this phenomenon was seen in each nonfixing of all three patients, suggesting a synergistic innervation between the abducens nerve and the upper and lower divisions of the oculomotor nerve.

EMG in one atypical case of vertical retraction syndrome showed cocontraction of the vertical recti in upgaze, downgaze, and adduction, and electro-oculography was also consistent with

an anomalous innervational pattern.[389] The clinical findings included exotropia; poor elevation and adduction; retraction of the globe on upgaze, downgaze, and adduction; and downshoot on adduction.

Marcus Gunn Jaw-Winking

Marcus Gunn jaw-winking is not usually accompanied by abnormal eye movements but is included here as another instance of anomalous innervation. This congenital trigemino-oculomotor synkinesis links innervation of jaw and eyelid levator muscles and is characterized by congenital ptosis, usually unilateral, with elevation of the ptotic lid when the jaw is moved. This ipsilateral associated ptosis accounts for 5% to 10% of all congenital ptosis.[57,193]

Etiology Because normal subjects demonstrate EMG cocontraction of the muscles supplied by the oculomotor nerve and certain muscles of mastication supplied by the trigeminal nerve,[427] Marcus Gunn jaw-winking may represent an exaggeration of a physiological synkinesis that is normally present but clinically undetectable. The precise mechanism for failure of higher inhibition remains unclear. EMG evidence and histological study of the levator muscles suggest an underlying brainstem process because the levator muscles are involved bilaterally.[204,299,427]

Clinical Features There are two major categories of trigemino-oculomotor synkinesis. The first, and most common, consists of external pterygoid-levator synkinesis and is characterized by lid elevation when the jaw is projected forward, thrust to the opposite side, or opened widely. In the second form, internal pterygoid-levator synkinesis, lid elevation is triggered by clenching of the teeth. Rarely, a number of stimuli other than pterygoid contraction can cause eyelid elevation, and these include smiling, inspiration, sternocleidomastoid contraction, tongue protrusion, and voluntary nystagmus. Conversely, in an unusual case of trigemino-oculomotor sykinesis, pterygoid contraction was associated with contraction of the inferior rectus rather than the levator, thereby producing monocular bobbing eye movements rather than eyelid elevation.[356]

Marcus Gunn jaw-winking typically presents shortly after birth with rhythmic elevation of the affected upper lid during feeding. The ipsilateral associated ptosis may be of any degree of severity. A significant number of patients have amblyopia,

anisometropia, strabismus, superior rectus palsy, or double elevator palsy.[57,193]

Natural History It is interesting to note that, in many cases, parents remark that the synkinesis seems less apparent as the child becomes older. As this observation is not supported by objective examination, it may occur because the child learns to control both lid position and excursion.

Systemic Associations Marcus Gunn jaw-winking can be bilateral; has been reported in association with other forms of anomalous innervation such as synergistic divergence, Duane's syndrome, and trigemino-abducens synkinesis; and is rarely familial or associated with heritable diseases such as Waardenburg syndrome, Rubinstein–Taybi syndrome (author's observation; M.M.), Hirschsprung megacolon, neuroblastoma, and neurofibromatosis type 1.[94,268,316]

Treatment Strabismus, amblyopia, and anisometropia are treated when necessary. Surgical management of the ptosis may be achieved by conventional levator resection in mild cases of jaw-winking. In moderate to severe cases, bilateral levator excision and bilateral frontalis suspension have been shown to provide satisfactory correction of both jaw-winking and ptosis. The frontalis suspensions may be achieved by using fascia lata, either autologous or homologous, or strips of the levator muscle after transsecting the muscle, but still attached distally via the aponeurosis to the tarsus.[45,259]

Seventh Nerve

The seventh nerve may also be involved in several anomalous innervational patterns that do not affect eye movements but may present to the ophthalmologist.

Intrafacial Synkinesis

Intrafacial synkinesis commonly appears after peripheral facial nerve palsies; branches of the regenerating seventh nerve are misrouted to inappropriate muscles. Frequently, for example, the orbicularis oculi contracts simultaneously with lower facial muscles, and there may be significant narrowing of the palpebral fissure with smiling. Other patterns can occur and, on occasion, are bothersome enough for a patient to require botulinus toxin injection or surgery.[22,390,411]

Marin–Amat Syndrome

This syndrome, also known as *inverse Marcus Gunn phenomenon*, is a rare disorder in which the upper eyelid *falls* when the mouth opens. This syndrome is observed after peripheral facial nerve palsies and has been suggested to be a result of aberrant reinnervation. However, EMG shows inhibition, rather than excitation, of the affected levator muscle during external pterygoid contraction,[296] and absence of orbicularis oculi activity may differentiate this condition from the typical forms of intrafacial synkinesis. Wide jaw opening causes synkinetic contraction of the orbicularis oculi and lid closure, possibly triggered by stretching of the facial muscles.[394]

DISORDERS AT THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis in Infancy

Myasthenia gravis in the infant takes one of three clinical forms.

Transient Neonatal Myasthenia

Transient neonatal myasthenia is seen in approximately one of seven infants born to mothers with myasthenia gravis. All these babies develop a weak cry and difficulty sucking in the first several days of life, and about half become generally hypotonic. This condition, caused by antiacetylcholine receptor antibody (anti-AChR antibody) received by the baby from the mother's circulation,[292] responds promptly to anticholinesterase agents but will resolve in 1 to 12 weeks if untreated.[344,530] There is no relapse or long-term sequela.

Familial Infantile Myasthenia Gravis

Familial infantile myasthenia is rare, appears in children of mothers without myasthenia gravis, and presents in early infancy with ptosis, poor suck and cry, and secondary respiratory infections. Episodic crises of severe respiratory depression and apnea are precipitated by fever, excitement, or vomiting.[151,180,406] Other features include hypotonia, proximal muscle weakness, and easy fatigability, but the extraocular muscles are usually not involved. Inheritance of familial infantile myasthenia gravis has been reported to be autosomal recessive

with localization to the telomeric region of chromosome 17, on 17p13.[90] A candidate gene under study for this disease in the 17p region is synaptobrevin-2, a synaptic vesicle protein; this protein probably participates in neurotransmitter release at a step between docking and fusion.[221] This disorder responds to anticholinesterase medications and tends to ameliorate with age.

CONGENITAL MYASTHENIC SYNDROMES

A third type of myasthenia seen in infants is the group of congenital myasthenic syndromes, a heterogeneous group of disorders that may affect presynaptic or postsynaptic mechanisms. Various acetylcholine receptor subunit defects as well as genetic defects in endplate acetylcholinesterase have been related to different congenital myasthenic syndromes.[144]

The frequency of congenital myasthenic syndromes varies from 8% to 21% in reported series of childhood myasthenia gravis, reportedly higher where consanguineous marriages are frequent.[18,340] In the fetal period, decreased fetal movements have been reported, resulting in arthrogryposis multiplex congenital, congenital flexures, and contractures of multiple joints.[498] Affected patients are born to mothers without myasthenia and may demonstrate ptosis and ophthalmoparesis during infancy. Severe generalized weakness may also present in the postnatal period with frequent apneic episodes, recurrent aspiration, failure to thrive, and poor sucking. Other patients may present during the first or second year of life with ocular signs and only mild systemic signs. Although ptosis was reported to be present in all of seven patients in one series,[340] it was generally mild and not incapacitating.

These disorders persist throughout life and can be distinguished from acquired myasthenia gravis and from each other by combining clinical, electrophysiological, ultrastructural, and cytochemical investigations.[144–146] Tensilon testing can be positive, and a patient may respond to a trial of pyridostigmine. Presence of anti-AChR antibody excludes this disease.[340] Inheritance in one type termed *slow-channel congenital myasthenia gravis* has been attributed to mutations in the AChR subunit genes, and depending on which subunit is mutated, the disease is transmitted in an autosomal dominant or autosomal recessive fashion. Treatment in congenital myasthenic syndrome patients is generally supportive, and the use of acetylcholinesterase

inhibitors is disease specific. Surgery for stable strabimsus in a child can yield a stable long-term result.[340]

Autoimmune Myasthenia Gravis

INCIDENCE

Acquired myasthenia gravis affects overall about 1 in 20,000 per year to 0.4 in 1,000,000 per year.[519] Girls are affected two to six times as frequently as boys, and the incidence of the condition increases progressively through childhood until the end of the second decade of life. Afer the age of 50 years, males predominate; the mean age of onset in women is 28 years and in men 42 years.[519] Among the various childhood forms of myasthenia gravis, a recent series identified 25 (71%) of 35 children as having the autoimmune disease.[340]

ETIOLOGY

Acquired myasthenia gravis is an autoimmune disorder. The myasthenic patient has fewer available skeletal muscle acetylcholine receptors because of antibodies produced against these receptors[130] and also because of complement activation.[16] Neuromuscular transmission is thereby poised to fail. Normally, with repetitive stimulation of a motor nerve, the amount of acetylcholine released from that nerve diminishes. In the delicately balanced myasthenic, this decrease in neurotransmitter may well lead to a failure of muscular response. In this context, it is easy to understand why muscle fatigue is the clinical hallmark of myasthenia gravis and why the constant activity of the extraocular muscles, among other activities,[243,354] particularly predisposes them to demonstrate fatigue. The exact reasons for predilection for the extraocular muscles are under study, one explanation potentially lying in the differential expression of acetylcholine receptor subunits in extraocular versus skeletal muscle.[47,244,301]

A number of medications are known to produce myasthenia gravis in normal individuals or to exacerbate already existing disease. The list includes D-penicillamine, antibiotics, anticonvulsants, intravenous contrast dye, anticholinesterase agents, neuromuscular blocking agents, antiarrhythmic drugs, phenothiazines, beta-blockers, and quinine. For example, myasthenia produced by D-penicillamine is indistinguishable from

primary acquired myasthenia clinically, immunologically, and electrophysiologically.[519]

Clinical Features

Several general clinical observations may be made concerning myasthenia gravis. Muscle weakness is not accompanied by other neurological signs; muscle function, which may fluctuate even within the course of an office visit, is improved by cholinergic medications; and extraocular, facial, and oropharyngeal muscles are most commonly involved. Beyond this, there are numerous variations of presentation, and no single sign is solely reliable.

Natural History

Of patients who present initially with purely ocular symptoms and signs, 50% to 80% subsequently develop generalized myasthenia within about 2 years.[519] In a large study of 1487 patients with myasthenia, 53% presented with ocular symptoms.[183,519] Of the entire group of myasthenic patients in this study, 15% continued to demonstrate purely ocular manifestations (with follow-up to 45 years; mean, 17 years). Of the 40% of patients in this study with strictly ocular involvement during the first month after onset of symptoms, 66% developed generalized disease. Of these who subsequently developed generalized disease, 78% did so within 1 year, and 94% within 3 years after onset of symptoms and signs.

In a series of 24 children in Toronto with acquired autoimmune myasthenia (age, 11 months to 16 years; median age, 4.7 years), 14 (58%) patients initially had ocular involvement only (median follow-up time, 2.6 years). Of these 14, 5 (36%) progressed to generalized myasthenia gravis in a mean time of 7.8 months (range, 1–23 months). Patients with ocular myasthenia presented at an average of 6.8 years; those with systemic disease presented on average at 7.1 years.[340]

Clinical Assessment

Variable diplopia or ptosis most often prompt an ophthalmologic evaluation. Patients with these symptoms are evaluated for signs and symptoms of generalized myasthenia such as facial weakness, dysphonia, arm or leg weakness, chewing weakness, and respiratory difficulties. In "ocular myasthenia," however,

the findings are restricted to the levator and extraocular muscles. Because there is no stereotypical myasthenic eye movement, this diagnosis should be considered in any child with an unexplained, acquired ocular motility disturbance and clinically normal pupils, particularly when the deviation is variable, whether or not ptosis is present. Any pattern of abnormal motility is suspect, including an apparent gaze palsy, internuclear ophthalmoplegia,[167] isolated cranial nerve palsy,[423] one and one-half syndrome,[116,468] incomitant strabismus, accommodative and vergence insufficiency,[101] and gaze-evoked nystagmus.[250,288] Prolonged OKN may demonstrate slowing of the quick phases; large saccades may be hypometric; small saccades may be hypermetric; and characteristic "quiver movements," which consist of an initial small saccadic movement followed by a rapid drift backward, may be seen.[46,288]

In addition to the eye movements, lid function is assessed. Ptosis can be elicited or accentuated by fatiguing the levator palpebrae superioris with prolonged upgaze or repeated lid closure. Because Hering's law of equal innervation applies to the levator muscles as it does to the extraocular muscles, the contralateral lid may be retracted but falls to a normal position when the ptotic lid is lifted with a finger. Through the same mechanism, in bilateral ptosis, manual elevation of one lid increases the amount of ptosis on the other side by diminishing the amount of innervation necessary to fixate. Cogan's lid twitch sign can be elicited in some myasthenic patients by having the patient look down for 20 s and then making an upward saccade to the primary position; the lid twitches upward one or more times and then slowly drops to its ptotic position. Finally, the orbicularis oculi muscles are often weak, and the patient may not be able to sustain lid closure.

Examination of the patient before and after the administration of anticholinesterase agents is, arguably, of more limited use in children than in adults. This method may be most helpful in children whose history and physical examination do not permit a clear diagnosis yet who have such significant deficits in lid elevation or ocular motility that a response is easily observed. A positive test consists of the direct observation of a weak muscle becoming stronger after the administration of intravenous edrophonium hydrochloride (Tensilon) or intramuscular neostigmine methylsulfate (Prostigmin). The initial dose is 2 mg, given up to 10 mg total. The onset of action for Tensilon is 30 s, lasting up to 5 min. This drug is contraindicated

in patients who are elderly or have heart disease, and other workup should be performed before considering the Tensilon test. Intramuscular Prostigmin is longer acting than Tensilon and allows more time for measurement of changes, but its absorption rate and hence onset of action are quite variable; its onset of action is generally between 15 to 20 min and the peak response occurs about 30 to 40 min after administration. In children the dose is 0.02 mg/kg, always with a total of less than 1.5 mg; and in adults the dose is 1.5 mg, with atropine 0.6 mg, coadministered.[279] Choice of drug can be individualized according to the endpoints that are being assessed and to the ability of the child to cooperate.

To make a decisive observation, it is important, both before and after giving these drugs, to quantitate as accurately as possible the function of the affected muscle(s) through measurement of pertinent indicators such as lid height in primary position, levator function, saccadic velocities, ocular movement, ocular alignment, and orbicularis strength. After administering Tensilon, the examiner observes for tearing and lid fasciculations as evidence of cholinergic effect, and draws no conclusion if a paradoxic decrease in muscle function occurs, because this may happen in the presence or absence of myasthenia. Positive responses after either drug are fairly reliable evidence for myasthenia but can, on rare occasions, occur in nonmyasthenic patients. False-negative responses, however, are common and therefore do not exclude myasthenia gravis.

Alternatively, a rest test may be used by allowing the patient to rest with eyes closed for a period of 10 to 15 min.[337] An "ice test" has also been reported to improve ptosis[173,278,425] and motility[142] after applying an ice pack to the eyes for 2 to 5 min. However, subsequent report of four patients[337] revealed no difference among an ice test, a heat test, or a rest test, so long as the rest period was at least 10 to 15 min.

Further diagnostic testing may include anti-AChR antibody titer and electromyography. EMG is particularly useful in generalized myasthenia but is difficult to perform in a frightened, uncooperative child. The electromyographer looks for a characteristic decrement in the muscle action potentials with repetitive supramaximal nerve stimulation and for the "jitter phenomenon" on single muscle fiber studies, difficult responses to elicit and observe even in a cooperative patient. Anti-AChR antibody is most helpful in generalized myasthenia as it is reportedly present in 80% to 90% of those patients but only 50%

or fewer of ocular myasthenics.[149,463,519] According to other reports, specifically on juvenile myasthenia gravis patients, the frequency of postive AChR antibody was between 56% and 63%.[4,15,19]

Systemic Associations

Associated immune disorders to be considered in children include rheumatoid arthritis, juvenile-onset diabetes mellitus, asthma, and thyroid disease; neoplasia (breast cancer, uterine cancer, carcinoma of the colon, pinealoma) is also seen.[408] Thymoma rarely occurs in children although it is recognized to accompany 10% of myasthenia gravis.

Inheritance

Inheritance is usually sporadic. Approximately 1% to 4% of cases are familial without a clear Mendelian pattern. This familial predisposition may be due to predilection for autoimmunity in general.

Treatment

Once the ophthalmologist diagnoses or strongly suspects myasthenia, a neurologist generally directs further testing and treatment. The ophthalmologist's role remains important, however. In addition to monitoring the motility and lid dysfunction and providing symptomatic relief for these disorders, the ophthalmologist should be alert to the possibility of amblyopia. If not promptly detected and attended to, amblyopia can be extremely difficult to treat, particularly when there is sufficient ptosis to necessitate taping or a ptosis crutch for the lid during occlusion of the sound eye.

Current therapy aims to increase the amount of acetylcholine available through the use of anticholinesterase agents or to diminish the autoimmune reaction with corticosteroids, other immunosuppressive agents, such as azathioprine, cyclosporin A, and mycophenolate mofetil,[93,150] plasmapheresis, or thymectomy. Supervision of these treatments is clearly in the bailiwick of the neurologist. It is worth noting that anticholinesterase agents are not as effective in ameliorating ocular motility as they are for other manifestations of myasthenia[149] nor are they as effective as steroids[462] or other treatments directed against the autoimmune response.[431] However, because

of the risks and complications, the use of steroids, immunosuppressives, plasmapheresis, and thymectomy in pure ocular myasthenia gravis remains controversial.[68,365,441] In a recent pilot study, cyclosporin A was found to be effective in a series of eight patients, resulting in complete remission in seven of the eight, with a mean follow-up of 14 months; the eighth patient was noncompliant.[80]

Strabismus surgery has been performed on patients with stable deviations of at least 5 months, using conventional strabismus surgical techniques.[115,360] The presence of systemic disease is an important consideration in deciding on the method of anesthesia, although general anesthesia is not an absolute contraindication when the disease is clinically controlled.

PROGNOSIS

The prognosis for survival, improvement, and remission in a child with myasthenia gravis is better than that in an adult, according to most studies.[327,408,462] Rodriquez and coworkers[408] studied 149 children who were less than 17 years old at the onset of autoimmune myasthenia gravis and had a median follow-up of 17 years with minimum follow-up of 4 years. An estimated 80% of these patients were alive at age 40, about 90% of the survival expected in the general population. Improvement or remission was seen in 79% of the 85 patients who underwent thymectomy and 62% of the remaining 64 patients. In the smaller Toronto series, children required an average of 2 years on medication before entering remission.[340] Complete remission in adults has been reported as 40% to 70%, generally achieved after 1 to 3 years of treatment.[519]

In 9% of children in the Rodriquez series, the disease remained strictly ocular; this is comparable to the 14% found in a large adult series observed over a similar interval.[183] In the Toronto series, 38% of the 24 children remained strictly ocular, although the mean follow-up period was 3.5 years.[340] Children with ocular myasthenia gravis may also show prolonged remissions and respond well to steroid therapy on relapse.[412,437]

The result of strabismus surgery for myasthenia gravis has reportedly been favorable in two studies, after a follow-up of 4 months to 14 years (median, 12 months).[115,360] In these two studies combined, 2 of 10 patients required reoperations, and 1 of the 10 required prisms postoperatively.

Botulism

Numerous pharmacological agents and toxins may interfere with transmission at the neuromuscular junction. The neurotoxin produced by the bacterium *Clostridium botulinum* irreversibly impedes the intracellular mechanisms responsible for the release of acetylcholine from the presynaptic nerve terminals.[458]

Etiology

The different neurotoxins produced in botulism exhibit different clinical characteristics. Type E botulism is usually associated with eating seafood; pupillary abnormalities and ptosis may be seen as early signs. Gastrointestinal symptoms are more prevalent in type E and type B. The most severe form is type A, which carries the highest risk for ventilatory support and the highest mortality.

Clinical Features

Children may develop botulism from ingestion of contaminated food, wound infection, or intestinal infection in infants. Infants usually come to attention because of lethargy, weakness, feeding difficulty, a feeble cry, and constipation.[240] Older children report nausea, vomiting, blurred vision, dysphagia, and pooling of secretions in the mouth, followed by generalized weakness and diplopia. In both groups, ophthalmologic findings are common and may include any type or degree of external ophthalmoplegia, dilated pupils that react poorly to light, and ptosis.[485]

In one outbreak of 27 patients in the U.K., the complaints were of blurred vision in 78%, drooping lids in 56%, and double vision in 30%. In this report, 11 of 14 (79%) of reviewed records revealed sixth nerve palsy and 13 of 14 (93%) revealed accommodative paresis, both of which were early ophthalmic signs. The severity of ophthalmoparesis was a good indicator of the overall severity and progression of disease. When there was ventilatory failure, it occurred 12 h after third cranial nerve palsy.[457]

In another report, it was noted that sixth cranial nerve palsy may be the initial neurological manifestation of type B botulism.[485] In 8 of 11 (73%) of their patients diagnosed with third nerve palsy, respiratory insufficiency eventually ensued.

Quivering eye movements on attempted saccades have also been observed and analyzed on eye movement recordings, consisting of hypometric saccades with subnormal and stuttering velocities.[200]

Clinical Assessment

Because botulism may be difficult to distinguish clinically from Guillain–Barre syndrome,[241] pupillary findings, which are rare in Guillain–Barre, become particularly important. Botulism may also be mistaken for myasthenia gravis (again, the pupils are helpful; a Tensilon test may be falsely positive in mild forms of botulism[457]), sudden infant death syndrome, and hypothyroidism in infants. In infants, EMG is the primary means of diagnosis.[241]

Treatment

Treatment is essentially supportive. Antitoxin has been shown only to shorten the duration of illness in type E botulism, but is considered in patients with botulism as soon as the diagnosis is suspected as it can only act before the toxin is irreversibly bound to its receptor. Adverse reactions to the antitoxin have been reported in up to 20% of patients. Guanidine, a drug that enhances release of acetylcholine from the presynaptic nerve terminal, has only a slight effect on limb and ocular muscles and no effect on respiratory muscles.[457]

Prognosis

Recovery does not occur until new neuromuscular junctions are established, a process that may take weeks to months. The mortality from this condition in the United States has been reported as 7.5%; this figure is higher in developing countries.[457]

DISORDERS OF THE EXTRAOCULAR MUSCLES

Abnormal extraocular muscles may limit eye movements through decreased function or through restriction. The pattern of limitation may simulate neural and neuromuscular disorders

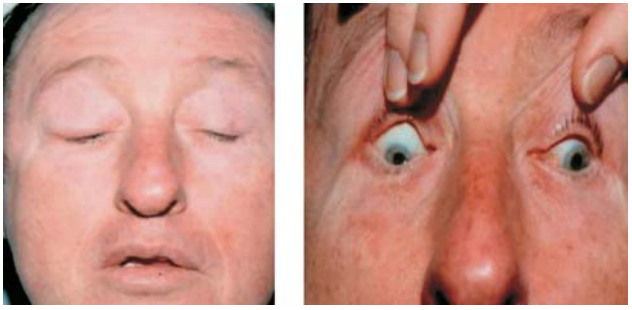


FIGURE 5-13. Fibrosis of the extraocular muscles. Severe ptosis (*right photo*) and eyes fixed in depression with minimal to no movement typical of severe fibrosis of the extraocular muscles.

so closely that force ductions, special imaging (echography, CT, MRI), or even surgical exploration may be necessary for differentiation.

These disorders may be either congenital or acquired. Congenital anomalies of the extraocular muscles include agenesis, duplication, abnormal origins and insertions, fascial anomalies, and fibrous bands.[297,500,508,509,529] *Congenital absence of one or more extraocular muscles* limits movement of the globe in the direction of action of the missing muscle(s) and may mimic a nerve palsy. Indeed, in one series of presumed congenital superior oblique palsies for which a superior oblique tuck was deemed necessary and attempted, 18% of the patients were found to have congenital absence of the superior oblique.[201] Agenesis and other forms of maldevelopment of the extraocular muscles have long been recognized and associated with craniofacial anomalies.[124,384]

At times, certain extraocular muscles mechanically restrict eye movements from birth, for example, in the *congenital fibrosis syndrome* (Fig. 5-13) or *congenital Brown's syndrome*. Acquired disorders such as *trauma*, *dysthyroid myopathy*, *acquired Brown's syndrome*, and *orbital myositis* may all cause weakness or restriction of extraocular muscles. Although investigation of these disorders requires careful attention to the history and systemic health of the child as well as local ocular and orbital signs, such advertence is frequently rewarded.

DISORDERS OF NERVE AND MUSCLE

Kearns–Sayre Syndrome (Chronic Progressive Ophthalmoplagia)

Clinical Features and Natural History

Ptosis and chronic progressive limitation of eye movements, usually without diplopia, are features of a variety of disorders. Among these, Kearns–Sayre syndrome (KSS) is singularly apt to come to attention in childhood, most often because of ocular signs. The triad of external ophthalmoplegia, heart block, and retinal pigmentary degeneration identified in the original description of KSS[256] remains the cornerstone of diagnosis, although a multitude of associated signs have since been recognized (Table 5-8).

The eye movements in KSS show gradually progressive limitation, which is usually symmetrical and affects all directions of gaze. Bell's phenomenon and eye movement responses to caloric stimulation or head rotation are also slowly lost. Anticholinesterase agents do not improve the range of eye movements. Pupils remain normal. The lids are typically ptotic and often close weakly because of involvement of the orbicularis

TABLE 5-8. Manifestations of Kearns–Sayre Syndrome.

System	*Findings*
Cardinal features	Chronic progressive external ophthalmoplegia; degenerative pigmentary retinopathy; cardiac conduction defects/sudden death; no family history
Musculoskeletal	Short stature; "ragged-red" fibers by light microscopy of muscle tissue; skeletal and dental anomalies
Neurological	Elevated CSF protein; deafness; vestibular dysfunction; cerebellar ataxia; "descending" myopathy of face and limbs; mild corticospinal tract signs; subnormal intelligence; demyelinating polyradiculopathy; slowed electroencephalogram; decreased ventilatory drive/sudden death; spongiform degeneration of cerebrum and brainstem
Endocrine	Diabetes mellitus; hypogonadism; hypoparathyroidism; growth hormone deficiency; adrenal dysfunction; hyperglycemic acidotic coma/death; elevated serum lactate and pyruvate
Other	Corneal edema; nephropathy

Source: Modified from Glaser JS, Bachynski BN. Infranuclear disorders of eye movement. In: Glaser JS (ed) Neuro-ophthalmology, 2nd edn. Philadelphia: Lippincott, 1990:402, with permission.[166]

oculi. Indeed, generalized facial weakness is frequent and contributes to a typical facial appearance.

Affected fundi demonstrate a diffuse pigmentary retinopathy that characteristically involves the posterior pole as well as the periphery and generally consists of a "salt-and-pepper" pattern of pigment clumping. Commonly both rod and cone function are reduced on electroretinography,[341] and although it has been noted that only 40% of patients have decreased visual acuity or night blindness,[54] photoreceptor function can diminish insidiously with time.

Systemic Associations

Cardiac conduction defects, a cardinal feature of KSS, can be heralded by an interval of enhanced conduction at the A-V node and may lead to death at any time.[88,404] Other systemic associations include small stature, ataxia, deafness, raised cerebrospinal fluid protein, diabetes, and hypoparathyroidism (see Table 5-8).

Clinical Assessment

On any patient suspected of KSS, an electrocardiogram is performed. Abnormal blood lactate and pyruvate levels may be found. On skeletal muscle biopsy, "ragged-red fibers" and abnormal mitochondria are expected. In diagnosing patients suspected of KSS but with an incomplete constellation of findings, analysis of muscle mtDNA to look for mitochondrial deletions may be more critical than mitochondrial morphological examination (see following).[178] The brain MRI of patients with KSS may show normal or atrophied brain, but the characteristic finding is a combination of high-signal foci in subcortical cerebral white matter, brainstem, globus pallidus, or thalamus.[92]

Etiology

A protracted and shifting debate over the etiology and nosology of KSS has continued for decades. Early on, *chronic progressive external ophthalmoplegia (CPEO)* was considered to be an isolated myopathy of the extraocular muscles, with occasional weakness of the extremities.[260] However, many subsequent reports described CPEO in conjunction with multisystem disease, with KSS itself serving as a good example. When spongiform degeneration of the brainstem and cerebrum, which is observed on neuropathological examination of patients with

KSS, was highlighted,[114] the neural structures governing eye movements became suspect. Next, myopathological findings pointed investigators in yet a different direction. In CPEO, light microscopy of muscle preparations processed with the modified Gomori trichrome stain frequently demonstrates "ragged-red" muscle fibers among normal extraocular muscle fibers, orbicularis oculi fibers, and, at times, other skeletal muscle fibers. With electron microscopy, these ragged-red fibers as well as other muscle fibers demonstrate markedly abnormal mitochondria. In KSS, such abnormal mitochondria were detected in a variety of other tissues as well, including sweat glands,[245] liver cells,[174] and cerebellar neurons.[438] Experimental infusion of a chemical that uncouples oxidative phosphorylation produced reversible ragged-red fibers.[318] This morphological evidence combined with biochemical abnormalities indicating mitochondrial dysfunction led to speculation about the role of mitochondrial DNA (mtDNA) in the pathogenesis of these disorders.

INHERITANCE

The majority of KSS and CPEO cases are sporadic. In one review, only a single family demonstrated more than one person manifesting the entire KSS.[420] When small pedigrees with multiple individuals exhibiting CPEO have been reported, transmission has generally been maternal and compatible with mitochondrial inheritance,[140,223,236] but paternal transmission of CPEO has also been observed, suggesting a defective autosomal nuclear gene in some cases.[139,140,467]

New techniques in molecular biology have triggered an explosion of studies of mtDNA in patients with KSS and CPEO.[178,334] A significant proportion of these patients show large-scale heteroplasmic deletions in mtDNA, and these deletions play a pivotal role in the pathogenesis of these disorders. *Heteroplasmy* denotes the presence of several different mtDNA in a cell, some of which may be pathogenic. KSS and CPEO patients have heteroplasmy in different proportions depending on the tissue studied[222]; large-scale deletions of mtDNA have been observed in muscle of 80% of KSS patients and 70% of those with CPEO.[178] Based on these observations, it has been suggested that CPEO and KSS are different severities along the same clinical spectrum.[131,178]

Another finding that may explain the overlap between the clinical presentations of KSS and CPEO is that patients with

these two diseases have identical mtDNA deletions, but in KSS they are localized to the muscle and neural tissues, whereas in CPEO they are localized to muscle. Another disease called Pearson syndrome also has the identical deletions as in KSS and CPEO but is localized to the blood. In fact, patients with Pearson syndrome may develop KSS later in life.

On the other hand, mtDNA duplications have been observed in KSS but not in CPEO patients,[178] a difference that lends support to the idea that these are two distinct clinical entities, as suggested earlier.[54]

The severity of disease in patients with mitochondrial deletions apparently depends on a variety of factors: (1) the degree of heteroplasmy, or the distribution of normal and mutant mitochondria; (2) the nature of the mitochondrial mutation; (3) reduction in absolute amounts of normal mtDNA; and (4) a homoplasmic mutation that leads to a large deletion.[178]

Treatment and Prognosis

The prognosis for patients with KSS is fair, and treatment is largely symptomatic. Patients can frequently be managed with a cardiac pacemaker[382] to obviate conducting fibers that, on pathological study, are fibrotic and infiltrated by fat.[156,160] Despite cardiac pacing, patients may die suddenly of inadequate brainstem ventilatory response to hypoxia.[82,104]

Abrupt and fatal endocrine dysfunction may also be triggered by steroids,[38] and there can be hypersensitivity to agents used during induction of general anesthesia.[233] For many pediatric patients, however, it is the relentless progression of neurological deficits, especially weakness and ataxia, rather than the possibility of sudden demise, that proves to be particularly trying.

Preliminary reports suggest that administration of coenzyme Q10, a quinone found in the mitochondrial oxidative system (with reported doses of 60–120 mg daily for 3 months in one patient,[357] 50 mg 3 times a day for 3 months in two others[359]), may improve A-V block as well as normalize serum pyruvate and lactate levels[358]; improve neurological function without an effect on the ophthalmoplegia or the electrocardiogram[70]; and increase respiratory vital capacity when used with succinate.[452]

Surgery is generally not recommended for either ptosis or strabismus in these patients as it is a progressive disease. Surgical correction of ptosis would involve a high risk of exposure

keratopathy, especially because the eye will lose its Bell's phenomenon during the course of the disease and corneal wetting would not occur. Diplopia from strabismus may be treated with prisms and, as a last resort, monocular occlusion.

Myotonic Dystrophy

Myotonic dystrophy, also known as dystrophia myotonica or Steinert's disease, is an autosomal dominant multisystem disorder with variable phenotype. Early investigators focused on muscle as the primary site of involvement; subsequent studies revealed that the nervous system[231] as well as a variety of other tissues are affected in addition to the muscles. At least two main types of myotonic dystrophy exist, termed DM1 and DM2. Two other described forms, called proximal myotonic myopathy (PROMM) and proximal myotonic dystrophy (PDM), are closely linked to the DM2 locus and may be caused by the same genetic defect with different phenotypic expression.

INCIDENCE

Myotonic dystrophy is considered as one of the most frequent "dystrophies" in adulthood, with a prevalence of approximately 5 in 100,000 in white European populations.[401]

ETIOLOGY

The fascinating pathogenesis of DM1 has been described as a result of various mechanisms.[319] The most important factor is the expanded trinucleotide cytosine-thymidine-guanine (CTG) repeats in the 3′-untranslated region of the disease gene, dystrophia myotonica protein kinase (DMPK) gene, which leads to decreased DMPK messenger RNA (mRNA) expression and protein levels. However, DMPK knockout mice showed only mild muscle weakness and abnormal cardiac conduction. On further investigation, it was found that the expanded trinucleotide repeat in the mRNA is toxic to the muscle, because when transgenic mice were developed that express human skeletal actin—unrelated to the DMPK gene—with expanded CTG repeats in the 3′-untranslated region, the mice developed myotonia and myopathy.[304]

A significant correlation exists between age of onset and number of CTG repeats and a general correlation between the degree of CTG expansion and the severity of disease manifesta-

tions. Mildly affected patients have 50 to 150 repeats, classic DM1 patients have 100 to 1000, and congenital cases may have more than 2000.[319]

The exact pathological mechanism remains unclear, but a theory unifying the protean manifestations of the disease has been proposed, namely that the fundamental defect is a generalized abnormality of cell membranes.[418] Recent evidence supports the hypothesis that DMPK deficiency is associated with sodium channel abnormality in DM.[336]

Clinical Features and Natural History

Unlike KSS, ocular motility abnormalities in myotonic dystrophy are commonly subclinical and have been observed for the most part in adults. A number of authors have described progressive limitation of voluntary eye movements as well as markedly decreased maximum saccadic velocity and reduced smooth pursuit gain, but it is not clear whether these eye movement disorders result from a neurological or myopathic defect or both.[14,123,143,290,364,449,484,503] Clinical myotonia, that is, delayed muscular relaxation, most strikingly affects the limb muscles (e.g., persistent grip), but may on occasion involve the extraocular muscles[134]; immediately after sustaining gaze in a certain direction, the patient cannot promptly move the eyes in the opposite direction. Bell's phenomenon is particularly useful to elicit sustained upgaze in an infant or uncooperative child.

Although the manifestations of myotonic dystrophy usually become apparent in adolescents or young adults, detailed questioning often documents symptoms during the first decade of life, and the disease can, at times, affect infants and young children distinctly.[127] For the ophthalmologist, a characteristic facial appearance (facial diplegia, triangular-shaped mouth, and slack jaw) and weak orbicularis function typically without ptosis suggests the possibility of myotonic dystrophy in a young child. Bilateral facial weakness is the most characteristic feature of early-onset myotonic dystrophy and is frequently misdiagnosed as Möbius syndrome (see following section). With increasing age, the more familiar facial appearance of myotonic dystrophy (narrow, expressionless, "hatchet" face with hollowing of cheeks and temples) evolves because wasting of the facial muscles occurs, and ptosis becomes far more common.

PROMM, PDM, and DM2 are also autosomal dominant myotonic dystrophy without the CTG repeat expansion at the

DM1 locus. PROMM and PDM predominantly involve proximal muscles, and DM2 involves distal muscles. All three have been linked to chromosome 3q21.3 and may be various phenotypes of the same disease. These patients also develop posterior subcapsular cataracts with onset before 50 years of age. They do not exhibit ophthalmoplegia, however.[320]

Clinical Assessment

Bilateral iridescent and posterior cortical lens opacities are useful for establishing a clinical diagnosis[27]; they may be identified in young children but are often not seen until the teenage years. Clear electroretinographic abnormalities with normal-appearing fundi may be observed early on,[69] and a subgroup of patients demonstrate visual loss and observable pigmentary retinopathy later in the course of the disease. Additional ophthalmic signs are listed in Table 5-9.[37] A negative family history does not exclude the diagnosis because a parent with myotonic dystrophy may be affected so mildly as to be unaware of it.[374] Careful evaluation of the parents can therefore prove helpful.

Beside the slit lamp examination for cataracts, other primary diagnostic tests include DNA testing for an enlarged CTG repeat, examination for muscle and nonmuscle manifestations, and EMG for subclinical myotonia. Secondary tests include serum creatinine kinase, which is often mildly elevated in

TABLE 5-9. Ophthalmic Manifestations of Myotonic Dystrophy.

Structure	*Findings*
Eyelids	Ptosis; myotonic lag (due to delayed relaxation of levator); orbicularis weakness; myotonic closure (due to delayed relaxation of orbicularis)
Motility	Slow saccades with full ductions and versions; myotonia induced by Bell's reflex, convergence, or eccentric gaze; partial to complete ophthalmoplegia (usually symmetrical)
Globe	Cataracts (subcapsular polychromatophilic opacities; posterior cortical spokes; posterior subcapsular plaques; mature cataracts); short depigmented ciliary processes; hypotony; iris neovascular tufts (resulting in spontaneous hyphema); keratitis sicca; macular and peripheral retinal pigmentary degeneration; miotic, sluggishly reacting pupils
Miscellaneous	Decreased ERG responses; elevated dark-adaptation thresholds; generalized constriction of visual fields

Source: From Ref. 37, with permission.

diseased individuals, and muscle biopsy, which frequently shows an increase in central nuclei, fiber atrophy, and ringed fibers.

Inheritance

The interesting feature of this disease is that when it is passed on from one generation to the next in autosomal dominant fashion, the severity of disease increases. The phenomenon of progressive earlier onset and greater severity of disease is termed *anticipation*; this is particularly true for cases of female transmission, which can lead to the congenital cases of the disease. Increased severity in the subsequent generations is associated with increased expansion of the CTG repeats.[303]

DM1 gene has been mapped to chromosome 19q13.3. DM2, PROMM, and PDM have all been linked to chromosome 3q21.3, but the gene defect(s) has not yet been identified.[320]

Systemic Associations

In addition to facial diplegia, infants frequently demonstrate hypotonia, delayed motor and intellectual development, feeding difficulties, neonatal respiratory distress, and talipes.[192] In adults, diabetes, pituitary dysfunction, widespread involvement of the smooth muscle of the gastrointestinal tract, premature balding, and gonadal atrophy may all be seen.

Treatment and Prognosis

Comprehensive medical care of patients with myotonic dystrophy is essential. Prompt intervention may become necessary at any time because of associated, potentially life-threatening, cardiac conduction defects. Periodic EKGs are obtained to detect heart block, which may require a pacemaker. Drugs such as procainamide, quinine, and propranolol are avoided in patients with cardiac involvement. Endocrinological management is necessary for those patients who also have diabetes or pituitary dysfunction.

Prostheses may be used for foot and hand weakness. Myotonia may be moderately reduced with mexiletine and tocainide, which have been found to be more effective than phenytoin and dysopyramide.

Any strabismus surgery for myotonic dystrophy patients is approached with caution because of the potential for friable and atrophic extraocular muscles.[306] Also any ptosis surgery risks

corneal exposure due to lack of Bell's phenomenon in the setting of ophthalmoplegia.

Life expectancy is reduced particularly in the case of early onset disease and proximal muscle involvement. The high mortality rate is due to an increase in deaths from respiratory diseases, cardiovascular diseases, and neoplasms, as well as sudden deaths from cardiac arrhythmias.[320]

Möbius Syndrome

Möbius[328,329] designated congenital, bilateral sixth and seventh nerve palsies as central features of what has come to be known as *Möbius' syndrome*, but subsequent clinical and pathological observations reveal greater complexity. It has become clear that the eponym has been applied to a heterogeneous group of congenital neuromuscular disorders that produce facial weakness in some combination with a variety of other findings (Table 5-10). It has been suggested that the term sequence is more appropriate because a sequence defines a cascade of secondary events after an embryonic insult from heterogeneous causes.[325]

Clinical Features and Systemic Associations

Typically, a short time after birth, an affected infant demonstrates difficulty feeding because of poor sucking and little, if

TABLE 5-10. Manifestations of Möbius Syndrome.

System	*Findings*
Cardinal features	Partial or complete facial paralysis, usually bilateral (may be unilateral)[203,324]
Ocular motor	Straight eyes, esotropia, or exotropia with no horizontal movements and preserved vertical movements[324,407,461]; total ophthalmoplegia[206,324,464]; cocontraction of horizontal recti[61]
Neurological	Unilateral or bilateral palsy of cranial nerves V, VIII, IX, X, or XII[42,475]; autism[325]
Orofacial	Abnormal tongue; bifid uvula; cleft lip/palate; micrognathia, microstomia; external ear defects[324,325]
Musculoskeletal	Syndactyly; brachydactyly; absent or supranumerary digits; arthrogryposis multiplex congenital; talipes; absence of hands or feet[324,325,409,461]
Miscellaneous	Mental retardation[325]; congenital heart defects; absent sternal head of the pectoralis major (second major component of the Poland anomaly)[324,325]; rib defects; Klippel–Feil anomaly; neuroradiologic cerebellar hypoplasia[51,190]; hypogonadotropic hypogonadism with or without anosmia[362,422]

any, facial expression, as a result of the involvement of cranial nerves IX and XII in addition to VII. Generally, horizontal eye movements are clearly abnormal, and vertical eye movements are preserved. If convergence is intact and used for cross-fixation, the ocular motility pattern may resemble that produced by bilateral sixth nerve palsies. On occasion, vertical eye movements may also be affected or total ophthalmoplegia may occur. Crocodile tears, micrognathia, dental anomalies, cleft palate, facial asymmetry, limb malformations, Poland's syndrome, epilepsy, mental retardation, and autism may be present.[325]

Etiology

Fifteen autopsied cases have been classified into four groups based on neuropathological findings in the brainstem.[489] Group I demonstrated absence or hypoplasia of relevant cranial nerve nuclei; group II, in addition to neuronal loss, showed evidence of neuronal degeneration suggesting peripheral nerve injury; group III, in addition to neuronal loss and neuronal generation, had frank necrosis of the tegmentum of the lower pons; group IV revealed no abnormalities in the brainstem and may represent a purely myopathic disorder. Cases of *facio-scapulo-humeral muscular dystrophy* and *congenital centronuclear (myotubular) myopathy* that clinically mimic Möbius syndrome would also presumably belong to group IV.[189,199]

A number of investigators have speculated that disruption of the vascular system causes hypoxia of vulnerable tissues between 4 and 7 weeks gestation.[190,294,396] It has been proposed that Möbius syndrome, the Poland anomaly, and the Klippel–Feil defect all result from a transient interruption during the sixth week of gestation in the development of the subclavian artery and its branches, including the basilar, vertebral, and internal thoracic arteries, which supply the brain, neck, pectoral muscles, and upper limbs; in addition, in Möbius syndrome, the primitive trigeminal artery that supplies the hindbrain during fetal life may regress before the establishment of adequate perfusion from the vertebral or basilar artery and thereby disturb development of the cranial nerve nuclei.[48] Such a mechanism would be consistent with the brainstem necrosis seen in group III Möbius' syndrome patients but would not account for the findings in groups I and II.

Inheritance

As might be expected, most reported cases have been sporadic, and the sexes are affected with equal frequency. At least five families with Möbius' syndrome have been reported without any one consistent chromosomal defect.[206,283,325,531] Chromosomal translocations (1;13 and 1;11), chromosome 13q12.2 deletion, and linkage to chromosome 3q21–22 have been reported by previous authors. The recurrence risk to siblings of isolated cases with these three manifestations appears to be less than 2%.[42]

Treatment and Prognosis

Depending on the severity and types of malformations, the treatment will vary.[325] Initially, sucking problems often require modification in type of bottle used. If lid lag is present from seventh nerve palsy, lubricants are necessary. Refractive errors, amblyopia, and strabismus often need attention.

Maximal medial rectus recessions with or without vertical displacement have been shown to suffice in some cases,[466,516] whereas others have advocated horizontal recession-resections[321,346,490] or vertical muscle transposition.[206,470]

Because of the lack of facial expression, parents and children may have psychological difficulty with bonding and social communication. Plastic surgeries do exist that can improve facial movement.[81,543] Finally, helping families cope by contacting others through a national organization, such as the Möbius Syndrome Foundation, is also important and appreciated, as is the case for other diseases or syndromes mentioned in this chapter.

References

1. Abdul-Rahim AS, et al. Cryptogenic oculomotor nerve palsy. The need for repeated neuroimaging studies. Arch Ophthalmol 1989; 107(3):387–390.
2. Afifi AK, et al. Recurrent lateral rectus palsy in childhood. Pediatr Neurol 1990;6(5):315–318.
3. Afifi AK, Bell WE, Menezes AH. Etiology of lateral rectus palsy in infancy and childhood. J Child Neurol 1992;7(3):295–299.
4. Afifi AK, Bell WE. Tests for juvenile myasthenia gravis: comparative diagnostic yield and prediction of outcome. J Child Neurol 1993; 8(4):403–411.

5. Aguirre-Aquino BI, Rogers DG, Traboulsi EI. A patient with de Morsier and Duane syndromes. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(4):243–245.
6. Ahn JC, Hoyt WF, Hoyt CS. Tonic upgaze in infancy. A report of three cases. Arch Ophthalmol 1989;107(1):57–58.
7. Aicardi J, et al. Ataxia-ocular motor apraxia: a syndrome mimicking ataxia-telangiectasia. Ann Neurol 1988;24(4):497–502.
8. Al-Din AN, et al. Brainstem encephalitis and the syndrome of Miller Fisher: a clinical study. Brain 1982;105(pt 3):481–495.
9. Aldrich MS, Beck RW, Albers JW. Familial recurrent Bell's palsy with ocular motor palsies. Neurology 1987;37(8):1369–1371.
10. Aleksic S, et al. Congenital ophthalmoplegia in oculoauriculovertebral dysplasia-hemifacial microsomia (Goldenhar–Gorlin syndrome). A clinicopathologic study and review of the literature. Neurology 1976;26(7):638–644.
11. Alfano J. Spasm of fixation. Am J Ophthalmol 1955;40:724–725.
12. Alvarez F, et al. Nervous and ocular disorders in children with cholestasis and vitamin A and E deficiencies. Hepatology 1983;3(3):410–414.
13. Amit R, Benezra D. Oculomotor ophthalmoplegic migraine in an infant. Headache 1987;27(7):390–391.
14. Anastasopoulos D, et al. Abnormalities of ocular motility in myotonic dystrophy. Brain 1996;119(pt 6):1923–1932.
15. Andrews PI, Massey JM, Sanders DB. Acetylcholine receptor antibodies in juvenile myasthenia gravis. Neurology 1993;43(5):977–982.
16. Andrews PI, et al. Race, sex, and puberty influence onset, severity, and outcome in juvenile myasthenia gravis. Neurology 1994;44(7):1208–1214.
17. Angelini L, et al. Hallervorden–Spatz disease: clinical and MRI study of 11 cases diagnosed in life. J Neurol 1992;239(8):417–425.
18. Anlar B, et al. Myasthenia gravis in childhood. Acta Paediatr 1996;85(7):838–842.
19. Anlar B. Juvenile myasthenia: diagnosis and treatment. Paediatr Drugs 2000;2(3):161–169.
20. Appukuttan B, et al. Localization of a gene for Duane retraction syndrome to chromosome 2q31. Am J Hum Genet 1999;65(6):1639–1646.
21. Araie M, Ozawa T, Awaya Y. A case of congenital ocular motor apraxia with cerebellospinal degeneration. Jpn J Ophthalmol 1977;21:355–365.
22. Armstrong MW, Mountain RE, Murray JA. Treatment of facial synkinesis and facial asymmetry with botulinum toxin type A following facial nerve palsy. Clin Otolaryngol 1996;21(1):15–20.
23. Arnold AC, et al. Internuclear ophthalmoplegia in the Chiari type II malformation. Neurology 1990;40(12):1850–1864.
24. Aroichane M, Repka MX. Outcome of sixth nerve palsy or paresis in young children. J Pediatr Ophthalmol Strabismus 1995;32(3):152–156.

25. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltim) 1969;48(3):173–215.
26. Aseff AJ, Munoz M. Outcome of surgery for superior oblique palsy with contracture of ipsilateral superior rectus treated by superior rectus recession. Binoc Vs Strabismus Q 1998;13(3):177–180.
27. Ashizawa T, et al. Diagnostic value of ophthalmologic findings in myotonic dystrophy: comparison with risks calculated by haplotype analysis of closely linked restriction fragment length polymorphisms. Am J Med Genet 1992;42(1):55–60.
28. Astle WF, Rosenbaum AL. Familial congenital fourth cranial nerve palsy. Arch Ophthalmol 1985;103(4):532–535.
29. Astle WF, Miller SJ. Acute comitant esotropia: a sign of intracranial disease. Can J Ophthalmol 1994;29(3):151–154.
30. Atwal AJ, Smith BH, Dickenson ES. Letter: Pseudo-internuclear ophthalmoplegia in polyneuritis. Arch Neurol 1976;33(6):457.
31. Avanzini G, et al. Oculomotor disorders in Huntington's chorea. J Neurol Neurosurg Psychiatry 1979;42(7):581–589.
32. Averbuch-Heller L, Leigh RJ. Eye movements. Curr Opin Neurol 1996;9(1):26–31.
33. Awan K. Duane's retraction syndrome and hypertelorism. J Pediatr Ophthalmol Strabismus 1975;12:100–102.
34. Awan K. Flocculi iridis and retraction syndrome: their coexistence and associated ocular anomalies. J Pediatr Ophthalmol Strabismus 1975;12:246–254.
35. Awan KJ. Association of ocular, cervical, and cardiac malformations. Ann Ophthalmol 1977;9(8):1001–1011.
36. Awaya Y, Sugie H, Fukuyama Y. A hereditary variant of spinocerebellar degeneration associated with choreoathetosis and ocular motor apraxia of early onset. Acta Paediatr Jpn 1986;28:271–272.
37. Babel J. Ophthalmological aspects of myotonic dystrophy. In: Huber A, Klein D (eds) Neurogenetics and neuro-ophthalmology. Amsterdam: Elsevier/North Holland, 1981.
38. Bachynski BN, et al. Hyperglycemic acidotic coma and death in Kearns–Sayre syndrome. Ophthalmology 1986;93(3):391–396.
39. Bailey PBD, Ducy PC. Intracranial tumors in infancy and childhood. Chicago: University of Chicago Press, 1939.
40. Bailey TD, et al. Ophthalmoplegic migraine. J Clin Neuroophthalmol 1984;4(4):225–228.
41. Balkan R, Hoyt CS. Associated neurologic abnormalities in congenital third nerve palsies. Am J Ophthalmol 1984;97(3):315–319.
42. Baraitser M. Genetics of Mobius syndrome. J Med Genet 1977;14(6):415–417.
43. Barlow C. Headaches and migraine in childhood. Philadelphia: Lippincott, 1984.
44. Barsoum–Homsy M. Congenital double elevator palsy. J Pediatr Ophthalmol Strabismus 1983;20(5):185–191.

45. Bartkowski SB, et al. Marcus Gunn jaw-winking phenomenon: management and results of treatment in 19 patients. J Craniomaxillofac Surg 1999;27(1):25–29.
46. Barton JJ. Quantitative ocular tests for myasthenia gravis: a comparative review with detection theory analysis. J Neurol Sci 1998;155(1): 104–114.
47. Barton JJ, Fouladvand M. Ocular aspects of myasthenia gravis. Semin Neurol 2000;20(1):7–20.
48. Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel–Feil, and Mobius anomalies. Am J Med Genet 1986;23(4):903–918.
49. Beck RW, Meckler RJ. Internuclear ophthalmoplegia after head trauma. Ann Ophthalmol 1981;13(6):671–675.
50. Becker WJ, Watters GV, Humphreys P. Fisher syndrome in childhood. Neurology 1981;31(5):555–560.
51. Beerbower J, et al. Radiographic findings in Moebius and Moebius-like syndromes. AJNR Am J Neuroradiol 1986;7(2):364–365.
52. Bell JA, Fielder AR, Viney S. Congenital double elevator palsy in identical twins. J Clin Neuroophthalmol 1990;10(1):32–34.
53. Benson P. Transient unilateral external rectus muscle in newborn infants. Br Med J 1962;1:1054–1055.
54. Berenberg RA, et al. Lumping or splitting? "Ophthalmoplegia-plus" or Kearns–Sayre syndrome? Ann Neurol 1977;1(1):37–54.
55. Betz R, et al. Children with ocular motor apraxia type Cogan carry deletions in the gene (NPHP1) for juvenile nephronophthisis. J Pediatr 2000;136(6):828–831.
56. Beutler E, Grabowski G. Gaucher disease. In: Scriver C, et al (eds) The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, 1995:2641–2670.
57. Beyer–Machule C, et al. The Marcus–Gunn phenomenon: a review of 80 cases (an update). Orbit 1985;4:15–19.
58. Biedner B, Geltman C, Rothkoff L. Bilateral Duane's syndrome associated with crocodile tears. J Pediatr Ophthalmol Strabismus 1979; 16(2):113–114.
59. Bielschowsky A. Lectures on motor anomalies of the eyes. II. Paralysis of individual muscles. Arch Ophthalmol 1935;13:33–59.
60. Bixenman WW, von Noorden GK. Benigh recurrent VI nerve palsy in childhood. J Pediatr Ophthalmol Strabismus 1981;18(3): 29–34.
61. Blodi FC. Electromyographic evidence for supranuclear gaze palsies. Trans Ophthalmol Soc UK 1970;90:451–469.
62. Bloom JN, Graviss ER, Mardelli PG. A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome. Am J Ophthalmol 1991;111(5):548–554.
63. Bodensteiner JB, et al. Macrocerebellum: neuroimaging and clinical features of a newly recognized condition. J Child Neurol 1997;12(6): 365–368.

64. Bodziner RA, Singer W, Hedges TR. Bilateral internuclear ophthalmoplegia in meningoencephalitis. Dev Med Child Neurol 1983;25(6):819–820.
65. Boger WP, et al. Recurrent isolated sixth nerve palsy in children. Ann Ophthalmol 1984;16(3):237–238, 240–244.
66. Boghen D, et al. Primary aberrant third nerve regeneration. Ann Neurol 1979;6(5):415–418.
67. Borchert MS, et al. Congenital ocular motor apraxia in twins. Findings with magnetic resonance imaging. J Clin Neuroophthalmol 1987;7(2):104–107.
68. Bowen J, Daltner C, Troost B. The treatment of ocular myasthenia with plasmapheresis: three case reports. Neuro-Ophthalmology 1986;6:109–112.
69. Breningstall GN, Smith SA, Purple RL. Electroretinography in the evaluation of childhood myotonic dystrophy. Pediatr Neurol 1985;1(4):238–241.
70. Bresolin N, et al. Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. Neurology 1988;38(6):892–899.
71. Brodsky MC, Frenkel RE, Spoor TC. Familial intracranial aneurysm presenting as a subtle stable third nerve palsy. Case report. Arch Ophthalmol 1988;106(2):173.
72. Brodsky MC, Pollock SC, Buckley EG. Neural misdirection in congenital ocular fibrosis syndrome: implications and pathogenesis. J Pediatr Ophthalmol Strabismus 1989;26(4):159–161.
73. Brodsky MC. Hereditary external ophthalmoplegia synergistic divergence, jaw winking, and oculocutaneous hypopigmentation: a congenital fibrosis syndrome caused by deficient innervation to extraocular muscles. Ophthalmology 1998;105(4):717–725.
74. Buckley SA, Elston JS. Surgical treatment of supranuclear and internuclear ocular motility disorders. Eye 1997;11(pt 3):377–380.
75. Burian H, Miller J. Comitant convergent strabismus with acute onset. Am J Ophthalmol 1968;45:55–64.
76. Butler T. Third nerve paralysis after mumps and chicken-pox. Br Med J 1930;1:1095.
77. Butler T. Ocular paralysis after mumps. Br Med J 1937;1:752–753.
78. Caccavale A, Mignemi L. Acute onset of a bilateral areflexical mydriasis in Miller–Fisher syndrome: a rare neuro-ophthalmologic disease. J Neuroophthalmol 2000;20(1):61–62.
79. Calabrese G, et al. Detection of an insertion deletion of region 8q13–q21.2 in a patient with Duane syndrome: implications for mapping and cloning a Duane gene. Eur J Hum Genet 1998;6(3):187–193.
80. Calvert P. Personal communication, 2001.
81. Carr MM, Ross DA, Zuker RM. Cranial nerve defects in congenital facial palsy. J Otolaryngol 1996;26(2):80–87.

82. Carroll JE, et al. Depressed ventilatory response in oculocraniosomatic neuromuscular disease. Neurology 1976;26(2):140–146.
83. Cassidy L, Taylor D, Harris C. Abnormal supranuclear eye movements in the child: a practical guide to examination and interpretation. Surv Ophthalmol 2000;44(6):479–506.
84. Catalano RA, Sax RD, Krohel GB. Unilateral internuclear ophthalmoplegia after head trauma. Am J Ophthalmol 1986;101(4):491–493.
85. Catalano RA, et al. Asymmetry in congenital ocular motor apraxia. Can J Ophthalmol 1988;23(7):318–321.
86. Chan CC, Sogg RL, Steinman L. Isolated oculomotor palsy after measles immunization. Am J Ophthalmol 1980;89(3):446–448.
87. Chan TK, Demer JL. Clinical features of congenital absence of the superior oblique muscle as demonstrated by orbital imaging. J Am Assoc Pediatr Ophthalmol Strabismus 1999;3(3):143–150.
88. Charles R, et al. Myocardial ultrastructure and the development of atrioventricular block in Kearns–Sayre syndrome. Circulation 1981; 63(1):214–219.
89. Chattha AS, Delong GF. Sylvian aqueduct syndrome as a sign of acute obstructive hydrocephalus in children. J Neurol Neurosurg Psychiatry 1975;38(3):288–296.
90. Christodoulou K, et al. Mapping of the familial infantile myasthenia (congenital myasthenic syndrome type Ia) gene to chromosome 17p with evidence of genetic homogeneity. Hum Mol Genet 1997;6(4): 635–640.
91. Christoff N. A clinicopathologic study of vertical eye movements. Arch Neurol 1974;31(1):1–8.
92. Chu BC, et al. MRI of the brain in the Kearns–Sayre syndrome: report of four cases and a review. Neuroradiology 1999;41(10):759–764.
93. Ciafaloni E, et al. Mycophenolate mofetil for myasthenia gravis: an open-label pilot study. Neurology 2001;56(1):97–99.
94. Clausen N, Andersson P, Tommerup N. Familial occurrence of neuroblastoma, von Recklinghausen's neurofibromatosis, Hirschsprung's agangliosis and jaw-winking syndrome. Acta Paediatr Scand 1989;78(5):736–741.
95. Cogan D. Neurology of the ocular muscles. Springfield: Thomas, 1948.
96. Cogan D. A type of congenital ocular motor apraxia presenting jerky head movement. Trans Am Acad Ophthalmol Otolaryngol 1952; 56:853–862.
97. Cogan D, et al. A long-term follow-up of congenital ocular motor apraxia: case report. Neuroophthalmology 1980;1:145–147.
98. Cogan DG. Congenital ocular motor apraxia. Can J Ophthalmol 1966;1(4):253–260.
99. Cogan DG. Internuclear ophthalmoplegia, typical and atypical. Arch Ophthalmol 1970;84(5):583–589.
100. Cogan DG, et al. Ocular motor signs in some metabolic diseases. Arch Ophthalmol 1981;99(10):1802–1808.
101. Cooper J, et al. Accommodative and vergence findings in ocular myasthenia: a case analysis. J Neuroophthalmol 2000;20(1):5–11.

102. Coppeto JR, Lessell S. Dorsal midbrain syndrome from giant aneurysm of the posterior fossa: report of two cases. Neurology 1983;33(6):732–736.
103. Couchot J, et al. Guillain–Barre syndrome following varicella. Nouv Presse Med 1978;7(1):47.
104. Coulter DL, Allen RJ. Abrupt neurological deterioration in children with Kearns–Sayre syndrome. Arch Neurol 1981;38(4):247–250.
105. Cox TA, Wurster JB, Godfrey WA. Primary aberrant oculomotor regeneration due to intracranial aneurysm. Arch Neurol 1979;36(9): 570–571.
106. Cross HE, Pfaffenbach DD. Duane's retraction syndrome and associated congenital malformations. Am J Ophthalmol 1972;73(3):442–450.
107. Cruysberg J, et al. Bilateral Duane's syndrome associated with congenital panhypopituitarism. Neuro-Ophthalmology 1986;3:165–168.
108. Cruysberg J, Huygen P. Congenital monocular adduction palsy with synergistic divergence diagnosed in a young infant. Neuro-Ophthalmology 1990;10:253–256.
109. Cruysberg JR, et al. Congenital adduction palsy and synergistic divergence: a clinical and electro-oculographic study. Br J Ophthalmol 1989;73(1):68–75.
110. Cuneo HMRC. Brain tumors of childhood. Springfield: Thomas, 1952.
111. Currie J, Lubin JH, Lessell S. Chronic isolated abducens paresis from tumors at the base of the brain. Arch Neurol 1983;40(4):226–229.
112. Dagi LR, Chrousos GA, Cogan DC. Spasm of the near reflex associated with organic disease. Am J Ophthalmol 1987;103(4):582–585.
113. Daroff R, Hoyt W. Supranuclear disorders of ocular control systems in man: clinical, anatomical, and physiological correlations. In: Bach-y-Rita P, Collins C, Hyde J (eds) The control of eye movements. New York: Academic Press, 1971.
114. Daroff RB, et al. Spongiform encephalopathy with chronic progressive external ophthalmoplegia. Central ophthalmoplegia mimicking ocular myopathy. Neurology 1966;16(2):161–169.
115. Davidson JL, Rosenbaum AL, McCall LC. Strabismus surgery in patients with myasthenia. J Pediatr Ophthalmol Strabismus 1993; 30(5):292–295.
116. Davis TL, Lavin PJ. Pseudo one-and-a-half syndrome with ocular myasthenia. Neurology 1989;39(11):1553.
117. De Graaf J, Cats H, deJager A. Gradenigo's syndrome: a rare complication of otitis media. Clin Neurol Neurosurg 1988;90:237–239.
118. de la Monte SM, et al. Keyhole aqueduct syndrome. Arch Neurol 1986;43(9):926–929.
119. Dehaene I, et al. Guillain–Barre syndrome with ophthalmoplegia: clinicopathologic study of the central and peripheral nervous systems, including the oculomotor nerves. Neurology 1986;36(6): 851–854.
120. Denslow GT, Sims M. Duane's retraction syndrome associated with optic nerve hypoplasia. J Pediatr Ophthalmol Strabismus 1980;17(1): 26–28.

121. Derakhshan I, Lotfi J, Kaufman B. Ophthalmoplegia, ataxia and hyporeflexia (Fisher's syndrome). With a midbrain lesion demonstrated by CT scanning. Eur Neurol 1979;18(6):361–366.
122. DeRespinis PA, et al. Duane's retraction syndrome. Surv Ophthalmol 1993;38(3):257–288.
123. Di Costanzo A, et al. Relative sparing of extraocular muscles in myotonic dystrophy: an electrooculographic study. Acta Neurol Scand 1997;95(3):158–163.
124. Diamond GR, et al. Variations in extraocular muscle number and structure in craniofacial dysostosis. Am J Ophthalmol 1980;90(3): 416–418.
125. Diamond S, Schear HE, Leeds MF. Pseudo-internuclear oculomotor ophthalmoplegia secondary to Guillain–Barre polyneuronitis simulating myasthenia gravis in a air transport pilot. Aviat Space Environ Med 1975;46(2):204–207.
126. Discepola MJ, et al. Autosomal recessive Duane's retraction syndrome. Can J Ophthalmol 1987;22(7):384–386.
127. Dodge P, et al. Myotonic dystrophy in infancy and childhood. Pediatrics 1965;35:3–19.
128. Donahue SP, Lavin PJ, Hamed LM. Tonic ocular tilt reaction simulating a superior oblique palsy: diagnostic confusion with the 3-step test. Arch Ophthalmol 1999;117(3):347–352.
129. Donaldson MD, et al. Familial juvenile nephronophthisis, Jeune's syndrome, and associated disorders. Arch Dis Child 1985;60(5):426–434.
130. Drachman D. Myasthenia gravis: immunobiology of a receptor disorder. Trends Neurosci 1983;6:446–450.
131. Drachman DA. Ophthalmoplegia plus. The neurodegenerative disorders associated with progressive external ophthalmoplegia. Arch Neurol 1968;18(6):654–674.
132. Duffner PK, et al. Survival of children with brain tumors: SEER Program, 1973–1980. Neurology 1986;36(5):597–601.
133. Durkan GP, et al. Recurrent painless oculomotor palsy in children. A variant of ophthalmoplegic migraine? Headache 1981;21(2):58–62.
134. Dyken P. Extraocular myotonia in families with dystrophia myotonica. Neurology 1966;16:738–740.
135. Ebner R. Angiography for IIIrd nerve palsy in children. J Clin Neuroophthalmol 1990;10(2):154–155.
136. Echaniz-Laguna A, et al. The Miller Fisher syndrome: neurophysiological and MRI evidence of both peripheral and central origin in one case. J Neurol 2000;247(12):980–982.
137. Eda I, et al. Computed tomography in congenital ocular motor apraxia. Neuroradiology 1984;26(5):359–362.
138. Edis RH, Mastaglia FL. Vertical gaze palsy in barbiturate intoxication. Br Med J 1977;1(6054):144.
139. Egger J, Lake BD, Wilson J. Mitochondrial cytopathy. A multisystem disorder with ragged red fibres on muscle biopsy. Arch Dis Child 1981;56(10):741–752.

140. Egger J, Wilson J. Mitochondrial inheritance in a mitochondrially mediated disease. N Engl J Med 1983;309(3):142–146.
141. Elizan TS, et al. Syndrome of acute idiopathic ophthalmoplegia with ataxia and areflexia. Neurology 1971;21(3):281–292.
142. Ellis FD, et al. Extraocular muscle responses to orbital cooling (ice test) for ocular myasthenia gravis diagnosis. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(5):271–281.
143. Emre M, Henn V. Central eye movement disorder in a case of myotonic dystrophy. Neuro-Ophthalmology 1985;5:21–25.
144. Engel A, et al. Molecular basis of congenital myasthenic syndromes: mutations in the acetylcholine receptor. Neuroscientist 1998;4:185–194.
145. Engel AG, et al. A newly recognized congenital myasthenic syndrome attributed to a prolonged open time of the acetylcholine-induced ion channel. Ann Neurol 1982;11(6):553–569.
146. Engel AG. Congenital myasthenic syndromes. J Child Neurol 1988; 3(4):233–246.
147. Eustace P, et al. Congenital ocular motor apraxia: an inability to unlock the vestibulo-ocular reflex. Neuro-Ophthalmology 1994;4: 167–174.
148. Evans JC, et al. Confirmation of linkage of Duane's syndrome and refinement of the disease locus to an 8.8-cM interval on chromosome 2q31. Hum Genet 2000;106(6):636–638.
149. Evoli A, et al. Ocular myasthenia: diagnostic and therapeutic problems. Acta Neurol Scand 1988;77(1):31–35.
150. Evoli A, et al. Therapeutic options in ocular myasthenia gravis. Neuromusc Disord 2001;11(2):208–216.
151. Fenichel GM. Clinical syndromes of myasthenia in infancy and childhood. A review. Arch Neurol 1978;35(2):97–103.
152. Fernandez E, et al. Oculomotor nerve regeneration in rats. Functional, histological, and neuroanatomical studies. J Neurosurg 1987; 67(3):428–437.
153. Fielder AR, et al. Congenital ocular motor apraxia. Trans Ophthalmol Soc UK 1986;105(pt 5):589–598.
154. Fink JK, et al. Clinical spectrum of Niemann–Pick disease type C. Neurology 1989;39(8):1040–1049.
155. Fisher C. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia, and areflexia). N Engl J Med 1956;255:57–65.
156. Flynn JT, et al. Hyperglycemic acidotic coma and death in Kearns–Sayre syndrome. Trans Am Ophthalmol Soc 1985;83:131–161.
157. Fox A. Angiography for third nerve palsy in children. J Clin Neuroophthalmol 1989;9:37–38.
158. Gabianelli EB, Klingele TB, Burde RM. Acute oculomotor nerve palsy in childhood. Is arteriography necessary? J Clin Neuroophthalmol 1989;9(1):33–36.
159. Galetta SL, Smith JL. Chronic isolated sixth nerve palsies. Arch Neurol 1989;46(1):79–82.

160. Gallastegui J, et al. Cardiac involvement in the Kearns–Sayre syndrome. Am J Cardiol 1987;60(4):385–388.
161. Gay A, Brodkey J, Miller J. Convergence retraction nystagmus. Arch Ophthalmol 1963;70:456–461.
162. Gentile M, et al. COACH syndrome: report of two brothers with congenital hepatic fibrosis, cerebellar vermis hypoplasia, oligophrenia, ataxia, and mental retardation. Am J Med Genet 1996;64(3):514–520.
163. Giroud M, et al. Miller–Fisher syndrome and pontine abnormalities on MRI: a case report. J Neurol 1990;237(8):489–490.
164. Gittinger JW Jr, Sokol S. The visual-evoked potential in the diagnosis of congenital ocular motor apraxia. Am J Ophthalmol 1982; 93(6):700–703.
165. Gittinger JW Jr, Hughes JP, Suran EL. Medial orbital wall blow-out fracture producing an acquired retraction syndrome. J Clin Neuroophthalmol 1986;6(3):153–156.
166. Glaser J, Bachynski B. Infranuclear disorders of eye movement. In: Glaser J (ed) Neuroophthalmology. Philadelphia: Lippincott, 1990.
167. Glaser JS. Myasthenic pseudo-internuclear ophthalmoplegia. Arch Ophthalmol 1966;75(3):363–366.
168. Glover AT, Powe LK. Ocular motor apraxia and neurofibromatosis. Arch Ophthalmol 1985;103(6):763.
169. Gobin MH. Surgical management of Duane's syndrome. Br J Ophthalmol 1974;58(3):301–306.
170. Goldman HD, Nelson LB. Acute acquired comitant esotropia. Ann Ophthalmol 1985;17(12):777–778.
171. Goldstein JH, Sacks DB. Bilateral Duane's syndrome. J Pediatr Ophthalmol 1977;14(1):12–17.
172. Goldstein JH, Schneekloth BB. Spasm of the near reflex: a spectrum of anomalies. Surv Ophthalmol 1996;40(4):269–278.
173. Golnik KC, et al. An ice test for the diagnosis of myasthenia gravis. Ophthalmology 1999;106(7):1282–1286.
174. Gonatas NK. A generalized disorder of nervous system, skeletal muscle and heart resembling Refsum's disease and Hurler's syndrome. II. Ultrastructure. Am J Med 1967;42(2):169–178.
175. Good WV, et al. Bilateral congenital oculomotor nerve palsy in a child with brain anomalies. Am J Ophthalmol 1991;111(5):555–558.
176. Goodman CR, Chabner E, Guyton DL. Should early strabismus surgery be performed for ocular torticollis to prevent facial asymmetry? J Pediatr Ophthalmol Strabismus 1995;32(3):162–166.
177. Gourdeau A, et al. Central ocular motor abnormalities in Duane's retraction syndrome. Arch Ophthalmol 1981;99(10):1809–1810.
178. Graeber MB, Muller U. Recent developments in the molecular genetics of mitochondrial disorders. J Neurol Sci 1998;153(2):251–263.
179. Green SH. Polyradiculitis (Landry–Guillain–Barre syndrome) with total external ophthalmoplegia: encephalo-myelo-radiculoneuropathy. Dev Med Child Neurol 1976;18(3):369–373.
180. Greer M, Schotland M. Myasthenia gravis in the newborn. Pediatrics 1960;26:101–108.

181. Gresty M, Ell J. Normal modes of head and eye co-ordination and the symptomatology of their disorders. In: Lennestrand G, Zee D, Keller E (eds) Functional basis of ocular motility disorders. New York: Pergamon, 1982;391–405.
182. Griffin JF, Wray SH, Anderson DP. Misdiagnosis of spasm of the near reflex. Neurology 1976;26(11):1018–1020.
183. Grob D, et al. The course of myasthenia gravis and therapies affecting outcome. Ann NY Acad Sci 1987;505:472–499.
184. Grose C, et al. Primary Epstein–Barr virus infections in acute neurologic diseases. N Engl J Med 1975;292(8):392–395.
185. Gross-Tsur V, et al. Oculomotor apraxia: the presenting sign of Gaucher disease. Pediatr Neurol 1090;5(2):128–129.
186. Grunnet ML, Lubow M. Ascending polyneuritis and ophthalmoplegia. Am J Ophthalmol 1972;74(6):1155–1160.
187. Hamed LM, Dennehy PJ, Lingua RW. Synergistic divergence and jaw-winking phenomenon. J Pediatr Ophthalmol Strabismus 1990;27(2): 88–90.
188. Hamed LM, et al. Synergistic divergence: saccadic velocity analysis and surgical results. J Pediatr Ophthalmol Strabismus 1992;29(1): 30–37.
189. Hanson PA, Rowland LP. Mobius syndrome and facioscapulohumeral muscular dystrophy. Arch Neurol 1971;24(1):31–39.
190. Harbord MG, et al. Moebius' syndrome with unilateral cerebellar hypoplasia. J Med Genet 1989;26(9):579–582.
191. Harley RD. Paralytic strabismus in children. Etiologic incidence and management of the third, fourth, and sixth nerve palsies. Ophthalmology 1980;87(1):24–43.
192. Harper P. Myotonic dystrophy in infancy and childhood. In: Myotonic dystrophy. London: Saunders, 1989.
193. Harrad RA, Graham CM, Collin JR. Amblyopia and strabismus in congenital ptosis. Eye 1988;2(pt 6):625–627.
194. Harris C, Taylor D, Velodi A. Eye movement recording in type 3 Gaucher disease: a preliminary report. Mol Med Ther 1997;5:7–10.
195. Harris CM, et al. Intermittent horizontal saccade failure ('ocular motor apraxia') in children. Br J Ophthalmol 1996;80(2):151–158.
196. Harris CM, et al. Familial congenital saccade initiation failure and isolated cerebellar vermis hypoplasia. Dev Med Child Neurol 1998; 40(11):775–779.
197. Harris CM, Taylor DS, Vellodi A. Ocular motor abnormalities in Gaucher disease. Neuropediatrics 1999;30(6):289–293.
198. Harris DJ Jr, et al. Familial congenital superior oblique palsy. Ophthalmology 1986;93(1):88–90.
199. Heckmatt JZ, et al. Congenital centronuclear (myotubular) myopathy. A clinical, pathological and genetic study in eight children. Brain 1985;108(pt 4):941–964.
200. Hedges TR III, et al. Botulin ophthalmoplegia. Clinical and oculographic observations. Arch Ophthalmol 1983;101(2):211–213.

201. Helveston EM, Giangiacomo JG, Ellis FD. Congenital absence of the superior oblique tendon. Trans Am Ophthalmol Soc 1981;79:123–135.
202. Helveston EM, et al. Surgical treatment of superior oblique palsy. Trans Am Ophthalmol Soc 1996;94:315–328.
203. Henderson J. The congenital facial diplegia syndrome. Clinical features, pathology, and aetiology. Brain 1939;62:381–403.
204. Hepler RS, Hoyt WF, Loeffler JD. Paradoxical synkinetic levator inhibition and excitation. An electromyographic study of unilateral oculopalpebral and bilateral mandibulopalpebral (Marcus Gunn) synkineses in a 74-year-old man. Arch Neurol 1968;18(4):416–424.
205. Hertle R. Diagnosis of isolated cyclovertical muscle overaction using a modification of the Parks' Three-Step Test. Strabismus 1993;1: 107–120.
206. Hicks A. Congenital paralysis of lateral rotators of the eyes with paralysis of muscles of face. Arch Ophthalmol 1943;30:38–42.
207. Hofmann RJ. Monozygotic twins concordant for bilateral Duane's retraction syndrome. Am J Ophthalmol 1985;99(5):563–566.
208. Holmes JM, Cronin CM. Duane syndrome associated with oculocutaneous albinism. J Pediatr Ophthalmol Strabismus 1992;28(1):32–34.
209. Holmes JM, et al. Pediatric third, fourth, and sixth nerve palsies: a population-based study. Am J Ophthalmol 1999;127(4):388–392.
210. Holtz SJ. Congenital ocular anomalies associated with Duane's retraction syndrome, the nervus of Ota, and axial anisometropia. Am J Ophthalmol 1974;77(5):729–731.
211. Holzman AE, et al. Duane's retraction syndrome in the fetal alcohol syndrome. Am J Ophthalmol 1990;110(5):565.
212. Honda Y, Yoshioka M. Duane's retraction syndrome associated with muscular dystrophy. J Pediatr Ophthalmol Strabismus 1978;15(3): 157–159.
213. Hotchkiss MG, et al. Bilateral Duane's retraction syndrome. A clinical-pathologic case report. Arch Ophthalmol 1980;98(5):870–874.
214. Hoyt CS, Billson FA, Alpins N. The supranuclear disturbances of gaze in kernicterus. Ann Ophthalmol 1978;10(11):1487–1492.
215. Hoyt CS, Mousel DK, Weber AA. Transient supranuclear disturbances of gaze in healthy neonates. Am J Ophthalmol 1980;89(5): 708–713.
216. Hoyt WF, Nachtigaller H. Anomalies of ocular motor nerves. Neuroanatomic correlates of paradoxical innervation in Duane's syndrome and related congenital ocular motor disorders. Am J Ophthalmol 1965;60(3):443–448.
217. Huber A. Electrophysiology of the retraction syndromes. Br J Ophthalmol 1974;58(3):293–300.
218. Huber A. Botulinum A toxin injections as a new treatment of blepharospasm and strabismus. In: Satoshi I (ed) Highlights in neurophthalmology. Proceedings of the sixth meeting of the

International Neurophthalmology Society. Amsterdam: Aeolus Press, 1897.
219. Hughes J, et al. Congenital vertical ocular motor apraxia. J Clin Neuroophthalmol 1985;5:153–157.
220. Hung TP. A polio-like syndrome in adults following acute hemorrhagic conjunctivitis. Int J Neurol 1981;15(3–4):266–278.
221. Hunt JM, et al. A post-docking role for synaptobrevin in synaptic vesicle fusion. Neuron 1994;12(6):1269–1279.
222. Hurko O, et al. Heteroplasmy in chronic external ophthalmoplegia: clinical and molecular observations. Pediatr Res 1990;28(5):542–548.
223. Iannaccone ST, et al. Familial progressive external ophthalmoplegia and ragged-red fibers. Neurology 1974;24(11):1033–1038.
224. Imes R, Monteiro M, Hoyt W. Ophthalmoplegic migraine with proximal posterior cerebral artery vascular anomaly. J Clin Neuroophthalmol 1984;4:221–223.
225. Ing EB, et al. Oculomotor nerve palsies in children. J Pediatr Ophthalmol Strabismus 1992;29(6):331–336.
226. Inocencio F, Ballecer R. Tuberculosis granuloma in the midbrain causing wall-eyed bilateral internuclear ophthalmoplegia (Webino). J Clin Neuroophthalmol 1985;5:31–35.
227. Inoue A, Koh C, Iwahashi T. Detection of serum anticerebellar antibodies in patients with Miller Fisher syndrome. Eur Neurol 1999; 42(4):230–234.
228. Inoue N, Izumi K, Mawatar S. Congenital ocular motor apraxia and cerebellar degeneration: report of two cases. Jpn J Clin Neurol 1971; 11:855–861.
229. Isenberg S, Urist MJ. Clinical observations in 101 consecutive patients with Duane's retraction syndrome. Am J Ophthalmol 1977; 84(3):419–425.
230. Isenberg S, Blechman B. Marcus Gunn jaw winking and Duane's retraction syndrome. J Pediatr Ophthalmol Strabismus 1983;20(6): 235–237.
231. Jamal GA, et al. Myotonic dystrophy. A reassessment by conventional and more recently introduced neurophysiological techniques. Brain 1986;109(pt 6):1279–1296.
232. Jamal GA, Ballantyne JP. The localization of the lesion in patients with acute ophthalmoplegia, ataxia and areflexia (Miller Fisher syndrome). A serial multimodal neurophysiological study. Brain 1988; 111(pt 1):95–114.
233. James RH. Induction agent sensitivity and ophthalmoplegia plus. Anaesthesia 1986;41(2):216.
234. Jampolsky A. Surgical leashes and reverse leashes in strabismus surgical management. In: Symposium on strabismus. Transactions of the New Orleans Academy of Ophthalmology. St. Louis: Mosby, 1978.
235. Jan JE, et al. Speech, cognition, and imaging studies in congenital ocular motor apraxia. Dev Med Child Neurol 1998;40(2):95–99.

236. Jankowicz E, et al. Familial progressive external ophthalmoplegia with abnormal muscle mitochondria. Eur Neurol 1977;15(6):318–324.
237. Jay WM, Hoyt CS. Abnormal brain stem auditory-evoked potentials in Stilling–Turk–Duane retraction syndrome. Am J Ophthalmol 1980;89(6):814–818.
238. Jimura T, et al. A case of synergistic divergence associated with Horner's syndrome. Folia Ophthalmol Jpn 1983;34:477–480.
239. Johnson LN, Pack WL. Transient oculomotor nerve misdirection in a case of pituitary tumor with hemorrhage. Case report. Arch Ophthalmol 1988;106(5):584–585.
240. Johnson RO, Clay SA, Arnon SS. Diagnosis and management of infant botulism. Am J Dis Child 1979;133(6):586–593.
241. Jones HR Jr. Guillain–Barre syndrome: perspectives with infants and children. Semin Pediatr Neurol 2000;7(2):91–102.
242. Jordan D, Miller D, Anderson R. Acquired oculomotor-abducens synkinesis. Can J Ophthalmol 1990;25:148–151.
243. Kaminski HJ, et al. Why are eye muscles frequently involved in myasthenia gravis? Neurology 1990;40(11):1663–1669.
244. Kaminski HJ, Kusner LL, Block CH. Expression of acetylcholine receptor isoforms at extraocular muscle endplates. Investig Ophthalmol Vis Sci 37(2):345–351.
245. Karpati H, et al. The Kearns–Shy syndrome: a multisystem disease with mitochondrial abnormality demonstrated in skeletal muscle and skin. J Neurol Sci 1973;19:133–151.
246. Katiyar BC, et al. Adult polio-like syndrome following enterovirus 70 conjunctivitis (natural history of the disease). Acta Neurol Scand 1983;67(5):263–274.
247. Kaufman LW, Folk ER, Miller MT. Monozygotic twins discordant for Duane's retraction syndrome. Case report. Arch Ophthalmol 1989;107(3):324–325.
248. Kawano K, Fujita S. Duane's retraction syndrome associated with morning glory syndrome. J Pediatr Ophthalmol Strabismus 1981; 18(1):51–54.
249. Keane J. Upward gaze paralysis as the initial sign of Fisher's syndrome. Arch Neurol 1982;32:781–782.
250. Keane JR, Hoyt WF. Myasthenic (vertical) nystagmus. Verification by edrophonium tonography. JAMA 212(7):1209–1210.
251. Keane JR, Davis RL. Pretectal syndrome with metastatic malignant melanoma to the posterior commissure. Am J Ophthalmol 1976; 82(6):910–914.
252. Keane JR. Neuro-ophthalmic signs and symptoms of hysteria. Neurology 1982;32(7):757–762.
253. Keane JR. Acute bilateral ophthalmoplegia: 60 cases. Neurology 1986;36(2):279–281.
254. Keane JR. Traumatic internuclear ophthalmoplegia. J Clin Neuro-ophthalmol 1987;7(3):165–166.

255. Keane JR. The pretectal syndrome: 206 patients. Neurology 1990; 40(4):684–690.
256. Kearns T, Sayre G. Retinitis pigmentosa, external ophthalmoplegia, and complete heart block. Arch Ophthalmol 1958;60:280–289.
257. Keith CG. Oculomotor nerve palsy in childhood. Aust N Z J Ophthalmol 1987;15(3):181–184.
258. Khodadoust AA, von Noorden GK. Bilateral vertical retraction syndrome. A family study. Arch Ophthalmol 1967;78(5):606–612.
259. Khwarg SI, et al. Management of moderate-to-severe Marcus-Gunn jaw-winking ptosis. Ophthalmology 1999;106(6):1191–1196.
260. Kiloh L, Nevin S. Progressive dystrophy of the ocular muscles (ocular myopathy). Brain 1951;74:115–143.
261. Kirkham TH. Cervico-oculo-acusticus syndrome with pseudo-papilloedema. Arch Dis Child 1969;44(236):504–508.
262. Kirkham TH. Duane's syndrome and familial perceptive deafness. Br J Ophthalmol 1969;53(5):335–339.
263. Kirkham TH. Duane's retraction syndrome and cleft palate. Am J Ophthalmol 1970;70(2):209–212.
264. Kirkham TH. Inheritance of Duane's syndrome. Br J Ophthalmol 1970;54(5):323–329.
265. Kirkham TH, Kamin DF. Slow saccadic eye movements in Wilson's disease. J Neurol Neurosurg Psychiatry 1974;37(2):191–194.
266. Kivlin JD, Lundergan MK. Acquired retraction syndrome associated with orbital metastasis. J Pediatr Ophthalmol Strabismus 1985; 22(3):109–112.
267. Knox DL, Clark DB, Schuster FF. Benigh VI nerve palsies in children. Pediatrics 1967;40(4):560–564.
268. Kodsi S. Marcus Gunn jaw winking with trigemino-abducens synkinesis. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(5): 316–317.
269. Kodsi SR, Younge BR. Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients. Am J Ophthalmol 1992; 114(5):568–574.
270. Koeppen AH, Hans MB. Supranuclear ophthalmoplegia in olivopontocerebellar degeneration. Neurology 1976;26(8):764–768.
271. Kommerell GBM. A new type of Duane's syndrome: twitch abduction on attempted upgaze and V-incomitance due to misinnervation of the lateral rectus by superior rectus neurons. Neuro-Ophthalmology 1986;6:159–164.
272. Kommerell G, et al. Oculomotor palsy with cyclic spasms: electromyographic and electron microscopic evidence of chronic peripheral neuronal involvement. Neuro-Ophthalmology 1988;8:9–21.
273. Kompf D, Christen H. Isolated abducens nerve palsy preceding infectious mononucleosis. Neuro-Ophthalmology 1984;4:101–105.
274. Kraft S, Scott W. Masked bilateral superior oblique palsy. Clinical features and diagnosis. J Pediatr Ophthalmol 1986;23:264–272.
275. Kraft S. A surgical approach for Duane syndrome. J Pediatr Ophthalmol Strabismus 1988;25:119–130.

276. Kraft SP, O'Donoghue EP, Roarty JD. Improvement of compensatory head postures after strabismus surgery. Ophthalmology 1992;99(8): 1301–1308.
277. Krohel GB. Blepharoptosis after traumatic third-nerve palsies. Am J Ophthalmol 1979;88(3 pt 2):598–601.
278. Kubis KC, et al. The ice test versus the rest test in myasthenia gravis. Ophthalmology 2000;107(11):1995–1998.
279. Kuncl R, Hoffman P. Myopathies and disorders of neuromuscular transmission. In: Miller N, Newman N (eds) Walsh & Hoyt's clinical neuro-ophthalmology. Baltimore: Williams & Wilkins, 1998.
280. Kushner BJ. The diagnosis and treatment of bilateral masked superior oblique palsy. Am J Ophthalmol 1988;105(2):186–194.
281. Kushner BJ. Errors in the three-step test in the diagnosis of vertical strabismus. Ophthalmology 1989;96(1):127–132.
282. Lambert SR, et al. Joubert syndrome. Arch Ophthalmol 1989;107(5): 709–713.
283. Lammens M, et al. Neuropathological findings in Moebius syndrome. Clin Genet 1998;54(2):136–141.
284. Lavy T, et al. Electrophysiological and eye-movement abnormalities in children with the Bardet–Biedl syndrome. J Pediatr Ophthalmol Strabismus 1995;32(6):364–367.
285. Lebensohn J. Parinaud's syndrome. From obstetric trauma with recovery. Am J Ophthalmol 1955;40:738–740.
286. Lee J, Flynn JT. Bilateral superior oblique palsies. Br J Ophthalmol 1985;69(7):508–513.
287. Lee MS, et al. Sixth nerve palsies in children. Pediatr Neurol 1999;20(1):49–52.
288. Leigh RJ, Zee DS. The neurology of eye movements, 3rd edn. Philadelphia: Davis, 1999.
289. Lepore FE, Glaser JS. Misdirection revisited. A critical appraisal of acquired oculomotor nerve synkinesis. Arch Ophthalmol 1980; 98(12):2206–2209.
290. Lessell S, Coppeto J, Samet S. Ophthalmoplegia in myotonic dystrophy. Am J Ophthalmol 1971;71(6):1231–1235.
291. Leung AK. Transient sixth cranial nerve palsy in newborn infants. Br J Clin Pract 1987;41(4):717–718.
292. Lindstrom JM, et al. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. Neurology 1976;26(11):1054–1059.
293. Lingua R, Walkoner F. Use of the posterior fixation suture in type I Duane syndrome. J Ocul Ther Surg 1985;4:107–111.
294. Lipson AH, et al. Moebius syndrome: animal model–human correlations and evidence for a brainstem vascular etiology. Teratology 1989;40(4):339–350.
295. Loewenfeld IE, Thompson HS. Oculomotor paresis with cyclic spasms. A critical review of the literature and a new case. Surv Ophthalmol 1975;20(2):81–124.

296. Lubkin V. The inverse Marcus Gunn phenomenon. An electromyographic contribution. Arch Neurol 1978;35(4):249.
297. Lueder GT, et al. Vertical strabismus resulting from an anomalous extraocular muscle. J Am Assoc Pediatr Ophthalmol Strabismus 1998;2(2):126–128.
298. Lyle D. A discussion of ocular motor apraxia with a case presentation. Trans Am Ophthalmol Soc 1961;59:274–285.
299. Lyness RW, et al. Histological appearances of the levator palpebrae superioris muscle in the Marcus Gunn phenomenon. Br J Ophthalmol 1988;72(2):104–109.
300. MacDonald AL, Crawford JS, Smith DR. Duane's retraction syndrome: an evaluation of the sensory status. Can J Ophthalmol 1974;9(4):458–462.
301. MacLennan C, et al. Acetylcholine receptor expression in human extraocular muscles and their susceptibility to myasthenia gravis. Ann Neurol 1997;41(4):423–431.
302. Magoon E. The use of botulinum injection as an alternative to surgery. Contemp Ophthalmic Forum 1987;5:222.
303. Mahadevan M, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3′ untranslated region of the gene. Science 1992; 255(5049):1253–1255.
304. Mankodi A, et al. Myotonic dystrophy in transgenic mice expressing an expanded CUG repeat. Science 2000;289(5485):1769–1773.
305. Manson JI. Ocular motor apraxia in childhood. Proc Aust Assoc Neurol 1973;10(0):27–29.
306. Marshman WE, Adams GG, Cree I. Extraocular muscle surgery in myotonic dystrophy. J Pediatr Ophthalmol Strabismus 1998;35(3): 169–171.
307. Marshman WE, et al. Congenital anomalies in patients with Duane retraction syndrome and their relatives. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(2):106–109.
308. Maruo T, et al. Duane's syndrome. Jpn J Ophthalmol 1979;23:453–468.
309. Marzetti G, Midulla M, Balducci L. Monolateral paralysis of the 3rd pair of cranial nerves due to A9 Coxsackie virus. Minerva Pediatr 1968;20(18):943–947.
310. Matteuci P. I difetti congenit di abduzione con particolare rifuardo all patogenesi. Rass Ital Ottal 1946;15:345–380.
311. McGettrick P, Eustace P. The w.e.b.i.n.o. syndrome. Neuro-Ophthalmology 1985;5:109–115.
312. McGovern ST, Crompton JL, Ingham PN. Trigemino-abducens synkinesis: an unusual case of aberrant regeneration. Aust N Z J Ophthalmol 1986;14(3):275–279.
313. Mehkri IA, et al. Double vision in a child. Surv Ophthalmol 1999;44(1):45–51; discussion 51–52.
314. Meienberg O, Ryffel E. Supranuclear eye movement disorders in Fisher's syndrome of ophthalmoplegia, ataxia, and areflexia. Report of a case and literature review. Arch Neurol 1983;40(7):402–405.

315. Meienberg O. Lesion site in Fisher's syndrome. Arch Neurol 1984; 41(3):250–251.
316. Meire F, et al. Waardenburg syndrome, Hirschsprung megacolon, and Marcus Gunn ptosis. Am J Med Genet 1987;27(3):683–686.
317. Mellinger J, Gomez M. Agenesis of the cranial nerves. In: Vinken P, Bruyn G (eds) Handbook of clinical neurology. New York: Elsevier, 1977.
318. Melmed C, Karpati G, Carpenter S. Experimental mitochondrial myopathy produced by in vivo uncoupling of oxidative phosphorylation. J Neurol Sci 1975;26(3):305–318.
319. Meola G. Myotonic dystrophies. Curr Opin Neurol 2000;13(5):519–525.
320. Meola G. Clinical and genetic heterogeneity in myotonic dystrophies. Muscle Nerve 2000;23(12):1789–1799.
321. Merz M, Wojtowicz S. The Mobius syndrome. Report of electromyographic examinations in two cases. Am J Ophthalmol 1967; 63(4):837–840.
322. Metz HS, Scott AB, Scott WE. Horizontal saccadic velocities in Duane's syndrome. Am J Ophthalmol 1975;80(5):901–906.
323. Miller MT, et al. Superior oblique palsy presenting in late childhood. Am J Ophthalmol 1970;70(2):212–214.
324. Miller MT, et al. Mobius and Mobius-like syndromes (TTV-OFM, OMLH). J Pediatr Ophthalmol Strabismus 1989;26(4):176–188.
325. Miller MT, Stromland K. The Mobius sequence: a relook. J Am Assoc Pediatr Ophthalmol Strabismus 1999;3(4):199–208.
326. Miller NR. Solitary oculomotor nerve palsy in childhood. Am J Ophthalmol 1977;83(1):106–111.
327. Millichap J, Dodge P. Diagnosis and treatment of myasthenia gravis in infancy, childhood, and adolescence: a study of 51 patients. Neurology 1960;10:1007–1014.
328. Möbius P. Uber angeborene doppelseitige Abducens-Facialis-Lahmung. Munch Med Wochenschr 1888;35:91–108.
329. Möbius P. Uber infantilen Kernschwund. Munch Med Wochenschr 1892;39:17–21.
330. Mohan K, et al. Treatment of congenital adduction palsy with synergistic divergence. J Pediatr Ophthalmol Strabismus 1998;35(3): 149–152.
331. Molarte AB, Rosenbaum AL. Vertical rectus muscle transposition surgery for Duane's syndrome. J Pediatr Ophthalmol Strabismus 1990;27(4):171–177.
332. Moore AT, Taylor DS. A syndrome of congenital retinal dystrophy and saccade palsy—a subset of Leber's amaurosis. Br J Ophthalmol 1984;68(6):421–431.
333. Moore LD, Feldon SE, Liu SK. Infrared oculography of Duane's retraction syndrome (type 1). Arch Ophthalmol 1988;106(7):943–946.
334. Moraes CT, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns–Sayre syndrome. N Engl J Med 1989;320(20):1293–1299.

335. Morimoto T, et al. A case of a rapidly progressive central nervous system disorder manifesting as a pallidal posture and ocular motor apraxia. Brain Dev 1985;7(4):449–453.
336. Mounsey JP, et al. Skeletal muscle sodium channel gating in mice deficient in myotonic dystrophy protein kinase. Hum Mol Genet 2000;9(15):2313–2320.
337. Movaghar M, Slavin ML. Effect of local heat versus ice on blepharoptosis resulting from ocular myasthenia. Ophthalmology 2000; 107(12):2209–2214.
338. Muchnick RS, Aston SJ, Rees TD. Ocular manifestations and treatment of hemifacial atrophy. Am J Ophthalmol 1979;88(5):889–897.
339. Mudgil AV, Repka MX. Ophthalmologic outcome after third cranial nerve palsy or paresis in childhood. J Am Assoc Pediatr Ophthalmol Strabismus 1999;3(1):2–8.
340. Mullaney P, et al. The natural history and ophthalmic involvement in childhood myasthenia gravis at the hospital for sick children. Ophthalmology 2000;107(3):504–510.
341. Mullie MA, et al. The retinal manifestations of mitochondrial myopathy. A study of 22 cases. Arch Ophthalmol 1985;103(12):1825–1830.
342. Muri RM, Meienberg O. The clinical spectrum of internuclear ophthalmoplegia in multiple sclerosis. Arch Neurol 1985;42(9):851–855.
343. Murray R, Steven P. Congenital levator and lateral rectus muscle associated reflex. Neuro-Ophthalmology 1986;6:29–31.
344. Namba T, Brown SB, Grob D. Neonatal myasthenia gravis: report of two cases and review of the literature. Pediatrics 1970;45(3):488–504.
345. Narbona J, Crisci CD, Villa I. Familial congenital ocular motor apraxia and immune deficiency. Arch Neurol 1980;37(5):325.
346. Neimann N, et al. Mobius' syndrome associated with atrophic myopathy. Ann Med Nancy 1965;4:1084–1092.
347. Nellhaus G. Isolated oculomotor nerve palsy in infectious mononucleosis. A report of an unusual case and review of the literature. Neurology 1966;16(2):221–224.
348. Nelson LB. Severe adduction deficiency following a large medial rectus recession in Duane's retraction syndrome. Arch Ophthalmol 1986;104(6):859–862.
349. Nelson S, Kline L. Acquired trigemino-abducens synkinesis. J Clin Neuroophthalmol 1990;10:111–114.
350. Nemet P, Ehrlich D, Lazar M. Benign abducens palsy in varicella. Am J Ophthalmol 1974;78(5):859.
351. Nemet P, Ron S. Ocular saccades in Duane's syndrome. Br J Ophthalmol 1978;62(8):528–532.
352. Nishizaki T, et al. Bilateral internuclear ophthalmoplegia due to hydrocephalus: a case report. Neurosurgery 1985;17(5):822–825.
353. Noel LP, Clarke WN. Adduction deficiency following medial recti recession in Duane's retraction syndrome. Case report. Arch Ophthalmol 1987;105(4):465.

354. Oda K, Shibasaki H. Antigenic difference of acetylcholine receptor between single and multiple form endplates of human extraocular muscle. Brain Res 1988;449(1–2):337–340.
355. O'Day J, Billson F, King J. Ophthalmoplegic migraine and aberrant regeneration of the oculomotor nerve. Br J Ophthalmol 1980;64(7): 534–536.
356. Oesterle CS, et al. Eye bobbing associated with jaw movement. Ophthalmology 1982;89(1):63–67.
357. Ogasahara S, et al. Improvement of abnormal pyruvate metabolism and cardiac conduction defect with coenzyme Q10 in Kearns–Sayre syndrome. Neurology 1985;35(3):372–377.
358. Ogasahara S, et al. Treatment of Kearns–Sayre syndrome with coenzyme Q10. Neurology 1986;36(1):45–53.
359. Ogasahara S, et al. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proc Natl Acad Sci USA 1989; 86(7):2379–2382.
360. Ohtsuki H, et al. Strabismus surgery in ocular myasthenia gravis. Ophthalmologica 1996;210(2):95–100.
361. Okihiro MM, et al. Duane syndrome and congenital upper-limb anomalies. A familial occurrence. Arch Neurol 1977;34(3):174–179.
362. Olson WH, et al. Moebius syndrome. Lower motor neuron involvement and hypogonadotrophic hypogonadism. Neurology 1970;20(10): 1002–1008.
363. O'Malley ER, Helveston EM, Ellis FD. Duane's retraction syndrome—plus. J Pediatr Ophthalmol Strabismus 1982;19(3):161–165.
364. Oohira A, Goto K, Ozawa T. Slow saccades in myogenic and peripheral neurogenic ophthalmoplegia. Late ocular myopathy in myotonic dystrophy. Neuro-Ophthalmology 1985;5:117–123.
365. Oosterhuis HJ. The ocular signs and symptoms of myasthenia gravis. Doc Ophthalmol 1982;52(3–4):363–378.
366. Osher RH, et al. Neuro-ophthalmological complications of enlargement of the third ventricle. Br J Ophthalmol 1978;62(8):536–542.
367. Osher RH, Schatz NJ, Duane TD. Acquired orbital retraction syndrome. Arch Ophthalmol 1980;98(10):1798–1802.
368. Ouhabi H, et al. Bilateral optic neuritis and ponto-mesencephalic involvement shown by MRI in Miller–Fisher syndrome. Rev Neurol (Paris) 1998;154(11):780–782.
369. Ozawa T, Naito M, Takasu T. Disorder of saccadic eye movement in cerebellar degeneration. Jpn J Ophthalmol 1974;18:363–380.
370. Parks M. Isolated cyclovertical muscle palsy. Arch Ophthalmol 1958;60:1027–1035.
371. Pasik P, Pasik T, Bender MB. The pretectal syndrome in monkeys. I. Disturbances of gaze and body posture. Brain 1969;92(3):521–534.
372. Pasik T, Pasik P, Bender MB. The pretectal syndrome in monkeys. II. Spontaneous and induced nystagmus, and "lightning" eye movements. Brain 1969;92(4):871–884.

373. Paysee EA, Coats DK, Plager DA. Facial asymmetry and tendon laxity in superior oblique palsy. J Pediatr Ophthalmol Strabismus 1995;32(3):158–161.
374. Pearse RG, Howeler CJ. Neonatal form of dystrophia myotonica. Five cases in preterm babies and a review of earlier reports. Arch Dis Child 1979;54(5):331–338.
375. Pebbenito R, Cracco J. Congenital ocular motor apraxia. Clin Paediatr 1988;27:27–31.
376. Pesando P, Nuzzi G, Maraini G. Vertical retraction syndrome. Ophthalmologica 1978;177(5):254–259.
377. Pfaffenbach DD, Cross HE, Kearns TP. Congenital anomalies in Duane's retraction syndrome. Arch Ophthalmol 1972;88(6):635–639.
378. Phillips MS, Stewart S, Anderson JR. Neuropathological findings in Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 1984;47(5): 492–495.
379. Pieroni D. Goldenhar's syndrome associated with Duane's retraction syndrome. J Pediatr Ophthalmol Strabismus 1969;6:16–18.
380. Pierrot–Deseilligny C, Gautier JC, Loron P. Acquired ocular motor apraxia due to bilateral frontoparietal infarcts. Ann Neurol 1988;23(2):199–202.
381. Plager DA. Tendon laxity in superior oblique palsy. Ophthalmology 1992;99(7):1032–1038.
382. Polak PE, Zijlstra F, Roelandt JR. Indications for pacemaker implantation in the Kearns–Sayre syndrome. Eur Heart J 1989;10(3): 281–282.
383. Pollard ZF. Aneurysm causing third nerve palsy in a 15-year-old boy. Arch Ophthalmol 1988;106(12):1647–1648.
384. Pollard ZF. Bilateral superior oblique muscle palsy associated with Apert's syndrome. Am J Ophthalmol 1988;106(3):337–340.
385. Pollard ZF. Accommodative esotropia after ocular and head injury. Am J Ophthalmol 1990;109(2):195–198.
386. Poppen JL, Marino R Jr. Pinealomas and tumors of the posterior portion of the third ventricle. J Neurosurg 1968;28(4):357–364.
387. Prasad P, Nair S. Congenital ocular motor apraxia: sporadic and familial. Support for natural resolution. J Neuroophthalmol 1994; 14(2):102–104.
388. Pressman SH, Scott WE. Surgical treatment of Duane's syndrome. Ophthalmology 1986;93(1):29–38.
389. Pruksacholawit K, Ishikawa S. Atypical retraction syndrome: a case study. J Pediatr Ophthalmol Strabismus 1976;13:215–220.
390. Putterman AM. Botulinum toxin injections in the treatment of seventh nerve misdirection. Am J Ophthalmol 1990;110(2):205–206.
391. Raab EL. Clinical features of Duane's syndrome. J Pediatr Ophthalmol Strabismus 1986;23(2):64–68.
392. Ramon Y, Cajal S. Degeneration and regeneration of the nervous system. London: Oxford University Press, 1928.
393. Ramsay J, Taylor D. Congenital crocodile tears: a key to the aetiology of Duane's syndrome. Br J Ophthalmol 1980;64(7):518–522.

394. Rana PV, Wadia RS. The Marin–Amat syndrome: an unusual facial synkinesia. J Neurol Neurosurg Psychiatry 1985;48(9):939–941.
395. Rappaport L, et al. Concurrence of congenital ocular motor apraxia and other motor problems: an expanded syndrome. Dev Med Child Neurol 1987;29(1):85–90.
396. Raroque HG Jr, Hershewe GL, Snyder RD. Mobius syndrome and transposition of the great vessels. Neurology 1988;38(12):1894–1895.
397. Rating D, et al. 4-Hydroxybutyric aciduria: a new inborn error of metabolism. I. Clinical review. J Inherit Metab Dis 1984;7(suppl 1):90–92.
398. Redding FK. Familial congenital ocular motor apraxia. Neurology 1970;20(4):405.
399. Reinecke RD, Thompson WE. Childhood recurrent idiopathic paralysis of the lateral rectus. Ann Ophthalmol 1981;13(9):1037–1039.
400. Reisner SH, et al. Transient lateral rectus muscle paresis in the newborn infant. J Pediatr 1971;78(3):461–465.
401. Ricker K. Myotonic dystrophy and proximal myotonic myopathy. J Neurol 1999;246(5):334–338.
402. Ro A, et al. Duane's retraction syndrome: southwestern Ontario experience. Can J Ophthalmol 1989;24(5):200–203.
403. Ro A, et al. Auditory function in Duane's retraction syndrome. Am J Ophthalmol 1990;109(1):75–78.
404. Roberts NK, Perloff JK, Kark RA. Cardiac conduction in the Kearns–Sayre syndrome (a neuromuscular disorder associated with progressive external ophthalmoplegia and pigmentary retinopathy). Report of 2 cases and review of 17 published cases. Am J Cardiol 1979;44(7):1396–1400.
405. Robertson DM, Hines JD, Rucker CW. Acquired sixth-nerve paresis in children. Arch Ophthalmol 1970;83(5):574–579.
406. Robertson WC, Chun RW, Kornguth SE. Familial infantile myasthenia. Arch Neurol 1980;37(2):117–119.
407. Rodrigues–Alves C, Caldeira J. Moebius' syndrome: a case report with multiple congenital anomalies. J Pediatr Ophthalmol Strabismus 1975;12:103–106.
408. Rodriguez M, et al. Myasthenia gravis in children: long-term follow-up. Ann Neurol 1983;13(5):504–510.
409. Rogers GL, Hatch GF Jr, Gray I. Mobius syndrome and limb abnormalities. J Pediatr Ophthalmol 1977;4(3):134–138.
410. Rogers GL, Bremer DL. Surgical treatment of the upshoot and downshoot in Duanes' retraction syndrome. Ophthalmology 1984;91(11):1380–1383.
411. Roggenkamper P, et al. Orbicular synkinesis after facial paralysis: treatment with botulinum toxin. Doc Ophthalmol 1994;86(4):395–402.
412. Rollinson RD, Fenichel GM. Relapsing ocular myasthenia. Neurology 1981;31(3):325–326.
413. Ropper A, Wijdicks E, Truax B. Guillain–Barre syndrome. Philadelphia: Davis, 1991.

414. Ropper AH. The CNS in Guillain–Barre syndrome. Arch Neurol 1983;40(7):397–398.
415. Ropper AH. Unusual clinical variants and signs in Guillain–Barre syndrome. Arch Neurol 1986;43(11):1150–1152.
416. Ropper AH. Three patients with Fisher's syndrome and normal MRI. Neurology 1988;38(10):1630–1631.
417. Rosenberg ML, Wilson E. Congenital ocular motor apraxia without head thrusts. J Clin Neuroophthalmol 1987;7(1):26–28.
418. Roses AD, Appel SH. Protein kinase activity in erythrocyte ghosts of patients with myotonic muscular dystrophy. Proc Natl Acad Sci USA 1973;70(6):1855–1859.
419. Rothner AD. The migraine syndrome in children and adolescents. Pediatr Neurol 1986;2(3):121–126.
420. Rowland LP. Molecular genetics, pseudogenetics, and clinical neurology. The Robert Wartenberg lecture. Neurology 1983;33(9):1179–1195.
421. Rozen S, et al. Marfanoid hypermobility syndrome associated with Duane's retraction syndrome. Ann Ophthalmol 1983;15(9):862–864.
422. Rubinstein AE, et al. Moebius syndrome in Kallmann syndrome. Arch Neurol 1975;32(7):480–482.
423. Rush J, Shafrin F. Ocular myasthenia presenting as superior oblique weakness. J Clin Neuroophthalmol 1982;2:125–127.
424. Rush JA, Younge BR. Paralysis of cranial nerves III, IV, and VI. Cause and prognosis in 1,000 cases. Arch Ophthalmol 1981;99(1):76–79.
425. Saavedra J, et al. A cold test for myasthenia gravis. Neurology 1979;29(7):1075.
426. Sakalas R, et al. Chronic sixth nerve palsy. An initial sign of basisphenoid tumors. Arch Ophthalmol 1975;93(3):186–190.
427. Sano K. Trigemino-ocular synkineses. Neurologia 1959;1:29–51.
428. Saraux H, Laroche L, Lacombe H. Congenital horizontal gaze paralysis and ear dysplasia in a boy with Duane's retraction syndrome and seventh nerve palsy. Ophthalmologica 1984;188(4):208–211.
429. Sargent MA, Poskitt KJ, Jan JE. Congenital ocular motor apraxia: imaging findings. AJNR Am J Neuroradiol 1997;18(10):1915–1922.
430. Sarkies NJ, Sanders MD. Convergence spasm. Trans Ophthalmol Soc UK 1985;104(pt 7):782–786.
431. Sarnat HB, McGarry JD, Lewis JE Jr. Effective treatment of infantile myasthenia gravis by combined prednisone and thymectomy. Neurology 1977;27(6):550–553.
432. Sato M. Magnetic resonance imaging and tendon anomaly associated with congenital superior oblique palsy. Am J Ophthalmol 1999; 127(4):379–387.
433. Scassellat-Sforzolini G. Una sindroma molto rare: diffeto congenito monolaterale della elevazione con retrazione del globe. Riv Otoneurooftalmol 1958;33:431–439.
434. Schapira AH, Thomas PK. A case of recurrent idiopathic ophthalmoplegic neuropathy (Miller Fisher syndrome). J Neurol Neurosurg Psychiatry 1986;49(4):463–464.

435. Scharf J, Zonis S. Benign abducens palsy in children. J Pediatr Ophthalmol 1975;12:165.
436. Schatz NJ, Savino PJ, Corbett JJ. Primary aberrant aculomotor regeneration. A sign of intracavernous meningioma. Arch Neurol 1977;34(1):29–32.
437. Schmidt D. Prognosis of ocular myasthenia in childhood. Neuro-Ophthalmology 1983;3:117–124.
438. Schneck L, et al. Ophthalmoplegia plus with morphological and chemical studies of cerebellar and muscle tissue. J Neurol Sci 1973;19(1):37–44.
439. Schraeder PL, Cohen MM, Goldman W. Bilateral internuclear ophthalmoplegia associated with fourth ventricular epidermoid tumor. Case report. J Neurosurg 1981;54(3):403–405.
440. Schumacher-Feero LA, et al. Third cranial nerve palsy in children. Am J Ophthalmol 1999;128(2):216–221.
441. Schumm F, et al. Thymectomy in patients with pure ocular symptoms. J Neurol Neurosurg Psychiatry 1985;48:332–337.
442. Scott A. Botulinum toxin treatment for strabismus. Am Orthop J 1985;35:28.
443. Scott AB, Wong GY. Duane's syndrome. An electromyographic study. Arch Ophthalmol 1971;87(2):140–147.
444. Scott AB, Kraft SP. Botulinum toxin injection in the management of lateral rectus paresis. Ophthalmology 1985;92(5):676–683.
445. Seaber J, Nashold B. Comparison of ocular motor effects of unilateral stereotactic midbrain lesions in man. Neuro-Ophthalmology 1980;1:95–99.
446. Sharf B, Hyams S. Oculomotor palsy following varicella. J Pediatr Ophthalmol 1972;9:245–247.
447. Sharpe JA, Johnston JL. Ocular motor paresis versus apraxia. Ann Neurol 1989;25(2):209–210.
448. Shauly Y, Weissman A, Meyer E. Ocular and systemic characteristics of Duane syndrome. J Pediatr Ophthalmol Strabismus 1993; 30(3):178–183.
449. Shaunak S, et al. Saccades and smooth pursuit in myotonic dystrophy. J Neurol 1999;246(7):600–606.
450. Shawkat FS, et al. Neuroradiological and eye movement correlates in children with intermittent saccade failure: "ocular motor apraxia." Neuropediatrics 1995;26(6):298–305.
451. Shawkat FS, et al. The role of ERG/VEP and eye movement recordings in children with ocular motor apraxia. Eye 1996;10(pt 1):53–60.
452. Shoffner JM, et al. Spontaneous Kearns–Sayre/chronic external ophthalmoplegia plus syndrome associated with a mitochondrial DNA deletion: a slip-replication model and metabolic therapy. Proc Natl Acad Sci USA 1989;86(20):7952–7956.
453. Shulman LM, Gallo BV, Weiner WJ. Acquired abducens-trigeminal synkinesis. Neurology 1998;50(5):1507–1508.
454. Sibony PA, Lessell S. Transient oculomotor synkinesis in temporal arteritis. Arch Neurol 1984;41(1):87–88.

455. Sibony PA, Lessell S, Gittinger JW Jr. Acquired oculomotor synkinesis. Surv Ophthalmol 1984;28(5):382–390.
456. Sibony PA, Evinger C, Lessell S. Retrograde horseradish peroxidase transport after oculomotor nerve injury. Investig Ophthalmol Vis Sci 1986;27(6):975–980.
457. Simcock PR, Kelleher S, Dunne JA. Neuro-ophthalmic findings in botulism type B. Eye 1994;8(pt 6):646–648.
458. Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. Pharmacol Rev 1981;33(3):155–188.
459. Slavin ML. Gaze palsy associated with viral syndrome. Am J Ophthalmol 1985;100(3):468–473.
460. Slavin ML. Transient comitant esotropia in a child with migraine. Am J Ophthalmol 1989;107(2):190–191.
461. Smith C. Nuclear and infranuclear ocular motility disorders. In: Miller N, Newman N (eds) Clinical neuro-ophthalmology. Baltimore: Williams & Wilkins, 1999:1238–1240.
462. Snead OC III, et al. Juvenile myasthenia gravis. Neurology 1980;30(7 pt 1):732–739.
463. Soliven BC, et al. Seronegative myasthenia gravis. Neurology 1988;38(4):514–517.
464. Spatz H, Ullrich O. Klinischer und anatomischer Beitrag zu den angeborenen Beweglichkeitsdefekten im Hirnnervenbereich. Z Kinderheilkd 1931;51:579–597.
465. Spielmann A, Richter J. Oculomotor surgery in Parinaud's syndrome. Ophtalmologie 1989;3(2):157–159.
466. Spierer A, Barak A. Strabismus surgery in children with Mobius syndrome. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(1):58–59.
467. Spiro AJ, et al. A cytochrome-related inherited disorder of the nervous system and muscle. Arch Neurol 1970;23(2):103–112.
468. Spooner JW, Baloh RW. Eye movement fatigue in myasthenia gravis. Neurology 1979;29(1):29–33.
469. Stamler J, Nerad J, Keech R. Acquired pseudo-Duane's retraction syndrome secondary to acute orbital myositis. Binoc Vision 1989;4:103–108.
470. Stansbury J. Moebius's syndrome. Am J Ophthalmol 1952;35:256–261.
471. Starr A. A disorder of rapid eye movements in Huntington's chorea. Brain 1967;90(3):545–564.
472. Steinlin M, et al. Congenital oculomotor apraxia: a neurodevelopmental and neuroradiological study. Neuro-Ophthalmology 1990;10:27–32.
473. Stell R, et al. Ataxia telangiectasia: a reappraisal of the ocular motor features and their value in the diagnosis of atypical cases. Mov Disord 1989;4(4):320–329.
474. Sternberg I, Ronen S, Arnon N. Recurrent, isolated, post-febrile abducens nerve palsy. J Pediatr Ophthalmol Strabismus 1980;17(5):323–324.

475. Sudarshan A, Goldie WD. The spectrum of congenital facial diplegia (Moebius syndrome). Pediatr Neurol 1985;1(3):180–184.
476. Sullivan S. Benign recurrent isolated VI nerve palsy of childhood. Clin Pediatr 1985;24:160–161.
477. Summers CG, MacDonald JT, Wirtschafter JD. Ocular motor apraxia associated with intracranial lipoma. J Pediatr Ophthalmol Strabismus 1987;24(5):267–269.
478. Swick HM. Pseudointernuclear ophthalmoplegia in acute idiopathic polyneuritis (Fisher's syndrome). Am J Ophthalmol 1974;77(5):725–728.
479. Sydnor CF, Seaber JH, Buckley EG. Traumatic superior oblique palsies. Ophthalmology 1982;89(2):134–138.
480. Tamura EE, Hoyt CS. Oculomotor consequences of intraventricular hemorrhages in premature infants. Arch Ophthalmol 1987;105(4):533–535.
481. Taylor MJ, Polomeno RC. Further observations on the auditory brainstem response in Duane's syndrome. Can J Ophthalmol 1983;18(5):238–240.
482. Tekkok IH, et al. Bilateral intranuclear ophthalmoplegia associated with fourth ventricular dermoid tumor. J Clin Neuroophthalmol 1989;9(4):254–257.
483. Teller J, Karmon G, Savir H. Long-term follow-up of traumatic unilateral superior oblique palsy. Ann Ophthalmol 1988;20(11):424–425.
484. Ter Bruggen JP, et al. Disorders of eye movement in myotonic dystrophy. Brain 1990;113(pt 2):463–473.
485. Terranova W, Palumbo JN, Breman JG. Ocular findings in botulism type B. JAMA 1979;241(5):475–477.
486. Thomas R, et al. Bilateral synergistic divergence. J Pediatr Ophthalmol Strabismus 1993;30(2):122–123.
487. Tjissen C, Goor C, van Woerkom T. Spasm of the near reflex: functional or organic disorder? Neuro-Ophthalmology 1983;3:59–64.
488. Toshniwal P. Demyelinating optic neuropathy with Miller–Fisher syndrome. The case for overlap syndromes with central and peripheral demyelination. J Neurol 1987;234(5):353–358.
489. Towfighi J, et al. Mobius syndrome. Neuropathologic observations. Acta Neuropathol (Berl) 1979;48(1):11–17.
490. Traboulsi EI, Maumenee IH. Extraocular muscle aplasia in Moebius syndrome. J Pediatr Ophthalmol Strabismus 1986;23(3):120–122.
491. Tredici TD, von Noorden GK. Are anisometropia and amblyopia common in Duane's syndrome? J Pediatr Ophthalmol Strabismus 1985;22(1):23–25.
492. Tripp JH, et al. Juvenile Gaucher's disease with horizontal gaze palsy in three siblings. J Neurol Neurosurg Psychiatry 1977;40(5):470–478.
493. Trobe JD, Glaser JS, Post JD. Meningiomas and aneurysms of the cavernous sinus. Neuro-ophthalmologic features. Arch Ophthalmol 1978;96(3):457–467.
494. Trobe JD. Cyclodeviation in acquired vertical strabismus. Arch Ophthalmol 1984;102(5):717–720.

495. Trobe JD. Third nerve palsy and the pupil. Footnotes to the rule. Arch Ophthalmol 1988;106(5):601–602.
496. Troost BT, et al. Upbeat nystagmus and internuclear ophthalmoplegia with brainstem glioma. Arch Neurol 1980;37(7):453–456.
497. Tsai L, et al. Oculomotor apraxia in a case of Gaucher's disease with homozygous T1448C mutation. Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih 1996;37:52–55.
498. Vajsar J, et al. Arthrogryposis multiplex congenita due to congenital myasthenic syndrome. Pediatr Neurol 1995;12(3):237–241.
499. Valbuena O, et al. Ataxia telangiectasia: review of 13 new cases. Rev Neurol 1996;24(125):77–80.
500. Valmaggia C, Zaunbauer W, Gottlob I. Elevation deficit caused by accessory extraocular muscle. Am J Ophthalmol 1996;121(4):444–445.
501. Vassella F, Lutschg J, Mumenthaler M. Cogan's congenital ocular motor apraxia in two successive generations. Dev Med Child Neurol 1972;14(6):788–796.
502. Velez FG, Clark RA, Demer JL. Facial asymmetry in superior oblique muscle palsy and pulley heterotopy. J Am Assoc Pediatr Ophthalmol Strabismus 2000;4(4):233–239.
503. Versino M, et al. Lateral gaze synkinesis on downward saccade attempts with paramedian thalamic and midbrain infarct. J Neurol Neurosurg Psychiatry 1999;67(5):696–697.
504. Victor DI. The diagnosis of congenital unilateral third-nerve palsy. Brain 1976;99(4):711–718.
505. Vincent C, et al. A proposed new contiguous gene syndrome on 8q consists of branchio-oto-renal (BOR) syndrome, Duane syndrome, a dominant form of hydrocephalus and trapeze aplasia; implications for the mapping of the BOR gene. Hum Mol Genet 1994;3(10):1859–1866.
506. Vincent FM, Vincent T. Relapsing Fisher's syndrome. J Neurol Neurosurg Psychiatry 1986;49(5):604–606.
507. Vivian A, Harris C, Kriss A. Oculomotor signs in infantile Gaucher disease. Neuro-Ophthalmology 1993;13:151–155.
508. von Ludinghausen M. Bilateral supernumerary rectus muscles of the orbit. Clin Anat 1998;11(4):271–277.
509. von Ludinghausen M, Miura M, Wurzler N. Variations and anomalies of the human orbital muscles. Surg Radiol Anat 1999;21(1):69–76.
510. von Noorden GK, Murray E. Up- and downshoot in Duane's retraction syndrome. J Pediatr Ophthalmol Strabismus 1986;23(5):212–215.
511. von Noorden GK. A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome. Am J Ophthalmol 1991;112(3):358–359.
512. Wadia NH, Swami RK. A new form of heredo-familial spinocerebellar degeneration with slow eye movements (nine families). Brain 1971;94(2):359–374.

513. Wadia NH, et al. A study of the neurological disorder associated with acute haemorrhagic conjunctivitis due to enterovirus 70. J Neurol Neurosurg Psychiatry 1983;46(7):599–610.
514. Wagner RS, Caputo AR, Frohman LP. Congenital unilateral adduction deficit with simultaneous abduction. A variant of Duane's retraction syndrome. Ophthalmology 1987;94(8):1049–1053.
515. Walsh F, Hoyt W. Clinical neuro-ophthalmology. Baltimore: Williams & Wilkins, 1969.
516. Waterhouse WJ, Enzenauer RW, Martyak AP. Successful strabismus surgery in a child with Moebius syndrome. Ann Ophthalmol 1993; 25(8):292–294.
517. Weeks CL, Hamed LM. Treatment of acute comitant esotropia in Chiari I malformation. Ophthalmology 1999;106(12):2368–2371.
518. Weinacht S, Huber A, Gottlob I. Vertical Duane's retraction syndrome. Am J Ophthalmol 1996;122(3):447–449.
519. Weinberg DA, Lesser RL, Vollmer TL. Ocular myasthenia: a protean disorder. Surv Ophthalmol 1994;39(3):169–210.
520. Weintraub MI. External ophthalmoplegia, ataxia, and areflexia complicating acute infectious polyneuritis. Am J Ophthalmol 1977;83(3): 355–357.
521. Welch R. Chicken-pox and the Guillain–Barre syndrome. Arch Dis Child 1962;37:557–559.
522. Werner DB, Savino PJ, Schatz NJ. Benign recurrent sixth nerve palsies in childhood. Secondary to immunization or viral illness. Arch Ophthalmol 1983;101(4):607–608.
523. Whitsel EA, Castillo M, D'Cruz O. Cerebellar vermis and midbrain dysgenesis in oculomotor apraxia: MR findings. AJNR Am J Neuroradiol 1995;16(suppl 4):831–834.
524. Wieacker P, et al. A new X-linked syndrome with muscle atrophy, congenital contractures, and oculomotor apraxia. Am J Med Genet 1985;20(4):597–606.
525. Wilcox LM Jr, Gittinger JW Jr, Breinin GM. Congenital adduction palsy and synergistic divergence. Am J Ophthalmol 1981;91(1):1–7.
526. Williams AS, Hoyt CS. Acute comitant esotropia in children with brain tumors. Arch Ophthalmol 1989;107(3):376–378.
527. Willison HJ, O'Hanlon GM. The immunopathogenesis of Miller Fisher syndrome. J Neuroimmunol 1999;100(1–2):3–12.
528. Wilson ME, Hoxie J. Facial asymmetry in superior oblique muscle palsy. J Pediatr Ophthalmol Strabismus 1993;30(5):315–318.
529. Wilson RS, Landers JH. Anomalous duplication of inferior oblique muscle. Am J Ophthalmol 1982;93(4):521–522.
530. Wise GA, McQuillen MP. Transient neonatal myasthenia. Clinical and electromyographic studies. Arch Neurol 1970;22(6):556–565.
531. Wishnick M, et al. Mobius syndrome and limb abnormalities with dominant inheritance. Ophthalmic Pediatr Genet 1983;2:77–81.
532. Woods CG, Taylor AM. Ataxia telangiectasia in the British Isles: the clinical and laboratory features of 70 affected individuals. Q J Med 1992;82(298):169–179.

533. Woody R, Reynolds J. Association of bilateral internuclear ophthalmoplegia and myelomeningocele with Arnold–Chiari malformation type II. J Clin Neuroophthalmol 1985;5:124–126.
534. Woody RC, Blaw ME. Ophthalmoplegic migraine in infancy. Clin Pediatr (Phila) 1986;25(2):82–84.
535. Wright PW, Strauss GH, Langford MP. Acute hemorrhagic conjunctivitis. Am Fam Physician 1992;45(1):173–178.
536. Wybar K. Disorders of ocular motility in brain stem lesions in children. Ann Ophthalmol 1971;3(6):645–647.
537. Yang MC, et al. Electrooculography and discriminant analysis in Duane's syndrome and sixth-cranial-nerve palsy. Graefe's Arch Clin Exp Ophthalmol 1991;229(1):52–56.
538. Yeh JH, et al. Miller Fisher syndrome with central involvement: successful treatment with plasmapheresis. Ther Apher 1999;3(1):69–71.
539. Yuki N. Pathogenesis of Guillain–Barre and Miller Fisher syndromes subsequent to *Campylobacter jejuni* enteritis. Jpn J Infect Dis 1999;52(3):99–105.
540. Zaret CR, Behrens MM, Eggers HM. Congenital ocular motor apraxia and brainstem tumor. Arch Ophthalmol 1980;98(2):328–330.
541. Zasorin NL, Yee RD, Baloh RW. Eye-movement abnormalities in ophthalmoplegia, ataxia, and areflexia (Fisher's syndrome). Arch Ophthalmol 1985;103(1):55–58.
542. Zee DS, Yee RD, Singer HS. Congenital ocular motor apraxia. Brain 1977;100(3):581–599.
543. Zuker RM. Facial paralysis in children. Clin Plast Surg 1990;17(1):95–99.