Chapter 7
Complex Ocular Motor Disorders in Children

Introduction

A number of complex ocular motility disorders are discussed in this chapter. The diversity of these conditions reflects the need for the ophthalmologist to maintain a broad working knowledge of pediatric neurologic disorders along with their ocular motor manifestations. Some clinical features of these conditions (e.g., congenital ocular motor apraxia, congenital fibrosis syndrome) are sufficiently unique that the diagnosis can be established solely on the basis of the clinical appearance. Other disorders either show overlapping manifestations or effectively masquerade as other entities. Unique features of some conditions, such as conjugate ocular torsion in patients with skew deviation, have been recently recognized and are considered worthy of emphasis because they significantly expand the differential diagnosis. Indeed, assessment of objective torsion (and subjective torsion when possible) is a necessary component of any comprehensive strabimological evaluation. Correction of coexisting torsion can be integrated into the surgical plan, except when the torsion serves a compensatory function, as in patients with skew deviation.

Although the clinical history and physical examinations remain the “gold standard” for establishing the diagnosis, neuroimaging has become an integral part of the diagnostic evaluation. High-resolution neuroimaging can now depict the presence or absence of most ocular motor nerves and the size, position, and dynamic function of the extraocular muscles. In patients with craniosynostosis, for example, heterotopic extraocular muscles within the orbit can produce a motility disorder indistinguishable from innervational inferior oblique muscle overaction, absence of the isolated extraocular muscles can produce complex ocular motility dysfunction, and retrodisplacement of the trochlea can produce a motility pattern indistinguishable from congenital superior oblique palsy. Optimal surgical treatment depends on accurate recognition of the specific cause of a given patient’s motility disturbance. Thus, a detailed knowledge of clinical findings that characterize each condition is necessary to perform the diagnostic workup in an efficient, timely, and cost-effective manner. A knowledgeable clinician is less likely to embark on “fishing expeditions.”

The emphasis of this chapter is on ocular motility disorders of neurologic origin and their differential diagnosis. The most current pathophysiologic concepts of the disorders are summarized. A section at the end of the chapter is devoted to a few common eyelid and pupillary abnormalities encountered in children. Some of these disorders, such as excessive blinking in children, commonly represent benign transient tics that receive very little attention in the ophthalmologic literature, but are not rare in clinical practice. These bear only superficial resemblance to the more chronic benign essential blepharospasm of adults although, rarely, childhood tics and adult blepharospasm show clustering in the same family, suggesting a possible link. Occasionally, underlying ocular surface abnormalities and seizure disorders may be uncovered in children with excessive blinking. Other disorders, such as hemifacial spasm, which is more common in adults, may be the harbingers of more serious central nervous system (CNS) disorders if encountered in very early childhood. Pediatric Horner syndrome is treated in some detail at the end of the chapter, owing to its potentially ominous association with certain neoplasms, especially neuroblastoma. The human immunodeficiency virus (HIV) infection has joined the ranks of other great mimickers (e.g., myasthenia gravis, syphilis), with an ever-expanding list of neuro-ophthalmologic manifestations. No part of the nervous system is spared. Even though it is not specifically covered in this chapter, HIV-related neurological disease should be included in the differential diagnosis of childhood ocular motor disorders of cortical, brain stem, cerebellar, or peripheral nervous system origin.

Strabismus in Children with Neurological Dysfunction

Common neurologic disorders of children are frequently associated with strabismus. These include cerebral palsy, Down syndrome, myelomeningocele, and hydrocephalus.
The features of the associated strabismus are often indistinguishable from the varieties found in otherwise normal children, but sufficient differences exist in a distinct minority of neurologically affected children to warrant separate consideration. Children with neurologic disorders, who have horizontal strabismus, have a higher prevalence of constant exotropia and primary superior oblique muscle overaction than otherwise healthy strabismic children (Fig. 7.1).334,341

Fig. 7.1  (a) Bilateral superior oblique overaction in child with lumbar myelomeningocele. Note resemblance to alternating skew deviation. (b) 1MR imaging characteristically associated Chiari II malformation with pronounced peaking of tectum and herniation of cerebellar vermis into cervical spinal canal
Cerebral palsy is perhaps one of the most common conditions seen in a pediatric neuro-ophthalmology practice. The term cerebral palsy defines a group of chronic neurologic disorders resulting from damage to the immature brain. Most cases nowadays are due to prematurity. Care should be taken to distinguish the static nature of cerebral palsy from the inexorably progressive neurodegenerative disorders such as Pelizaeus–Merzbacher disease.

Cerebral palsy is characterized by the onset of neurologic deficits in the neonatal period and absence of progression. In addition to motor disorders, such as paralysis, weakness, and incoordination, children with cerebral palsy may display sensory deficits, as exemplified by the frequent findings of optic atrophy, deafness, and cortical visual impairment. Patients with cerebral palsy show ophthalmologic abnormalities with a frequency ranging from 50 to 90%. These include optic atrophy, ambylopia, refractive errors, visual field defects, congenital cataracts, corneal leukomas, retinal dystrophies with a frequency ranging from 50 to 90%. These include optic atrophy, ambylopia, refractive errors, visual field defects, congenital cataracts, corneal leukomas, retinal dystrophies, choroiditis, macular or iris colobomas, retinopathy of prematurity, potois, spastic eyelids, abnormal head postures, and ocular motility disorders. The latter include concomitant strabismus, ocular motor nerve palsy, nystagmus, gaze palsy, and other supranuclear disturbances of ocular movements.

Children with cerebral palsy have a markedly increased incidence of strabismus. The strabismic deviations are usually horizontal and nonparalytic. Associated vertical incomitance is often seen, with A-pattern strabismus being particularly common. In one series, 54% of strabismic children with cerebral palsy showed A pattern, and 46% showed V pattern. Variability of the magnitude and direction of the strabismus are commonly noted in cerebral palsy. Some studies note a predominance of esotropia, while others have found exotropia to be more common.

Momentary fluctuation from esotropia to exotropia has been termed dyskinetic strabismus and is considered unique to cerebral palsy. Dyskinetic strabismus is unrelated to accommodative effort or attention. In addition to the dyskinetic strabismus of cerebral palsy, the differential diagnosis of a variable strabismus shifting from esotropia to exotropia includes exotropia with a high AC/A ratio, as well as surgically overcorrected accommodative esotropia with high AC/A ratio, and exotropia with dissociated horizontal deviation. Patients with oculomotor palsy with cyclic spasm may also appear to switch from esotropia to exotropia during a spasm phase, but the associated features are unique enough to obviate diagnostic confusion.

Generally, the subset of children with cerebral palsy who exhibit dyskinetic strabismus are poor candidates for surgical correction. Children with stable deviations respond favorably to strabismus surgery, although their overall outcome is not as good as in strabismic children without cerebral palsy. Unlike children with infantile esotropia, some esotropic children with cerebral palsy convert spontaneously to an exotropia over several years. For this reason, current trends toward early surgery for infantile esotropia should not be loosely applied to these patients, and it is important to rule out occult neurologic disease when early strabismus surgery is contemplated in seemingly normal children.

As children with cerebral palsy and esotropia seem to have a strong predilection for surgical overcorrection, standard surgical doses for treating esotropia should be reduced. In our experience, however, it is not necessary to reduce doses for bilateral lateral rectus muscle recession in neurologic esotropia. As detailed in Chap. 1, children with cerebral palsy may have abnormalities of gaze affecting pursuit and saccadic movements and vestibulo-ocular reflex suppression by fixation.

The craniosynostosis syndromes often present with complex forms of horizontal and vertical strabismus that are both neurologic and anatomical in origin. Although hypertelorism is classically associated with exotropia with a V pattern, esotropia can also be seen. Good stereopsis is rare in the syndromic craniosynostosis and may sometimes be confined to certain positions of gaze. Some patients develop esotropia following craniofacial surgery, which can disrupt stereopsis.

The frequent finding of overelevation of the adducting eye in children with bilateral craniosynostosis was previously attributed to recession of the frontal processes, creating a mechanical disadvantage for the superior oblique muscle. It now appears that excyclorotation of both orbits alters the horizontal rectus muscle positions, positioning the lateral rectus muscles lower than normal and the medial rectus muscles higher than normal (Fig. 7.2). This orbital excyclorotation is associated with marked excyclorotation of the globes, as is evident on retinal examination. Although the resulting motility pattern is indistinguishable from that produced by primary inferior oblique muscle overaction, inferior oblique weakening procedures produce negligible improvement. Rectus muscle transposition, in addition to superior oblique muscle strengthening (Harada–Ito procedure), is necessary to treat this condition.

Other mechanisms for vertical deviations in the craniosynostosis include absent or anomalous superior rectus (or other) muscles. Preoperative orbital imaging allows the surgeon to anticipate the multitude of orbital anatomical disturbances that contribute to strabismus in children with craniosynostosis.

**Visuovestibular Disorders**

Some forms of esotropia and their associated ocular motility signs signify benignity. From a neuro-ophthalmological perspective, horizontal strabismus can be subdivided into the
common conditions that presumably arise from unequal visual input to the two eyes and the less common conditions associated with neurologic disease. The former conditions constitute the visuovestibular disorders (Table 7.1), which may present as acquired and thereby may simulate neurologic disease. As these conditions arise from unbalanced binocular visual input to the central vestibular system, they signify benignity, although it can be argued that they constitute a “physiologic” form of neurologic disease. Although they are more commonly associated with esotropia, patients with early-onset exotropia present with the same constellation of dissociated ocular motor signs discussed in the following lines. Brodsky and Fray have theorized that infantile esotropia may itself arise from a dissociated deviation. This occurs when unequal visual input generates dissociated esotonus, which leads to the gradual development of infantile esotropia, and explains the preponderance of infantile esotropia over infantile exotropia in nonneurologic infants.

Visuovestibular eye movements produce binocular rotations that are evoked by unequal visual input to the two eyes. These consist of latent nystagmus, dissociated vertical

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**Table 7.1** Visuovestibular disorders

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<th>Disorder</th>
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<td>Dissociated vertical divergence</td>
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<td>Infantile esotropia (dissociated esotonus)</td>
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<td>Latent nystagmus</td>
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<td>Primary Inferior Oblique Overaction</td>
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![Fig. 7.2 Craniocynostosis](image)

Left: Coronal orbital MR image in a girl with Crouzon’s disease and bilateral inferior oblique muscle overaction, V-pattern, and fundus extorsion showing excyclorotated extraocular muscle positions. Inferior oblique recession produced no improvement. Right: Schematic diagram showing affect of extraocular muscle heterotopia on binocular rotations.
**Dissociated vertical divergence** and **primary oblique muscle overaction**. These pretermatral ocular rotations recapitulate the primitive eye movements induced by light or optokinetic stimulation in lateral-eyed animals. They are mediated by subcortical pathways extending from the optic nerves to the contralateral vestibular nucleus and cerebellum. Although present to a small degree in normals, they develop almost exclusively when infantile strabismus precludes the development of normal binocular cortical connections. As these visual reflexes are corrective for a central vestibular imbalance, they are not associated with dizziness, oscillopsia, or other neurologic symptoms that characterize vestibular disease. They are evoked by physiologic stimuli rather than by neurologic lesions. In the clinic, mechanical occlusion of one eye and cortical suppression of one eye can both activate in the subcortical visuovestibular pathways that evoke this visuovestibular response.

The resurgence of visuovestibular movements in humans with infantile strabismus shows that our eyes function not only as visual organs, but as balance organs. Because they recapitulate visual reflexes in lateral-eyed animals, the absence of early cortical binocular development is a permissive factor that allows them to develop, the retention of primitive subcortical reflexes is the proximate cause of these movements. Infantine strabismus provides a natural experiment to uncover the primitive visual reflexes that lie buried within us. By disrupting the development of frontal binocular vision, infantile strabismus allows these reflexes to “bubble to the surface.” The resulting ocular motor “intrusions” correspond to an imbalance of binocular visual input in three planes of physical space.

**Latent nystagmus** is characterized by conjugate horizontal nystagmus induced by monocular occlusion or cortical suppression. The fast phase (in both eyes) is directed toward the side of the fixating eye. Latent nystagmus corresponds to the optokinetic component of ocular rotation that is driven monocularly by nasal optic flow during a turning movement of the body in lateral-eyed animals. When infantile esotropia disrupts the establishment of binocular visual connections, visual input from the fixating eye to the contralateral nucleus of the optic tract evokes a counterrotation of the eyes which corresponds to a turning movement of the body toward the object of regard. The clinical expression of this visual reflex is also evident in the monocular nasotemporal asymmetry to horizontal optokinetic stimulation that characterizes infantile strabismus.

**Dissociated vertical divergence** is characterized by an upward drift (sometimes accompanied by a dynamic extorsional movement) of a covered or cortically suppressed eye. Dissociated vertical divergence corresponds to the dorsal light reflex that has been observed in fish and other lateral-eyed animals when unequal luminance to the two eyes evokes a body tilt or vertical divergence of the eyes toward the side with greater luminance. In humans, dissociated vertical divergence is a visual balancing reflex that uses weighted binocular visual input to orient eye position to the perceived vertical. The exaptation of a cycloversional movement into the human dorsal light reflex permits active modulation of perceived visual tilt when the eyes are frontally positioned.

**Primary oblique muscle overaction** consists of bilateral overerelevation or overdepression of the adducting eye. Primary inferior oblique muscle overaction corresponds to a similar dorsal light reflex that is induced in fish when a forward or backward shift in overhead luminance evokes an ipsidirectional body pitch or torsional rotation of the eyes backward to reorient the body with respect to the light. These binocular torsional rotations of the eyes constitute a physiologic form of primary oblique muscle overaction that can be induced by altering binocular visual input. In humans, a forward or backward rotation relative to overhead light sends excitatory innervation to each of the elevators or each of the depressors. Because the vestibular system segregates innervation to its target extraocular muscles, the vertical actions of the human oblique muscles can summate in adduction with those of the rectus muscles to produce the innervational overerelevation of the adducting eye that defines primary inferior oblique muscle overaction.

The fundamental association of primary oblique muscle overaction with loss of binocular vision in humans suggests that the brain registers loss of binocular visual input as forward rotation of the body. Although primary superior oblique muscle overaction is considered as a sign of neurologic disease (see section on “Skew Deviation”) in the United States and Europe, it is reported to accompany infantile esotropia more commonly than primary inferior oblique overaction in Argentina and South Africa, suggesting that it may also arise from a visuovestibular imbalance.

**Neurologic Esotropia**

A variety of prenuclear neurologic diseases are characterized by an esotropic deviation of the eyes (Tables 7.2 and 7.3). Spielmann has suggested that organic spasm of the near reflex, (Parinaud syndrome with convergence-retraction nystagmus or convergence excess), and thalamic esotropia

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<th>Table 7.2</th>
<th>Complex neurologic disorders predisposing to esotropia</th>
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<td>Acute comitant esotropia</td>
<td>Congenital cranial dysinnervation syndromes</td>
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<td>Exercise-induced diplopia</td>
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<td>Spasm of the near reflex</td>
<td>Thalamic esotropia</td>
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fall into a group of neurological diseases characterized by convergence excess. Many of these disorders have been detailed in their specific clinical context in other chapters. As many neurologic patients take medications with strong anticholinergic side effects, esotropia of neurologic origin must be distinguished from anticholinergic esotropia, a condition in which excessive accommodative effort leads to accommodative esotropia. Several recent cases of esotropia induced by systemic anticholinergic medications have recently been described. Anticholinergic esotropia seems to be precipitated by increased convergence of the eyes due to the increased accommodative effort in patients with an inherent tendency to develop esotropia.

**Spasm of the Near Reflex**

Spasm of the near reflex is characterized by intermittent episodes of miosis, convergence, and accommodation. Patients exhibit variable esotropia and varying pupillary size. Unlike in other patients with intermittent esotropia, monocular refixation during alternate occlusion is often slow and inaccurate. The name “spasm of the near reflex” should not be used interchangeably with either accommodation spasm or convergence insufficiency. Patients with isolated spasm of the near reflex may improve with reassurance. Some patients require psychiatric counseling. Current ophthalmologic treatment of spasm of the near reflex involves administering cycloplegic eye drops and providing bifocal glasses for reading. Historically, some patients have shown improvement with miotic drops, placebo drops, benzodiazepines, special glasses with occlusion of the inner third of each lens, monocular occlusion, or narcosuggestion during an amobarbital sodium interview. In patients with underlying organic disease, spasm of the near reflex (like essential blepharospasm) may be a type of dystonia. Like other types of dystonia, some cases respond to botulinum injection. In patients without organic disease, this problem usually resolves spontaneously over months to years.

**Exercise-Induced Diplopia**

Exercise-induced diplopia has rarely been reported in children. This condition may represent a breakdown of an esophoria but warrants neuroimaging to rule out a midline cerebellar tumor.
Neurologic Exotropia

The differential diagnosis of constant exotropia includes cortical visual insufficiency, craniofacial synostosis, and congenital fibrosis syndrome. Isolated infantile exotropia is a rare but well-recognized nonneurologic condition in which a large-angle exotropia is associated with the same constellation of visuovestibular disorders that accompany infantile esotropia. Some early-onset cases of intermittent exotropia also fall into this group. Some cases of infantile exotropia are hereditary, showing an autosomal dominant inheritance pattern. Nevertheless, the clinician must maintain a high index of suspicion for neurologic disease in the child with infantile exotropia.

In our experience, constant exotropia is most commonly seen in the setting of cortical visual insufficiency secondary to hypoxic-ischemic encephalopathy. Associated signs include horizontal conjugate gaze deviation with little or no nystagmus and mild or sectoral pallor of the optic discs. Because children with congenital homonymous hemianopia may develop a constant exotropia that serves to expand the existing visual field, confrontation visual fields should be checked in this setting. Signs of craniofacial disease are usually apparent on initial examination. As detailed below, fixed downgaze, associated ptosis, sparing of pupillary function, and similar findings in other family members provide clinical clues to the diagnosis of congenital fibrosis syndrome.

Convergence Insufficiency

Convergence insufficiency is a common condition characterized by: (1) diplopia or blurring at near, (2) decreased convergence amplitudes, and (3) a recessed near point of accommodation. It seems to afflict intelligent patients and is considered to be the one form of strabismus that is treatable with eye exercises. Convergence training has been shown to improve proximal and tonic convergence, but not accommodative or fusional convergence.

Convergence insufficiency is most commonly a primary condition presenting in young adults. In this setting, it is presumably caused by an inborn deficiency or acquired imbalance of vergence eye movements that has yet to be identified. In this setting, patients may present with sleeping on reading or near work, tearing, heavy lids, uncomfortable eyes, asthenopic symptoms, double vision, or blepharitis (from frequent rubbing of the eyes). These patients perform their near work optimally immediately after awakening.

Convergence insufficiency is also a prominent accompaniment of neurologic disease, having been reported in association with head trauma, neurodegenerative disorders, infarction, thyroid ophthalmopathy, myasthenia gravis, toxic agents, medications, inflammation, decompression sickness, whiplash injuries, and attention-deficit hyperactivity disorder (ADHD). In the last mentioned condition, it is not always clear whether convergence insufficiency is the cause or effect, whether they are comorbid conditions, or whether medications used to treat the ADHD may contribute to the convergence insufficiency.

Some believe that accommodative insufficiency is the primary source of symptoms in children diagnosed with convergence insufficiency, although this issue continues to be debated. Therefore, accommodative amplitudes and dynamic retinoscopy should be examined to rule out an underlying or associated accommodative paresis. It is also important to check for undetected ocular torsion, which can secondarily impair convergence. The potential pharmacological role of any medications in impairing accommodation should always be considered.

Convergence insufficiency should not be confused with convergence paralysis, another neurologic disorder in which there is a constant exotropia at near. Although convergence exercises are the mainstay of treatment for convergence insufficiency, treatment with base in prisms has also been used successfully.

Fig. 7.3 Spasm of near reflex. Twelve-year-old boy had undergone small left medial rectus muscle resection for presumed convergence insufficiency. Four months later, he was noted to have episodic, pronounced spasm of near reflex (large esotropia, miosis, induced myopia with blurred vision) associated with severe spasms involving eyelids and facial musculature (a). In between spasms, only small esotropia was variably present (b).
reported to be effective.\textsuperscript{721} In patients with convergence paralysis or convergence insufficiency that does not respond to these measures, bimedial resections\textsuperscript{325,360,464,786} and superior transpositions of the medial rectus muscles (to induce a physiologic V pattern and allow for single binocular near vision in downgaze) (Buckley EG: verbal communication) have been used. Because convergence insufficiency represents a kinetic problem rather than a static deviation, strabismus surgery may not provide an optimal approach. The superimposition of convergence insufficiency on a baseline exodeviation produces an exodeviation that is greater at near, which is often a soft sign of neurologic disease.\textsuperscript{616} Neurologic forms of exotropia are summarized in Table 7.3.

\section*{Skew Deviation}

Skew deviation of the eyes is a prenuclear vertical strabismus that is usually associated with posterior fossa lesions, particularly those affecting the brainstem tegmentum or the cerebellum.\textsuperscript{419} While causative lesions are usually structural, skew deviation does rarely result from elevated intracranial pressure due to idiopathic intracranial hypertension.\textsuperscript{281} The misalignment may be comitant or incomitant, simulate a paresis of an extraocular muscle, and alternate with time (slowly alternating skew deviation) or on lateral gaze (alternating skew on lateral gaze). As discussed below, it is usually accompanied by binocular torsion and torticollis. Although skew deviation has been historically considered to be a non-localizing sign, simply indicating involvement of the posterior fossa without further reference to a specific region, our understanding of its value as a clinical localizing sign has been revised in recent years. While early studies reported the absence of torsion in patients with skew deviation,\textsuperscript{94} this myth has now been dispelled.\textsuperscript{92,93} The degree of ocular torsion may or may not be equal in the two eyes.

Skew deviation usually presents in the more general context of the \textit{ocular tilt reaction}. The ocular tilt reaction is caused by unilateral injury to the otolithic pathways, which causes the brain to perceive the visual world as tilted.\textsuperscript{116} The ocular tilt reaction is a “righting reflex” that results from alteration in the otolithic and/or vertical semicircular canal pathways that occurs in patients with lesions of either peripheral or central vestibular system. The ocular tilt reaction rotates the eyes and head toward the tilted visual world to restore vertical orientation (Fig. 7.4). The result is an oculocephalic synkinesis consisting of vertical divergence of the eyes (skew deviation), head tilt in the direction of the lower eye, and ocular torsion in the direction of head tilt.\textsuperscript{92} These compensatory roll rotations strive to realign the interpupillary axis, head, and torsional position of the eyes, respectively, to the orientation that the patient erroneously perceives as vertical. The ocular tilt reaction has been reported in patients with intra-axial brainstem lesions (midbrain tegmentum, dorso-lateral medulla oblongata), unilateral vestibular neurctomy, and labyrinthectomy (performed in patients with severe Meniere’s disease or acoustic neuroma).\textsuperscript{512} The skew deviation that accompanies the ocular tilt reaction may be subdivided into at least three distinct types, each with distinct clinical features, ocular torsion, and localizing significance.\textsuperscript{93}

Because all three components of the ocular tilt reaction are compensatory for a subjective visual tilt, the head tilt does not serve to promote vertical fusion as it does in superior oblique palsy.\textsuperscript{116} Consequently, prismatic or surgical correction of the vertical deviation does not eliminate the associated head tilt. Patients with the ocular tilt reaction may be misdiagnosed as having a superior oblique muscle palsy, because the skew deviation may be incomitant, and both disorders can show a positive Bielschowsky Head Tilt test.\textsuperscript{284}
The diagnosis of ocular tilt reaction should be considered in patients with suspected superior oblique muscle palsy who show intorsion of the higher eye. Donahue et al\textsuperscript{217} described five patients with incomitant skew deviation that simulated superior oblique muscle palsy on the Bielschowsky Three Step test, and intorsion of the higher eye and extorsion of the lower eye. In the patient with superior oblique palsy, the finding of intorsion (rather than the expected extorsion) of the higher eye (on both Double Maddox rod testing and indirect ophthalmoscopy) should therefore signal the diagnosis of skew deviation. In other patients, skew deviation can simulate isolated inferior oblique palsy.\textsuperscript{217}

Recently, Pareluker et al found that the vertical and torsional deviations associated with skew deviation resolve in the reclined position, a finding that provides another useful clue to the diagnosis.\textsuperscript{610} For reasons that are not understood, the utricles become functionally deafferented in the reclined position,\textsuperscript{113} which explains the disappearance of skew deviation and the disappearance of compensatory head tilt in supine patients with superior oblique palsy\textsuperscript{712} (once asymmetrical utricular output can no longer be accessed to neutralize the vertical deviation).

The localizing value of skew deviation is now well established.\textsuperscript{93,94} In a study of 56 adults with unilateral brainstem infarctions and skew deviations, clinical and neuroimaging analysis revealed the following: (1) The ipsilateral eye was hypotropic with caudal pontomedullary lesions and higher with rostral pontomesencephalic lesions. (2) All patients with skew deviation showed simultaneous conjugate bilateral ocular torsion toward the hypotropic eye. Ocular torsion was evaluated from fundus photographs. This and other studies demonstrate that skew deviation is a sensitive brainstem sign of localizing and lateralizing value.\textsuperscript{93,94}

While the skew deviation in adults results primarily from infarction, skew deviation in children may be associated with a wide variety of conditions, including tumors,\textsuperscript{158} Chiari malformation,\textsuperscript{173} autoimmune disease,\textsuperscript{632} paroxysmal hemiparesis of childhood,\textsuperscript{214,357} and increased intracranial pressure.\textsuperscript{52,281,530} In one case, skew deviation was diagnosed on prenatal MR images in a fetus with a glioblastoma involving the brainstem.\textsuperscript{158}

Incomitant skew deviation may mimic a primary overaction of an oblique extraocular muscle. One type of skew deviation, termed alternating skew on lateral gaze or bilateral abducting hypertropia, closely resembles bilateral superior oblique overaction (Fig. 7.5).\textsuperscript{332,339,341,567} Affected patients typically display a right hypotropia on downgaze and to the left and left hypotropia on downgaze and to the right. One study of children with brainstem tumors\textsuperscript{341} showed that alternating skew deviation on lateral gaze localizes to the lower

Fig. 7.5 Alternating skew on lateral gaze: Patient presented with new onset of downbeat nystagmus and oscillopsia. He was diagnosed with spinocerebellar degeneration. He was orthotropic in primary position (b) but displayed left hypotropia on gaze down and to right (a) and right hypotropia on gaze down and to left (c). Note similarity to bilateral overaction of superior oblique muscles.
brainstem or cerebellum. Given the similar localization of neuroanatomic lesions in patients with myelomeningocele (most whom have Chiari II malformation) and the observation that these patients show a predilection for superior oblique overaction (Fig. 7.1), Hamed et al have argued that primary superior oblique overaction and skew deviation are phenomenologically indistinguishable. This hypothesis is further supported by the observation that strabismic children who have superior oblique overaction show a higher frequency of associated neurologic disorders compared with a control population consisting of strabismic children without superior oblique overaction. Superior oblique overaction is commonly seen in conjunction with more generalized neurologic disease such as cerebral palsy, myelomeningocele, and hydrocephalus.

Brandt and Dieterich later suggested that overlapping pathways modulate roll and pitch function of the vestibuloocular reflex, making efficient use of the vestibular network. According to their hypothesis, a unilateral skew deviation reflects a central graviceptive imbalance in the roll plane, while bilateral paramedian lesions or bilateral dysfunction of the cerebellar flocculus produces a tone imbalance in the pitch plane. The principle behind this operation resembles the guidance system of airplanes, wherein unilateral activation of a brake flap causes the plane to roll, while bilateral activation results in downward pitch.

In a bilateral ocular tilt reaction, the vertical components summate to produce the slow phase vertical drift of both eyes while the torsional components cancel each other out. Thus, a roll imbalance manifests as an ocular tilt reaction, while bilateral otolithic imbalance produces upbeat or downbeat nystagmus in conjunction with an alternating skew deviation on lateral gaze. Zee presented an interesting model in lateraled-eyed animals to demonstrate how a pitch disturbance (forward or backward) would generate the patterns of vertical deviation in lateral gaze that are seen in humans with bilateral alternating skew deviation.

Thus, while unilateral skew deviation corresponds to central graviceptive dysfunction of otolithic pathways in the roll (tilt) plane, lateral alternating skew deviation corresponds to a central graviceptive dysfunction of otolithic pathways in the pitch plane. By viewing a pencil slanted forward or backward in the pitch plane, then closing one eye and then the other, the reader can see that each image appears tilted in opposite directions when viewed monocularly.

Guyton and Weingarten hypothesized that primary oblique muscle overaction and A- and V-pattern strabismus are a result of sensory torsion that arises when fusion is absent. However, it now appears that true oblique muscle overaction, caused by premotor disinhibition in the presence of early binocular visual loss, is the cause, rather than the effect, of primary oblique muscle overaction.

While most primary oblique muscle overaction is innervational in origin, heterotopia of the extraocular muscles and their surrounding connective tissues has been recognized as an anatomical cause of apparent primary oblique muscle overaction. Other conditions causing overdepression of the adducting eye (mimicking primary superior oblique muscle overaction) include inferior rectus muscle palsy, apparent overaction of the oblique muscles in exotropia, downshoot of the eye in Duane syndrome, physiologic “overaction” of the oblique muscles in eccentric gaze, and other restrictive or paretic conditions. Overerelevation or overdepression in adduction is therefore an ocular sign that may reflect a variety of conditions. It is now possible to conceptualize oblique muscle overaction as comprising a visuovestibular type (primary inferior oblique muscle overaction), a bilateral vestibular injury (primary superior oblique muscle overaction), a leash-effect type (Duane syndrome), and a muscle heterotopia type.

### Gaze Palsies, Gaze Deviations, and Ophthalmoplegia

This section discusses conditions causing ophthalmoplegia (i.e., mixed vertical and horizontal ocular paresis), or gaze palsies (horizontal or vertical). Gaze palsy may reflect abnormalities of saccadic eye movements, as may result from frontal lobe or frontomesencephalic saccadic pathway damage, pursuit eye movements, as may result from occipito-parieto-mesencephalic damage, or both, as may result from damage to the brainstem gaze center. It is sometimes difficult to distinguish a horizontal gaze palsy from a unilateral oculomotor or abducens nerve paresis with a compensatory head turn. An infant or toddler with an abducens nerve palsy may appear to have a gaze palsy when he or she adopts a compensatory head position to achieve binocularity and resists any gaze shift out of the zone of binocularity. In such cases, one must place a patch on the suspected paretic eye, which leads to resolution of the head turn in ocular motor nerve paresis, but not in gaze palsy. Complete resolution of such a head turn may occasionally require several days of patching.

### Horizontal Gaze Palsy in Children

The causes of horizontal gaze palsy in children are shown in Table 7.4. Generally speaking, inability to conjugately move the eyes horizontally to one side is caused by a lesion in the contralateral frontal eye field or the ipsilateral paramedian pontine reticular formation (PPRF) or abducens nucleus.
Such a lesion may be distinguishable with reflex maneuvers (e.g., caloric stimulation, Doll’s head maneuver) that would drive the eyes into the parietic gaze if the PPRF and abducens nuclei are intact. Neuronopathic Gaucher disease with hepatosplenomegaly can be associated with isolated horizontal gaze palsy. Children with type 2 Gaucher disease may also show a “fixed” esotropia, while those with type 3 may be accompanied by head thrusts suggestive of COMA. Causes of horizontal gaze palsy that are now classified as congenital cranial dysinnervation syndromes (such as congenital horizontal gaze palsy with scoliosis) are detailed later in this chapter.

Congenital bilateral paralysis of horizontal gaze has been reported in association with facial paralysis, most likely representing a form of Möbius sequence (facial diplegia and sixth nerve palsy). It has also been described without facial paralysis. In the latter cases, the most typical findings are total absence of conjugate horizontal gaze, both volitionally and after stimulation of optokinetic and vestibular systems; preserved convergence with substitution of convergence movements for conjugate eye movements upon attempting horizontal lateral gaze; cross-fixation; and apparently normal vertical eye movements. These cases, which show overlap with the Wildervanck syndrome, have occurred either as an isolated abnormality or in association with other findings that included kyphoscoliosis, facial contracture and myokymia, and the Klippel–Feil syndrome (fusion of cervical and upper thoracic vertebrae) in one patient. The precise cause of these cases is unknown, but the underlying defect has been speculated to represent selective maldevelopment affecting either the horizontal gaze center in the PPRF or the motor neurons and interneurons in the abducens nuclei. Yee et al reviewed the evidence and concluded that a developmental anomaly affecting the abducens nucleus, but not the horizontal gaze center in the PPRF, is most consistent with the clinical findings in this syndrome. They further speculated that the involvement of the facial musculature associated with some cases may result from a similar developmental anomaly of the facial nucleus. Some cases of bilateral horizontal gaze paralysis are familial. In children with pontine gliomas, involvement of the abducens nuclei and/or the PPRF may lead to horizontal gaze palsy (Fig. 7.6).

### Table 7.4 Causes of horizontal gaze palsy in children

<table>
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<tr>
<th>Condition</th>
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<tr>
<td>Brainstem arteriovenous malformation</td>
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<td>Bilateral Duane syndrome</td>
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<tr>
<td>Congenital horizontal gaze palsy and scoliosis</td>
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<td>Congenital horizontal gaze paralysis and ear dysplasia</td>
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<td>Familial, congenital paralysis of horizontal gaze</td>
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<td>Leigh syndrome</td>
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<td>Möbius sequence</td>
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<td>Neuronopathic Gaucher disease</td>
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<tr>
<td>Pontine glioma</td>
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<td>Wildervanck syndrome</td>
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### Congenital Ocular Motor Apraxia

Apraxia (Greek: inaction) literally denotes the inability to perform volitional, purposeful motor activity despite the absence of paralysis. In the context of eye movements, the term apraxia should be limited to describe conditions in which volitional saccades are defective, but reflex and random movements are preserved (i.e., the quick phases of vestibular or optokinetic nystagmus), underscoring the presence of intact lower motor neuron pathways. This apraxic defect becomes more readily understandable by noting the presence of at least two major classes of cerebrally triggered saccades, namely, intrinsically triggered (volitional) saccades and extrinsically triggered (reflexive) saccades. Children with true saccadic apraxia show a defect in the first class of saccades, but not in the second.

COMA is characterized by the selective absence of horizontal saccades with preservation of vertical saccades. COMA was so named because it was thought to fulfill the strict definition of apraxia outlined above, namely, the reflex and random eye movements as well as the fast phases of optokinetic nystagmus are preserved. However, there is no clear evidence for a cortical etiology and it is now recognized that the quick reflexive fast phases are also defective in these patients. For these reasons, Harris et al advocate use of the term intermittent saccadic failure.

Ocular motor apraxia is divided into congenital and acquired varieties. The acquired form is usually encountered in adults, following bilateral basal ganglia or cerebral hemispheric lesions, although some acquired cases have been reported in children. For example, two children developed isolated ocular motor apraxia following cardiac surgery. In children, the idiopathic form of COMA must be differentiated from the forms seen in Gaucher disease, ataxia telangiectasia, and Leigh disease (discussed later). Acquired ocular motor apraxia seldom fulfills the strict definition of an apraxic disorder. Most acquired cases more closely reflect a global saccadic dysfunction rather than an apraxic disorder and may be better designated as horizontal saccadic palsies or gaze palsies, depending on whether or not smooth pursuit is also affected. The natural history is one of gradual resolution over several years (with persisting subclinical defects), which may reflect the normal maturation process or the development of blink-induced saccades.

A prominent feature of this syndrome is large-amplitude horizontal head thrusting to achieve visual fixation. However, head thrusting need not always be present. The quick phases of induced vestibular nystagmus and optokinetic nystagmus are intermittently or completely absent, causing the eyes to deviate and “lock up” at the mechanical limit of gaze at the end of the slow phase. The classical explanation of the head thrusts is that they are compensatory,
which explains why the head is thrust in the direction of an eccentric target, and the eyes rotate conjugately in the opposite direction under the influence of the resulting vestibulo-ocular reflex. The head excursion must then overshoot the intended target to allow the controversively rotated eyes to fixate the desired target. Once fixation is achieved, the head slowly reassumes its neutral position to allow a direct, straight gaze. The child is usually noted to blink at the onset of head thrusts.

The concept that head thrusts are always compensatory has been challenged by evidence suggesting that a thrust-saccade synkinesis is the explanation for head thrusts; in that, the thrusts may actually facilitate the initiation of saccades in a subgroup of patients. Eustace et al questioned whether, rather than being compensatory, the head thrusts in COMA may be a defect that reflects an inability to unlock or cancel the effects of the vestibulo-ocular reflex. Interestingly, some children with COMA display occasional head thrusts.
The head thrusts so characteristic of COMA appear when the baby acquires head and neck control (usually at 6 months). Therefore, although congenital, the disorder is rarely diagnosed until late infancy. At an earlier age, blindness may be suspected due to failure to follow objects. This failure to visually pursue objects is understandable given the defective saccadic system, because infants “follow” with a series of hypometric saccades. In this context, failure to pursue may be misconstrued as a visual deficit. Evaluation of the vestibuloocular response in such infants by spinning them elicits a slow but not a fast component, which helps establish the diagnosis.

Although isolated COMA is usually sporadic, familial cases have been documented. Phillips et al described COMA in four children of an affected father, indicating probable autosomal dominant transmission. COMA has been associated with a wide variety of conditions ranging from the relatively benign to the rapidly progressive neurometabolic degenerations. COMA may be congenital or acquired. It may also be idiopathic or associated with structural brain abnormalities (e.g., cerebellar hypoplasia, agenesis of the corpus callosum), neurodegenerative disorders (e.g., ataxia telangectasia, Gaucher disease), perinatal problems (e.g., hypoxia, cerebral palsy, hydrocephalus), or acquired disease (e.g., herpes encephalitis, posterior fossa tumors, ischemia) (Table 7.5). These disorders should be suspected when vertical saccades are affected or when saccades are slow.

While affected children are often judged to be otherwise healthy, most have associated deficits in other motor spheres, resulting in problems in oral-motor planning affecting speech output (speech apraxia), as well as truncal ataxia, hypotonia, developmental delay, or perceptual visual-spatial difficulties. In a recent study, 11 of 14 patients with no structural abnormality on neuroimaging showed abnormal neurodevelopment, although it has been stated that speech delay in ocular motor apraxia is expressive and due to verbal apraxia. These included delayed speech and reading, and abnormalities of language development involving both receptive (comprehension) and expressive (language) development. One mother of a 3-year-old girl stated, “Her speech has been good in terms of word acquisition, but she has an odd linking of phrases – lots of backwards phrases.” These studies indicate that COMA is the salient feature of a more generalized neurological disorder and that “isolated” cases are at risk for mild-to-moderate educational difficulties.

The association of COMA with CNS lesions has long been recognized. Neuromaging often discloses vermian hypoplasia and dilatation of the fourth ventricle at the upper brainstem level. Sargent et al found hypoplasia of the cerebellar vermis in approximately 50% of patients with COMA, with preferential involvement of the inferior portion. Additional involvement of the superior portion correlated with more severe feeding difficulties, speech apraxia, or more severe generalized motor problems. Kim et al reported COMA with spasmus nutans in a child with cerebellar vermian hypoplasia. They speculated that hypoplasia of the vermal cortex could disinhibit the caudal fastigial nucleus, leading to an abnormally increased activity in the fixation region of the superior colliculus and results in the inhibition of saccadic generation. On the other hand, Harris et al found vermian hypoplasia in only one of two siblings with COMA, suggesting that this defect may not be causative, but a marker of some other underlying pathology. Shawkat et al found abnormal scans in 61% of patients with saccadic initiation failure. Most abnormalities involved the brainstem and cerebellar vermis, although other abnormalities of the cerebral cortex and basal ganglia were also detected.

Other neuroimaging abnormalities have been reported less frequently, including porencephalic cyst, agenesis or hypoplasia of the corpus callosum, posterior fossa tumors such as medulloblastoma or lipoma, and gray matter heterotopias. Recently, a subgroup of autosomal recessive cerebellar ataxias was identified. It includes four distinct subtypes: ataxia-telangiectasia, ataxia-telangiectasia-like disorder, and ataxia with ocular motor ataxia types 1 and 2. The phenotypes share similarities, and the responsible genes ATM, MRE11, APTX, and SETX, respectively, are all implicated in DNA break repair. As in many other DNA repair deficiencies, neurodegeneration is a hallmark of these diseases. The first two conditions are detailed in Chap. 10. The third, ataxia with ocular motor apraxia type 1 (AOA type 1) is a recently described autosomal-recessive condition of childhood onset that is caused by mutations in the APTX gene, which encodes the protein aprataxin. Onset is usually 2–10 years (mean, 6.8 years), with gait and limb ataxia, dysarthria, ocular motor apraxia, mild peripheral neuropathy, and progression of neurological deficits. MR imaging may show cortical and cerebellar atrophy that is most prominent in the mid-vermis. Aprataxin mutations are associated with low coenzyme Q10 levels in muscle, which is not associated with duration, severity, or progression of the disease.

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<thead>
<tr>
<th>Table 7.5 Neurometabolic causes of congenital ocular motor apraxia (Adapted from Harris et al)</th>
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<tr>
<td>Ataxia telangiectasia</td>
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<td>Gaucher disease</td>
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<td>Joubert syndrome</td>
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<td>Krabbe disease</td>
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<td>Niemann–Pick–syndrome</td>
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<td>Cockayne syndrome</td>
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<td>Pelizaeus–Merzbacher disease</td>
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<td>Recessive ataxia with ocular apraxia</td>
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<td>Spinocerebellar ataxia type 2</td>
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Ataxia with ocular motor apraxia type 2 (AOA type 2) is an autosomal recessive disorder associated with mutations in the Senataxin (SETX) gene. The age of onset is later (11–20 years), with sensory motor neuropathy, primary ovarian failure, chorea, and ocular motor apraxia in about half of affected patients. An elevated level of serum alpha-fetoprotein is a consistent finding.

Ocular motor apraxia can also be a clinical manifestation of other well-known neurologic or systemic diseases. The association of COMA and a “molar tooth sign” should suggest the diagnosis of Joubert syndrome and Related Disorders (JRSD). First described in 1969, Joubert syndrome is characterized by the variable combination of episodic neonatal tachypnea and apnea, rhythmic protrusion of the tongue, ataxia, hypotonia, and a variable degree of psychomotor retardation. The episodic tachypnea presents in the neonatal period and alternates with periods of apnea, resembling the panting of a dog, and usually resolves or improves over time. Typical facial features include high rounded eyebrows, broad nasal bridge, anteverted nostrils, and low-set ears. The associated congenital retinal dystrophy was at first labeled as a variant of Leber congenital amaurosis but subsequently considered different because the visual loss is not as profound (20/60 to 20/200) in JRSD, compared with counting fingers or worse in Leber congenital amaurosis. In addition, the visual evoked potentials (VEPs) are relatively spared (mild-to-moderate reduction in amplitudes, compared with absent or highly attenuated signals). Both conditions show flat or highly attenuated electroretinograms (ERGs). Other ophthalmologic findings include ptosis, congenital ocular fibrosis, and colobomas. Systemic manifestations have been infrequently reported, including meningoencephalocele, microcephaly, polydactyly, kidney abnormalities, soft tissue tumors of the tongue, liver disease, and duodenal atresia.

Ocular motor disorders described in JSRD include slow, hypometric saccades, ocular motor apraxia, strabismus, periodic alternating gaze deviation, pendular torsional nystagmus, seesaw nystagmus, skew deviation, and defective smooth pursuit, as well as optokinetic and vestibular responses. The ocular motor apraxia in JRSD differs from COMA in that both volitional saccades and quick phases of nystagmus are impaired in both the horizontal and vertical directions, and the problem does not resolve with time. The most common ocular motor abnormalities are saccadic dysfunction with head thrusts and primary position nystagmus (typically, seesaw nystagmus). Joubert syndrome is characterized by hypoplasia of the cerebellar vermis and a particular midbrain–hindbrain “molar tooth” sign, a finding shared by a group of Joubert syndrome-related disorders with a wide phenotypic variability. The molar tooth sign is a complex malformation of the hindbrain–midbrain (brainstem isthmus) characterized by cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa. As first described by Maria, axial MR imaging at the pontomesencephalic level has shown that this malformation produces a peculiar appearance resembling a molar tooth (Fig. 7.7). The pathological findings include vermian hypoplasia or dysplasia, elongation of the caudal midbrain tegmentum, and marked dysplasia of the caudal medulla.

The molar tooth sign (and the absence of associated hydrocephalus) distinguishes Joubert syndrome from the vermian agenesis that occurs with the Dandy–Walker variant, but 10% of patients with a Dandy–Walker-like cyst have the molar tooth sign and are clinically similar to classic Joubert syndrome patients. Such patients were referred to as “Dandy–Walker Plus” by Maria et al. Importantly, the molar tooth sign is not seen in isolated vermian hypoplasia because the cerebellar peduncles and interpeduncular fossa can be normal in several vermian hypoplasia syndromes. The deep interpeduncular fossa and decreased anteroposterior diameter of the brainstem isthmus in the molar tooth sign can best be explained by nondecussation of the ascending superior cerebellar peduncles. The coincident finding of asymmetrical VEPs in some patients with seesaw nystagmus suggests failure of chiasmal decussation. This finding, together with the absence of decussation in both the superior cerebellar peduncles and the corticospinal tracts at the medullary pyramids,
suggests that patients with Joubert syndrome have a defect of axon guidance in the motor circuits.\textsuperscript{265,432,626,715}

Although the molar tooth sign is still considered essential to the diagnosis of Joubert syndrome, there are a number of Joubert syndrome-related disorders such as COACH, Arima, Debakan, and Senior-Løken that are much more rare and which may also show a molar tooth sign on MR imaging. In these conditions, there are numerous other abnormalities in addition to the neurological features of the Joubert syndrome; involvement of other organs such as eye, kidney, and liver, have been described.\textsuperscript{673,675} The Arima syndrome exhibits pigmentary degeneration suggestive of Leber congenital amaurosis, severe psychomotor retardation, hypotonia, characteristic facies, polycystic kidneys, and absent cerebellar vermis. Joubert and Arima syndromes may be distinguished by such clinical features as neonatal tachypnea, which is one of the cardinal features of Joubert syndrome.

The identification of mutations in seven different cilium genes in up to 20% of patients with Joubert syndrome suggests that a certain percentage of Joubert syndrome is a celiopathy that can affect various organ systems, including the connecting cilium of photoreceptors.\textsuperscript{432,609} Although patients with the NPHP1 deletion often have juvenile nephronophthisis and rarely have retinal dystrophy, patients with AHI1 mutations seem less likely to develop retinal dystrophy.\textsuperscript{609,767} Mutations in the AHI1 gene can also be associated with other CNS malformations (in non-Joubert patients) such as corpus callosal abnormalities, polymicrogyria, hydrocephalus, and encephalomingocele.\textsuperscript{292} Patients with the CEP290 mutation seem to have both nephronophthisis and retinal dystrophy.\textsuperscript{81,679,772} Other phenotypes have included nonspecific renal cortical cysts, ocular colobomas, and encephalocoeles.\textsuperscript{91,432,679,772}

Joubert syndrome may be sporadic or familial, with familial cases inherited in an autosomal recessive pattern. Recent genetic analyses have suggested at least three loci, JBTS1 (9q34.3), JBTS2 (11.2-q12.3), and JBTS3 (6q23).\textsuperscript{770} Only the JBTS3 gene, AHI1, encoding Jouberin, has been cloned. JBTS1 and 3 primarily show features restricted to the CNS, with JBTS1 showing largely pure cerebellar and midbrain–hindbrain junction involvement, and JBTS3 displaying cerebellar, midbrain–hindbrain junction, and cerebral cortical features, most notably polymicrogyria. Conversely, JBTS2 is associated with multiorgan involvement of kidney, retina, and liver, in addition to the CNS features, and results in extreme phenotypic variability.\textsuperscript{771}

Occasionally, COMA is one of the manifestations of a degenerative disorder such as ataxia telangiectasia.\textsuperscript{55,727} Some children with ataxia telangiectasia may pose a diagnostic quandary by showing no overt immune dysfunction, inconspicuous oculocutaneous telangiectasia, and an atypical neurological presentation with dystonia predominating over cerebellar ataxia.\textsuperscript{166} Vertical saccades are usually involved to some degree when COMA is associated with systemic disease. Although ataxia telangiectasia is said to be associated with slow saccades, eye movement recordings in patients with ataxia telangiectasia have showed saccadic velocities to be faster than normal, but followed by slow eye movements that were not clearly saccadic in origin.\textsuperscript{792}

A syndrome mimicking ataxia telangiectasia with slowly progressive ataxia, choreoathetosis, and ocular motor apraxia in the horizontal and vertical plane has been described.\textsuperscript{712} Although the neurological findings are indistinguishable from those of ataxia telangiectasia, the onset tends to be later and patients have not shown evidence of multisystem involvement. Ocular motor apraxia is often found in patients with Gaucher disease,\textsuperscript{253} a lysosomal storage disorder, and may even be the presenting feature of the disease.\textsuperscript{716} Other children with Gaucher disease show a supranuclear horizontal gaze palsy.\textsuperscript{851}

In most patients with COMA, the ability to generate saccades improves over the first decade, with better eye movements and less noticeable head thrusts.\textsuperscript{777} This spontaneous improvement led Cogan to favor a delayed maturation of the ocular motor pathways rather than congenitally absent initiation pathway for horizontal saccades as the underlying cause. While the ocular motor abnormalities tend to improve with age, most affected children show some degree of delayed motor, speech, or cognitive development.\textsuperscript{726} Notwithstanding the benign course in most cases, it is advisable to obtain MR imaging to rule out intracranial pathology (tumor, congenital structural malformations), the occurrence of which has been well documented in a minority of children. Treatment of underlying pathology may ameliorate or cure the apraxia in some cases,\textsuperscript{833} but not in all.\textsuperscript{731} For instance, Zaret et al\textsuperscript{833} described a case of COMA that showed rapid improvement after surgical evacuation of a large cystic tumor in the rostral brainstem, while complete resection of a posterior fossa lipoma in a 10-month-old girl had no effect on the apraxia.

Although typical COMA involves a bilateral palsy of volitional horizontal saccades and unilateral cases,\textsuperscript{146,634} cases involving only vertical saccades have been described.\textsuperscript{953,645}

### Vertical Gaze Palsies in Children

Vertical gaze disturbances are generally less common than horizontal ones and, among vertical disorders, upgaze palsy and combined upgaze and downgaze paralysis are more common than downgaze palsies (Fig. 7.8). Most vertical gaze palsies are supranuclear and conjugate (i.e., upgaze palsy, downgaze palsy, and vertical gaze palsy). Supranuclear disconjugate vertical gaze syndromes are rare, and their topographic correlation is less precisely determined. They include skew deviation and variants (e.g., slowly alternating skew deviation), seesaw nystagmus, monocular upgaze palsy,
ocular tilt reaction, vertical one-and-a-half syndrome, and V-pattern pseudobobbing. Some of these disorders are not only location-specific, but also point to a specific mechanism of injury (e.g., acute downgaze palsy suggests bilateral infarction of the posterior thalamo-subthalamic paramedian territory). Occasionally, cases involving complete vertical ophthalmoplegia are described that remain unexplained despite thorough evaluation. Nightingale and Barton\(^5\) described a 6-year-old girl who had episodes of severe ataxia and vertical supranuclear ophthalmoplegia. Horizontal eye movements were not affected, and the patient was normal in between attacks.

Congenital vertical ocular motor apraxia may occur as a benign nonprogressive condition similar to the horizontal variety or may signal the presence of intracranial tumors, especially if other neurological signs are present.\(^2\)\(^3\)\(^1\) Ebner reported a case of purely vertical ocular motor apraxia in a 4-year-old boy whose MR imaging demonstrated bilateral subthalamic lesions.\(^2\)\(^3\)\(^1\) Rare cases of isolated vertical COMA have also been associated with birth asphyxia.\(^2\)\(^7\)\(^8\)\(^3\)\(^6\)\(^4\)\(^5\) The association of this disorder with perinatal hypoxic encephalopathy implicates injury to the frontal eye fields and posterior parietal cortex or their descending projections through the internal capsule and basal ganglia to the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).

### Downgaze Palsy in Children

Isolated downgaze palsy usually results from a bilateral lesion (usually infarction) involving the midbrain reticular formation and affecting the lateral parts of the riMLF bilaterally.
In general, an acquired isolated downgaze paralysis requires bilateral lesions at the level of the upper midbrain tegmentum, while a unilateral lesion may be sufficient to produce an upgaze palsy or a combined upgaze and downgaze palsy. Green et al. reported a 9-year-old girl with selective downgaze paralysis following pneumococcal meningitis. MR imaging showed bilateral lesions in the riMLF. In the setting of a bilateral midbrain lesion, the examiner can often use horizontal eye movements to assess which side of the midbrain is more severely affected. If the right side of the midbrain is more severely affected, the patient will have a saccadic deficit to the left and a pursuit deficit to the right, because saccadic innervation from the hemispheres is crossed and pursuit innervation is uncrossed.

In adults, downgaze paresis is most commonly an early sign of progressive supranuclear palsy. Kumagai et al. described a patient with selective downgaze paresis who had a pineal germinoma with bilateral involvement of the thalamo-mesencephalic junction. Rhythmic vergence eye movements (alternating convergence and divergence) were observed at a rate of 3 Hz during eyelid closure.

Downgaze palsy in children is a well-known feature of DAF (downgaze palsy, ataxia or athetosis, and foam cells in the bone marrow) syndrome, a neurovisceral storage disease considered to be a variant of Niemann–Pick disease type C. It is characterized by supranuclear gaze palsy in the vertical plane (typically downgaze palsy), hepatosplenomegaly, slowly progressive ataxia, mental deterioration, and other CNS disorders. Foamy cells or sea-blue histiocytes in the bone marrow as well as accumulation of sphingomyelin, cholesterol, and other glycosphingolipids are characteristic histopathologic findings. The acronym DAF was coined by Cogan to denote this triad of findings. Rarely, patients show predominantly horizontal supranuclear gaze palsy. An autosomal recessive inheritance pattern is suspected.

The age of onset of neurologic symptoms is between 5 and 15 years. In addition to abnormalities indicated by the acronym, affected patients have hepatosplenomegaly, dementia, and widespread CNS dysfunction. Other neurological symptoms and signs include poor coordination, slurred speech, dysphagia, seizures, cerebellar dysfunction, hyperreflexia, and involuntary movements (dystonia, chorea, or athetosis). The DAF variant of Niemann–Pick disease should be suspected when evaluating school-aged children who have suffered a recent decline in intelligence or school performance and who show progressive neurologic disease and vertical supranuclear ophthalmoplegia.

An acquired condition of bilateral downgaze palsy with monocular elevation palsy, termed the vertical one-and-one-half syndrome, has been reported in a patient with bilateral infarction in the mesodiencephalic region. The authors speculated that the lesions may have affected the efferent fibers of the riMLF bilaterally and the supranuclear fibers to the contralateral superior rectus subnucleus and ipsilateral inferior oblique subnucleus. This disorder should be distinguished from a different condition, also termed a one-and-one-half syndrome, consisting of bilateral upgaze palsy and monocular depression deficit due to thalamosencephalic infarction ipsilateral to the downgaze paresis.

### Upgaze Palsy in Children

The most common causes of upgaze palsy in children include hydrocephalus (congenital and acquired) and various conditions associated with the dorsal midbrain syndrome, such as a tumor in the pineal region, arteriovenous malformations, encephalitis, and third ventricular tumors. Midbrain infarction, multiple sclerosis, and syphilis are rare causes in children. The eye signs of hydrocephalus are detailed in the chapter on neuro-ophthalmologic signs of intracranial disease. Ocular motility disorders reported in hydrocephalus are listed in Table 7.6.

Upgaze paresis is the hallmark of the dorsal midbrain syndrome. Mild cases involve only upward saccades, but severe cases show paralysis of all upward movements. Attempts to produce upward saccades, best elicited by fixating a downward rotating optokinetic nystagmus drum, evoke convergence-retraction nystagmus. The pupils are usually mid-dilated and show light-near dissociation. The upper eyelid shows pathologic lid retraction (Collier’s sign) and lid lag, due to disruption of inhibitory fibers from the posterior commissure to the central caudal nucleus. The setting sun sign is unique to children and is suggestive of congenital hydrocephalus. It is not clear why a similar sign is not seen in adults with acquired hydrocephalus. The setting sun sign may be thought of as a combination of Collier’s sign and tonic downgaze, which has been reported in some children with hydrocephalus, with or without associated intraventricular hemorrhage.

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<thead>
<tr>
<th>Table 7.6</th>
<th>Ocular motility disorders in hydrocephalus</th>
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<tr>
<td>A-pattern esotropia with superior oblique muscle overaction</td>
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<tr>
<td>Convergence insufficiency</td>
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<td>Convergence-retraction nystagmus</td>
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<td>Convergence spasm</td>
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<td>Fixation instability</td>
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<td>Lid retraction</td>
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<td>Mydriasis with light-near dissociation</td>
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<tr>
<td>Pseudo-abducens palsy</td>
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<td>Setting sun sign (in infants)</td>
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<td>Skew deviation</td>
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<td>Superior oblique palsy (unilateral or bilateral)</td>
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<tr>
<td>Upgaze paralysis (affecting saccades more than pursuit)</td>
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<tr>
<td>V-pattern pseudobobbing (with shunt failure)</td>
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The upgaze palsy of congenital hydrocephalus usually improves dramatically and quickly after shunt placement. Incomplete, delayed improvement over months to years suggests damage to the upgaze pathway either as a result of thalamic hemorrhage and infarction or by the hydrocephalus itself.\(^{735}\)

Children with severe, congenital visual loss may have difficulty moving their eyes volitionally. In this context, upward gaze is the most severely affected.\(^{393}\) Jan et al\(^{393}\) theorized that a selective upgaze deficit exists because children with marked visual impairment rarely look up, because they see much more with their limited vision when viewing closer objects sideways or downward.

Isolated paralysis of upgaze may be the presenting sign of the Miller Fisher syndrome.\(^{423}\) It may also result from vitamin B\(_1\) or B\(_{12}\) deficiency.\(^{671}\) Isolated bilateral elevation deficiency may be due to congenital restriction of the inferior rectus muscles in the congenital fibrosis syndrome.\(^{259}\) Diagnostic confusion arises because congenital fibrosis syndrome can produce convergent movements of the eyes in attempted upgaze, which simulates convergence retraction nystagmus. The distinguishing clinical feature is that patients with congenital fibrosis syndrome display ptosis rather than lid retraction. As discussed below, these restrictive phenomena can also be differentiated from the dorsal midbrain syndrome by the positive family history, positive forced ductions, and the finding of hypoplasia of the intracranial nerves and extraocular muscles in the congenital fibrosis syndrome, but not in dorsal midbrain syndrome.

In adult patients, upgaze palsy is usually less disabling than downgaze palsy, because the superior visual space is comparatively less important. This is in contrast to downgaze palsies, which cause significant visual deficits due to the importance of downgaze for such tasks as reading, walking, and eating. However, the visual significance of upgaze palsy is much more profound in children who, by virtue of their short stature, spend a considerable amount of their time looking up.

**Table 7.7** Diffuse ophthalmoplegia in children

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<th>Disorder</th>
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<tr>
<td>Bickerstaff brainstem encephalitis</td>
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<td>Botulism</td>
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<td>Chronic progressive external ophthalmoplegia</td>
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<td>Intrinsic brain stem tumors</td>
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<td>Kearns–Sayre syndrome</td>
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<td>Maple syrup urine disease</td>
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<tr>
<td>Medications (e.g., toxic doses of phenytoin, amitriptyline)</td>
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<tr>
<td>Miller Fisher syndrome</td>
</tr>
<tr>
<td>Mitochondrial encephalopathy (CPEO, MELAS, MERRF, MNGIE, MDS, Pearson syndrome)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Olivopontocerebellar degeneration</td>
</tr>
<tr>
<td>Tick fever</td>
</tr>
<tr>
<td>Toxicity of chemotherapeutic agents (e.g., vincristine)</td>
</tr>
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**Chronic Progressive External Ophthalmoplegia**

Chronic progressive external ophthalmoplegia (CPEO) is an umbrella term that includes a number of diverse conditions having in common insidious onset of slowly progressive, typically symmetric, multidirectional external ophthalmoplegia. The various conditions encompassing CPEO range from disorders limited to the eyelids and extraocular muscles to ones that include systemic and encephalopathic features. Extraocular muscles have smaller motor unit sizes, higher motor neuron discharge rates, higher blood flow, and higher mitochondrial volume fractions than skeletal muscles.\(^{688}\) These differences suggest that the energy demands and therefore the susceptibility to mitochondrial dysfunction are greater in extraocular muscle.

Because of the often gradual and symmetric involvement of the extraocular muscles, patients with CPEO generally do not experience diplopia.\(^{59,614,639,713}\) Ptosis and ophthalmoplegia generally occur together, but each can occur alone, and the ptosis can be asymmetrical. When strabismus does occur, the most common deviation is exotropia, with or without a vertical deviation.\(^{639,700}\) Confirmation of the diagnosis usually requires fresh muscle biopsy for histopathological examination (using cytochrome oxidase stain with electron microscopy to look for “parking lot” inclusions) and Southern blot analysis to look for deletions. Polymerase chain reaction (PCR) has recently been used to detect the mutation in swabbed buccal cells.\(^{386}\)

Mitochondrial encephalopathy is divided into several clinical phenotypes, including Kearns–Sayre syndrome; the
syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS); mitochondrial neurointellectual encephalopathy (MNGIE); and the syndrome of myoclonus, epilepsy, and ragged red fibers (MERRF).688 The later syndrome is not generally associated with external ophthalmoplegia.

Kearns–Sayre syndrome is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and heart block. Most cases are sporadic. The onset of the disorder occurs before age 20. Affected patients have short stature, other neurologic disorders, and an elevated protein concentration (>100 mg/dL) in the cerebrospinal fluid (CSF). Other findings may include hearing loss, cerebellar signs, mental retardation, delayed puberty, vestibular abnormalities, and “ragged red fibers” on muscle biopsy.688 mental deterioration, pyramidal signs, and diabetes.59,212,424,472,705,838 In addition to complete heart block, cardiac conduction abnormalities include bundle branch block, bifascicular disease, and intraventricular conduction defects and are thought to result from an associated cardiomyopathy. The heart block generally occurs years after onset of the ocular signs and may cause sudden death. The retinal pigmentary degeneration progresses slowly and may be too subtle early on to detect ophthalmoscopically. The associated ptosis may become visually significant, but surgical correction should be approached with caution because the limited eye movements and the absence of Bell’s phenomenon render patients prone to exposure keratopathy.

Orbital neuroimaging is probably of little value in CPEO. One study found marked atrophy of the extraocular muscles,608 while another showed little or no reduction in extraocular muscle volume.601 Furthermore, myasthenia gravis may also show atrophic extraocular muscles late in the course of the disease, making it difficult to distinguish from CPEO.605 It has been suggested that the myopathic process that results in chronic progressive external ophthalmoplegia renders rectus muscle recessions less effective than resections for correcting the associated strabismus that occasionally develops in these patients.607,715 Postoperative prisms are occasionally necessary to fine-tune single binocular vision.791

CPEO may be sporadic, show Mendelian inheritance, or show maternal inheritance.386 Almost half of CPEO cases are sporadic and associated with single deletions of mtDNA.74,314,315,476,676 In sporadic cases of CPEO and Kearns–Sayre syndrome, all the mutant mtDNAs in an individual have the same deletion. Because Kearns–Sayre syndrome is an artificial construct of the most severe cases of the CPEO syndromes, it is always more likely to have deletions (90%) than CPEO in general, and it is more likely to be sporadic. However, some members of severe autosomal dominant CPEO pedigrees have had a high deletion load express the full-blown Kearns–Sayre syndrome phenotype, while other family members do not.74

Autosomal dominant or recessive inheritance is noted in about 15% of patients with CPEO. Autosomal dominant inheritance is characterized by accumulation of multiple deletions of mtDNA in the patient’s tissues. Most single deletions are not inherited, but occur spontaneously after fertilization of the oocyte. Individuals with multiple different deletions likely come from pedigrees in which there is a nuclear mutation in a gene encoding a protein that regulates mitochondrial DNA replication and therefore is inherited mendelially (usually autosomal dominant or autosomal recessive).59,74,315,838 No clinical difference between hereditary and sporadic CPEO can be demonstrated.59,838 Many patients without structural abnormalities of mitochondrial DNA have point mutations at many different nucleotide positions, which are inherited maternally.386 Point mutations causing CPEO are often homoplasmic. Large-scale deletions resulting in CPEO are almost always heteroplasmic; the more tissue with the deletions (i.e., the greater the degree of heteroplasm), the more likely the phenotype will be severe (i.e., more toward Kearns–Sayre syndrome phenotype rather than the simple CPEO phenotype).607,783 While mitochondrial disorders that have both dominant and recessive modes of inheritance are usually caused by mutations at different loci, both can be caused by mutations in the polymerase gamma (POLG) gene.184,267a

The risk of developing a severe phenotype (i.e., additional CNS symptoms with neurological manifestations) is higher when the age of onset is before age 9 and lower when the onset is after age 20.47 While mitochondrial disorders associated with ophthalmoplegia tend to affect adults, early symptoms are often experienced in childhood. MELAS is the mitochondrial disease that is most consistently associated with retrochiasmal visual loss. MELAS is characterized by recurrent abrupt attacks of headache, vomiting, focal and generalized seizures, and focal neurologic symptoms and signs lasting hours to days.78 There is a posterior cerebral predilection for damage, and visual disturbances have been reported in more than half of patients. It is not uncommon for patients with MELAS to have CPEO, pigmentary retinopathy, optic atrophy, or homonymous hemianopia. Patients may present with stroke-like episodes, seizures, headaches, progressive dementia, and exercise intolerance.530 Classically, the brain MRI of patients with MELAS demonstrates lesions that may mimic ischemia, except that they usually do not respect vascular territories and are often restricted to the cortex with relative sparing of deep white matter.366 However, lesions spanning both gray and white matter have been reported.534

The diagnosis of MELAS is established made from the characteristic neuroimaging findings, elevated lactate acid levels, ragged red fibers on muscle biopsy, or genetic sequencing. MELAS is often maternally inherited, with 80% of patients harboring the A3243G transition within the mitochondrial genome, although many other mutations have also been reported.562 Patients with MERRF syndrome present with combinations of myoclonic epilepsy, ataxia, spasticity, generalized seizures, optic atrophy, and/or dementia.315 They may
also have muscle weakness, myopathy, neuropathy, ophthalmoplegia, ptosis, headache, foot deformity, cervical lipoma, or sensorineural hearing loss. Myoclonus is usually the presenting symptom and is often precipitated by noise, photic stimulation, or action. Myopathy is generally subclinical or mild.

Biochemical aberrations may include elevations of serum pyruvate, or pyruvate and lactate, and reduced activities of complexes I and IV. The most common mutation, accounting for 80% of MERRF cases, is at np 8344 within the tRNA. Other mutations in the same tRNA gene, t8356C and G8363C, are also found in association with this phenotype.

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) syndrome is an autosomal recessive syndrome characterized by chronic progressive external ophthalmoplegia intestinal hypomotility, and neuropathy. Clinical presentation is usually in childhood, although gastrointestinal symptoms may be problematic long before other features of the disease appear. Some patients have diabetes mellitus, heart block, or cardiomyopathy. Long-term prognosis is poor, with most patients dying in early-to-mid adulthood from weight loss and other gastrointestinal complications. MR imaging may show an unsuspected leukoencephalopathy of the brain.

Most patients have mutations in the nuclear-encoded thymidine phosphorylase gene.

In the child with progressive external ophthalmoplegia, a history of marrow failure with transfusion-dependent sideroblastic anemia, and exocrine pancreatic dysfunction causing malabsorption or diarrhea should raise suspicion for the Pearson syndrome. This disorder is characterized by a progressive pigmentary retinopathy that initially spares the posterior pole. Older patients may develop symptoms of Kearn Sayre syndrome. It is caused by deletions in mitochondrial DNA.

Myasthenia Gravis

Myasthenia gravis was the first recognized autoimmune neurologic disease. Myasthenia gravis is a disorder of neuromuscular transmission characterized by fatigability and fluctuating muscular weakness, with a predilection for the extraocular muscles. In severe cases, acute respiratory failure and death may occur. About half of all patients with myasthenia present with ophthalmologic symptoms. These include ptosis, strabismus, and limited ocular ductions, all with a tendency to be highly variable. No pupillary involvement is clinically discerned in myasthenia, and the presence of pupillary signs effectively excludes the diagnosis.

Myasthenia gravis has a well-known predilection for extraocular muscle involvement. Factors that may predispose the extraocular muscles to preferential involvement in myasthenia gravis include their higher discharge rates, differences in complement inhibitor proteins, and lack of action potentials in the tonic fibers. The more constant activity also makes the orbital extraocular muscle fibers more susceptible to fatigue. It has also been suggested that antibodies directed against the fetal form of the acetylcholine receptor, which may be found at synapses on extraocular but not skeletal muscles, may be an important factor that predisposes the extraocular muscles to involvement by myasthenia. Nearly 90% of patients with myasthenia develop ocular involvement at some point during their illness. Most patients with ocular myasthenia who develop systemic symptoms and signs do so within 2 years of onset.

Three distinct myasthenic syndromes may be encountered in the pediatric age group: transient neonatal, congenital, and juvenile. This classification is not based on age at presentation but on pathophysiology. Both congenital myasthenia and juvenile myasthenia may present any time between infancy and adulthood, but are distinguished primarily by the fact that congenital myasthenia is not immune-mediated. However, this distinguishing feature is not absolute because juvenile- and adult-onset myasthenia may also be antibody-negative. Also, the defect in acquired myasthenia is postsynaptic, while the defect in congenital myasthenia may be either at the presynaptic or postsynaptic level.

Transient Neonatal Myasthenia

Transient neonatal myasthenia gravis is due to transfer of antibody from the mother, tends to spare eye movements. Approximately 12% of newborn infants of myasthenic mothers develop transient myasthenic symptoms, presumably due to passive transplacental transfer of anti-AChR IgGs. Serum AChR antibody titers of affected neonates follow the same pattern as their mothers. Neonatal disease does not appear to correlate with the severity of maternal symptoms; affected mothers commonly have active myasthenia, but they may be in remission or, rarely, have undiagnosed subclinical disease. The onset of transient neonatal myasthenia occurs within a few hours after birth in two-thirds of patients, and within the first 3 days in all of them. Affected infants present with temporary skeletal muscle weakness producing hypotonia, a feeble cry, difficulty sucking and swallowing, facial diparesis, and mild respiratory distress. Occasionally, they may suffer respiratory depression that requires mechanical ventilation. Transient neonatal myasthenia tends to spare eye movements. Ocular involvement, including ptosis, limited eye movements, and orbicularis weakness, affects 15% of infants.

An atypical, more severe form of transient neonatal myasthenia includes the above-mentioned manifestations in addition to multiple joint contractures and occasional prenatal difficulties such as polyhydramnios or decreased fetal movement. Unlike the typical variety, response to oral or parenteral
anticholinesterase agents is poor. Severe cases may rarely require assisted mechanical ventilation for up to 1 year.

The pathogenesis of the disorder is increasingly understood. It is controversial and uncertain whether the maternal and neonatal antibodies are similar and passively transferred, or different, with the neonate synthesizing their own antibodies, or whether both mechanisms are in play. Transient neonatal myasthenia is not fully explained by passive transplacental IgG transfer because these antibodies are also found in the serum of many newborns who are asymptomatic. Other infants are symptomatic without detectable antibodies in their maternal serum. Also, high IgG levels have been found in a few asymptomatic infants. There is now a report of transient neonatal myasthenia in an infant with anti-MuSK antibodies.

Clinical symptoms usually last 2 or 3 weeks, but may resolve in 1 week or linger on for 2 months before complete recovery. Response to oral (e.g., pyridostigmine bromide) or parenteral anticholinesterase agents is very good, and these agents should be administered until spontaneous resolution occurs. No permanent neuromuscular sequelae are detectable after resolution. If this condition is not recognized and promptly treated, some affected infants may deteriorate from respiratory depression to respiratory arrest and death.

The characteristic clinical features and the history of maternal myasthenia should be enough to confirm the diagnosis, but the diagnosis may be delayed if the mother’s disease has not been previously detected. Further verification of the diagnosis may be derived from a favorable response to neostigmine methylsulfate, with improvement of symptoms 10–15 min after intramuscular injection of 0.15 mg/kg of body weight. Alternatively, intramuscular edrophonium chloride (Tensilon) may be administered intramuscularly or subcutaneously (0.15 mg/kg) or intravenously (0.10 mg/kg).

Sufficient differences exist between transient neonatal myasthenia and the congenital myasthenic syndromes (see below) to render diagnostic confusion rare. Congenital myasthenia does not occur in infants born to mothers with acquired myasthenia. The other condition affecting neuromuscular transmission in this age group, infant botulism, is readily ruled out because it occurs after the second week of life, 5 days after the infant ingests food contaminated with *Clostridium botulinum*, whereas the onset of transient neonatal myasthenia is within the first 3 days of life only.

**Congenital Myasthenic Syndromes**

Congenital myasthenia constitutes a heterogeneous group of genetic disorders affecting neuromuscular transmission that presents in the first year of life, producing mainly ptosis, and usually has a benign course. Although rare, congenital myasthenic syndromes are an important cause of seronegative myasthenia gravis. Congenital myasthenic syndromes occur in infants born to nonmyasthenic mothers and that are associated with hypotonia and weakness. Congenital myasthenic syndromes should be suspected in patients with seronegative myasthenia gravis, in infants with hypotonia and poor development of motor milestones, and in patients with a childhood history of neuromuscular difficulties affecting cranial, respiratory, truncal, or limb muscles. In some patients, however, symptoms may not appear until later childhood or even adulthood. Forty-two percent of the cases present before the age of 2 years, and over 60% before 20 years. In contradistinction to juvenile and adult-onset myasthenia, which have an autoimmune basis and are attributable to antibodies that bind to the acetylcholine receptor and cause increased turnover and destruction of the receptor, congenital myasthenia is not immune-mediated.

The congenital myasthenia syndromes are caused by structural or functional alterations at the myoneural junction. Most cases present in the neonatal period or shortly thereafter with poor feeding, failure to thrive, and weakness. Three congenital myasthenia syndromes (slow-channel syndrome, prolonged channel open time syndrome, and limb girdle myasthenia) may present later in childhood or adolescence and represent a specific, rare group of potential differential diagnoses. A distinction between congenital and acquired myasthenia cannot be made with certainty on the basis of the age of onset because both types may manifest during the neonatal period, infancy, or childhood, and acquired myasthenia may also be antibody-negative. Congenital myasthenia is usually characterized by ocular musculature with ophthalmoparesis, orbicularis weakness, and ptosis.

We described a unique child who had a congenital oculomotor nerve palsy with aberrant regeneration and fatigable ptosis associated with congenital myasthenia gravis. During periods of levator fatigability, gaze activation of the ipsilateral superior or medial rectus muscles produced instantaneous levator retraction with no fatigability (Fig. 7.9). The ability of this child’s synkinetic neuromuscular connections to override her myasthenia suggested that there was selective sensitivity of the myasthenic levator muscle to the misdirected oculomotor axons, which presumably provided fresh synaptic reserve of acetylcholine to their target fibers.

Congenital myasthenic syndromes can arise from presynaptic, synaptic, or postsynaptic defects. The major syndromes in which the defect is presynaptic are related to defects in ACh synthesis, mobilization, or release. Presynaptic congenital myasthenic syndromes were previously called “familial infantile myasthenia.” Postsynaptic syndromes are mainly caused by endplate acetylcholinesterase deficiency and ACh receptor kinetics, including the fast- and slow-channel syndromes. The array of disorders and involved genes identified has increased significantly. While genes have been identified for many
forms of congenital myasthenic syndromes, mutation analysis is not yet available on a commercial basis.\textsuperscript{60,239,240} Some cases may be familial, with other siblings affected, supporting a genetic basis for the disorder.\textsuperscript{733}

Most commonly, congenital myasthenic syndromes are caused by mutations that reduce the expression or alter the kinetics of the acetylcholine receptor.\textsuperscript{245} Reduced receptor expression is also caused by mutations in \textit{rapsyn}, a molecule that is produced by muscle and is important for acetylcholine receptor aggregation on the postsynaptic membrane.\textsuperscript{245}

The second most common congenital myasthenic syndrome is caused by mutations of the acetylcholinesterase molecule.\textsuperscript{242} Mutations of choline acetyltransferase, the rate-limiting enzyme in the synthesis of acetylcholine, cause the congenital myasthenic syndrome associated with episodic apnea (previously known as “familial infantile myasthenia”).\textsuperscript{591} Recently, a unique congenital myasthenic syndrome caused by mutations of a perijunctional skeletal muscle sodium channel has been discovered.\textsuperscript{521}

Congenital myasthenia is not immune-mediated, in contradistinction to juvenile- and adult-onset acquired myasthenia, which have an autoimmune basis and are attributed to antibodies that bind to the acetylcholine receptor and cause increased turnover and destruction of the receptor.\textsuperscript{28} Serum antiacetylcholine receptor antibodies and other autoantibodies are absent. Congenital myasthenia is not associated with any autoimmune
Table 7.8 Classification of congenital myasthenic syndromes (based on 271 index cases evaluated at Mayo Clinic)

**Presynaptic defects (7%)**
- Choline acetyltransferase (ChAT) deficiency
- Paucity of synaptic vesicles
- Congenital Lambert–Eaton-like syndrome
- Other unclassified presynaptic defects

**Synaptic defect (basal lamina) (14%)**
- Endplate AChE deficiency

**Postsynaptic defects (79%)**
- Reduced AChR expression (with or without minor AChR kinetic abnormality)
  - AChR mutations (isolated or with plectin deficiency)
    - Rapsyn mutations
    - MuSK mutations
    - DOK-7 mutations (formerly “Limb-Girdle” myasthenia)
  - AChR kinetic abnormality (some with mild reduced AChR expression)
    - Slow-channel syndrome
    - Fast-channel syndrome
- Sodium channel mutations

*AChE* acetylcholinesterase; *AChR* acetylcholine receptor; *ChAT* choline acetyltransferase; *MuSK* muscle specific kinase

Disease or any particular human leukocyte antigen genotype, and cytohistochemical studies fail to reveal immune complexes at the myoneural junction. The condition is generally nonremitting. Once thought to be a single disorder, it is now known to represent a group of diverse disorders distinguishable by the specific site of dysfunction at the myoneural junction (Table 7.8). Multiple inherited defects of neuromuscular transmission at presynaptic or postsynaptic levels are known, but some defects have not yet been characterized. The putative inheritance of most of these defects is autosomal recessive, with the exception of the slow-channel syndrome, which is autosomal dominant.

The precise characterization of these defects requires the combined use of clinical, electromyographic, in vitro electrophysiological, and morphological data. It is probably impractical to perform all tests needed for accurate characterization of the myoneural defect on each infant suspected with the diagnosis, especially when the infant is ill. However, determination of the specific subtype of congenital myasthenia would be helpful for therapeutic purposes and would enhance our understanding of the heretofore incompletely understood disorders that constitute congenital myasthenia. Certainly, a detailed history should be obtained on each child regarding the onset and severity of feeding difficulty, breathing dysfunction, choking episodes, drooling, facial weakness, ophthalmoparesis, ptosis, hypotonia, and muscular fatiguability. This would start the process of differentiation between the different syndromes involved. For example, a syndrome characterized by defective AChR shows neonatal respiratory difficulty, feeding difficulty, and ophthalmoparesis, while a syndrome characterized by impaired ACh release shows few, if any, of these features.

The developmental milestones, progression or regression of symptoms and signs during infancy and childhood, response to any therapeutic modalities, and a complete family pedigree should be recorded. In some congenital myasthenia syndromes, a specific diagnosis can be made by simple histological or EMG studies while, in others, a complex panel of in vitro electrophysiological, ultrastructural, and immunocytochemical investigations are needed for accurate diagnosis.244

Because the congenital myasthenic syndromes are not immune-mediated, neither plasmapheresis nor immunosuppression has any beneficial effect. Thymectomy usually produces negligible benefits, although a transient improvement has been reported in two patients, one of whom had an abnormal thymus.170,803 Because of the diversity of the underlying abnormalities, no specific conclusion can be drawn regarding the efficacy of the anticholinesterase preparations. Some types of congenital myasthenia (e.g., congenital acetylcholine receptor deficiency) respond favorably to anticholinesterase preparations, while other types (e.g., acetylcholinesterase deficiency, slow-channel syndrome) are refractory to such treatment and may even be made worse by it. Therefore, an effort to differentiate juvenile myasthenia from congenital myasthenia and to specifically identify the type of congenital myasthenic syndrome has important therapeutic implications. On the basis of the identified pathophysiology of the congenital myasthenic syndrome, a number of other pharmacologic interventions are tried in individual children, including fluoxetine, ephedrine, albuterol, and 3,4-diaminopyridine.

**Juvenile Myasthenia**

Juvenile myasthenia is said to be similar to the adult form, but more frequently familial, showing slower progression, characterized by more severe ophthalmpoplegia, and having a higher rate of spontaneous remissions.778 Children with myasthenia often first present to the ophthalmologist with symptoms such as ptosis, diplopia, strabismus, and ophthalmpoplegia.90,285 Juvenile myasthenia is otherwise similar to the adult variety in presentation, pathogenesis, clinical course, and response to therapy. While it has been observed that there is an increased incidence of autoimmune disorders in children with acquired autoimmune myasthenia gravis and their first-degree relatives, acquired autoimmune myasthenia gravis is probably not a familial disease. However, some studies reveal the juvenile variety to be more frequently familial,571,574 to show more severe ophthalmpoplegia, and to have slower progression and a higher rate of spontaneous remissions. An acute fulminating form of myasthenia gravis has been described, with onset between 2 and 10 years of age, with respiratory crisis as the presenting feature of the disorder.264
Many medications have been reported to incite or worsen myasthenia. These drugs may interfere with neuromuscular transmission pre- or postsynaptically. Cardiovascular drugs (antiarrhythmics and beta adrenergic receptor-blocking agents), anticholinergic, anticonvulsants, antirheumatics, immunosuppressives, psychotropics, and antibiotics have all been reported in association with myasthenia. Many antibiotics, including kanamycin, ampicillin, imipenem with cilastatin, ciprofloxacin, erythromycin, and clarithromycin, have also been reported to cause myasthenia. Interferon-alpha, a drug frequently used in the treatment of malignancies and viral hepatitis, has been found to exacerbate myasthenia. Wasserman reported ocular myasthenia in a 10-year-old girl taking nitrofurantoin that resolved after discontinuation of the drug.

Rarely, myasthenia gravis in children can be precipitated by a viral illness. Molecular mimicry between the acetylcholine receptor and viral proteins may be involved in the pathogenesis of postinfections myasthenia gravis. Autoimmune manifestations of hyperthyroidism and myasthenia gravis occasionally overlap. The finding of lid retraction in a myasthenic child should lead to suspicion of this phenomenon.

A large proportion of young patients with juvenile myasthenia gravis are seronegative. Careful differentiation from late-onset congenital myasthenic syndromes is necessary in these cases. Children younger 5 years of age, who present with ocular symptoms of myasthenia gravis, frequently respond to anticholinesterase medications without requiring immunomodulating therapy and have low rates of progressing to generalized involvement. However, one retrospective study found a 43% prevalence of systemic involvement. Several studies have found that pediatric myasthenia gravis shows a female-to-male ratio of about 4:1. Myasthenia gravis can often be diagnosed on clinical grounds when ptosis or ophthalmoplegia is accompanied by certain neuro-opthalmologic signs. These include fatiguable ptosis, orbicularis weakness, variable strabismus, quiver-like eye movements, and a Cogan lid twitch sign. A Cogan lid twitch is elicited by having a patient rapidly refixate the eyes from a depressed position to the primary position, with a positive lid twitch sign indicated by the lids overshooting briefly upward before settling in their usual ptotic position. If the lid is first fatigued by sustained upward gaze, the lid twitch sign becomes more exaggerated. Apparently, the short relaxation of the upper lid allowed by fixing an object in downgaze allows for transient recovery of strength by the myasthenic levator muscle.

Although ptosis is the most common sign, lid retraction may occasionally be encountered, especially unilaterally in patients with contralateral ptosis. This seemingly paradoxical finding is explained by Hering’s law of equal innervation, as the patient attempts to elevate the contralateral ptotic lid. Bilateral lid retraction, which is also rarely reported in myasthenia, is not readily explained by Hering’s law. In such cases, the possibility of concurrent thyroid eye disease must be excluded.

Children with diffuse myasthenic ophthalmoplegia rarely present with myopia. Myopia occurs when medial rectus weakness leads to exotropia, which necessitates excessive accommodative convergence to maintain single binocular vision. These children are caught in the unpleasant situation of having to sacrifice clear vision to avoid diplopia. Jacqueline Winterkorn, M.D., has observed another unique ocular motor sign of myasthenia that can be elicited in patients with diffuse ophthalmoplegia. An optokinetic drum is spun horizontally for approximately 30 s, as the patient attempts to follow the targets. The drum is then spun diagonally and the resultant optokinetic movements are observed. In myasthenic ophthalmoplegia, the resultant movements are vertical rather than diagonal because the horizontal component has been prefatigued. Conversely, if the drum is first spun vertically for 30 s and then diagonally, the resultant optokinetic movements are horizontal (Winterkorn sign). In nonmyasthenic ophthalmoplegia, optokinetic preconditioning does not alter the trajectory of the patient’s diagonal optokinetic responses.

Systemic myasthenia is often first suspected when weakness is demonstrated to be fatigable (worsening with use or exercise and relieved by periods of rest). The diagnosis of myasthenia may be confirmed with certain ancillary tests, including serologic testing for antibodies, clinical neurophysiologic testing (repetitive stimulation of motor nerves, needle electromyography, including single fiber testing), and pharmacologic testing. Because children with acquired autoimmune ocular myasthenia gravis have a higher incidence of seronegativity and normal clinical neurophysiologic testing, the diagnosis often depends on other measures.

There are three main confirmatory procedures for myasthenia: response to acetylcholinesterase inhibitors, electrophysiologic testing, and antibody assays. In general, all share the same problem of a lower sensitivity in ocular myasthenia gravis than in generalized myasthenia gravis. The sensitivity of the edrophonium test is approximately 95% in generalized myasthenia gravis and is similar in patients with ocular myasthenia gravis with ptosis. However, diplopia fails to respond in approximately one-third of patients, and long-standing myasthenia may not respond at all. The repetitive nerve stimulation test is positive in most patients with generalized myasthenia gravis, but may be normal in well over 50% of patients with ocular myasthenia gravis. Single-fiber EMG of the orbicularis oculi is currently the most sensitive test for ocular myasthenia. When coupled with the standard EMG, it usually distinguishes myasthenia from other disorders such as mitochondrial myopathy or oculopharyngeal dystrophy. The sensitivity of single-fiber EMG is more than 90% in generalized myasthenia gravis and approximately 85% in ocular myasthenia gravis. Since needle
EMG and repetitive nerve stimulation are usually positive in systemic myasthenia, these tests should first be performed to rule out denervation or atrophy in patients with limb weakness. Only when these tests are negative, or when there are purely ocular signs, is single-fiber EMG indicated. Because it is painful and requires patient cooperation, it may be difficult or impossible to perform in young children.

Positive acetylcholinesterase antibodies are found in 90% of cases of systemic myasthenia, but in only 50% of cases of ocular myasthenia. Because myasthenic children have a higher frequency of negative anticholinesterase antibodies, a negative test is not especially useful in this setting. The recent identification of muscle-specific kinase (MuSK) as a target of the autoimmune process in a subset of patients indicates that autoimmune myasthenia gravis includes at least two distinct immunologic disorders directed against different antigens in the postsynaptic membrane of the neuromuscular junction.24 Autoantibodies targeting MuSK have been demonstrated in approximately 40% of seronegative patients.257,368,468 Although the numbers are small, our experience is that the anti-MuSK variant tends to be more severe and less responsive to therapy.

The Tensilon (edrophonium hydrochloride) test is the most commonly utilized. For children less than 34 kg, a test bolus of intravenous edrophonium should be 0.1 cc or 1 mg, followed by repeated boluses at 1-min intervals to the point of positive response or maximum injection of 5 mg total dose. Cardiac monitoring is advisable. The dose of atropine given for excess parasympathetic response (primarily bradycardia or bradyarrhythmias) should be 0.02 mg/kg/dose, with a maximum of 0.5 mg/dose in younger children and a maximum of 1 mg/dose in adolescents (Fig. 7.10). Results of the Tensilon test may be equivocal, falsely negative, or falsely positive. False-negative results are more common than false-positive ones. Therefore, if the clinical findings are suggestive of myasthenia, repeating an initially negative Tensilon test is recommended. False-positive results have been reported in patients with compressive lesions (brain tumors, intracranial aneurysm), botulism, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, poly-myelitis, transverse myelitis, Guillain–Barré syndrome, and myositis.211,357 Because severe bradyarrhythmias, conduction pauses, and cardiac arrests have been reported, albeit rarely,389 cardiac monitoring and pretreatment with atropine should be considered in “at-risk” patients.

In young children, neostigmine (Prostigmine) is administered intramuscularly, which produces a more prolonged response in myasthenic patients than does edrophonium chloride. Neostigmine can produce a more prolonged clinical response (onset, 10 min; duration, 60 min), which can allow for more leisurely assessment of the response. Doses are 0.04 mg/kg/dose administered intramuscularly or subcutaneously, with a maximum of 0.5 mg/dose. Side effects related to excess parasympathetic activity can also last up to 60 min and, as clinically indicated, are treated with atropine in a dose of 0.02 mg/kg/dose, intravenously, with a maximum 0.05 mg/kg/dose in younger children and 1 mg/dose in adolescents.

To avoid the complications of pharmacological testing, a “sleep test” has been devised wherein the patient is evaluated for improvement of ocular signs immediately after a 30-min period of sleep (or eye closure) and for worsening of these signs shortly thereafter (Fig. 7.11).588 The “ice test,” performed in an outpatient setting, can similarly differentiate a neuromuscular transmission defect from other causes of ptosis.234,235,254,300,453 In this test, a surgical glove filled with ice...
chips is placed over the ptotic eyelid for 2 min after the eyelid has been fatigued by prolonged upgaze. Measurement of the millimeters of ptosis before and after the cooling is used to objectively measure response with lessening of the ptosis, suggesting the presence of myasthenia. The ice test is based on the observation that increased temperature has a detrimental effect, and decreased temperature a beneficial effect, on muscle force generation in myasthenia gravis. Both tests and the sleep test often produce dramatic resolution of myasthenic ptosis, and some of the observed effect of the ice test may be attributable to resting of the closed lid.

The medical treatment of juvenile myasthenia is similar to that of the adult variety in that the ptosis shows a good therapeutic response while the strabismus often does not. In a recent retrospective study, children with ocular myasthenia were found to have a high incidence of ptosis (96%) and strabismus (88%), most commonly with exotropia and vertical heterotropia, and ambylophia (21%). The ptosis showed a good therapeutic response in 87%, but the strabismus improved in only 29%. Combined pyridostigmine and prednisone were most commonly used. Treatment with a short course of prednisone and long-term azathioprine is reported to reduce the risk and severity of generalized symptoms and to promote remission of the disease.

Although thymomas are rare in myasthenic children, thymectomy has been observed to be associated with an increased rate of clinical remission in children with autoimmune myasthenia gravis. Early surgery (within 2 years of clinical onset), bulbar involvement without ocular signs of generalized weakness, clinical onset during adolescence (12–16 years of age) and presence of other autoimmune disorders were associated with increased probability of clinical remission after thymectomy. Surgeons have developed a technique of using video-assisted thorascopic thymectomy that has significantly decreased operative morbidity compared to transsternal thymectomy. Unanswered questions, regarding the impact of thymectomy early in life on the developing immune system, have kept thymectomy limited to children with generalized weakness and will likely lead to additional review of the effectiveness of this operation as a therapeutic option.

Because the disease is immune-mediated, unlike in congenital myasthenia, immunosuppression and plasmapheresis have a therapeutic role. Systemic therapy of myasthenia helps control ocular symptoms in most patients. In addition to producing superior resolution of ocular misalignment and diplopia, treatment with oral prednisone appears to reduce the conversion of ocular to systemic myasthenia gravis. After an initial period with immune suppressing dose of corticosteroids, the benefit may be maintained with doses that do not suppress the immune system and appear to cause few major systemic adverse effects.

There is a theoretical basis for using corticosteroid treatment to prevent generalized myasthenia, even at doses that do not cause immunosuppression. Corticosteroid treatment of in vitro human muscle cultures increases the number of acetylcholine receptors and prevents receptor loss induced by the serum from generalized myasthenia gravis patients. Neuromuscular junctions increase in size, and the length, number, and depths of postsynaptic folds increase after weeks of corticosteroid exposure. In patients with ocular misalignment, strabismus surgery has been used to manage both stable and unstable diplopia with long-standing success.

Brain tumors rarely produce clinical findings that are indistinguishable from myasthenia. These findings are attributed to a putative compression of the central caudal nucleus in the dorsal midbrain. Ragge and Hoyt described an adolescent girl with neurofibromatosis type I and a dorsal midbrain astrocytoma who had fatiguable ptosis, upgaze paresis, and a positive “lid twitch” sign. These findings improved significantly following radiotherapy of the astrocytoma, confirming that the muscular fatiguability was central in origin. Straube and Witt described four patients with posterior fossa tumors who presented only with fluctuating weakness of the external ocular muscles and/or the pharyngeal muscles, leading to an incorrect diagnosis of ocular myasthenia. Moreover, as noted earlier, false-positive results of Tensilon testing may...
occur in some instances involving tumors or even aneurysms. Branley et al. reported a 7-year-old girl who developed an ocular motor nerve palsy of subacute onset due to a cerebral artery aneurysm. The condition was initially confused with myasthenia gravis because the ptosis improved after Tensilon administration (false-positive result), but the key clinical distinguishing findings were the presence of aberrant innervation and pupillary involvement, which are not features of myasthenia. Chemotherapeutic agents, such as, vincristine, may also cause neurological findings (ptosis, ophthalmoplegia, jaw pain) that can confound the diagnostic picture in children with intracranial tumors.

### Olivopontocerebellar Atrophy

The nomenclature regarding olivopontocerebellar atrophy and the related hereditary spinocerebellar ataxias has undergone revision, first to the clinically based autosomal dominant cerebellar ataxias and, more recently, to the genetically defined spinocerebellar ataxias. Olivopontocerebellar atrophy (OPCA) is a pathological label implying not only olivopontocerebellar changes, but also cases with more widespread lesions involving the CNS. OPCA may also be part of the pathological hallmark of other disorders such as mitochondrial encephalomyopathies, prion disorders, and hereditary metabolic diseases. In 1983, Harding developed a clinicogenetic classification, which has been subsequently modified according to molecular genetic advances. Older diagnostic categories, such as olivopontocerebellar atrophy, are now known to carry mutations for spinocerebellar ataxia (SCA1, SCA2, and SCA3).

The hereditary ataxias and loci now comprise around 80 loci, with 28 belonging to spinocerebellar ataxia and designated as SCA1–28 in order of discovery. Several SCA subtypes (SCA1, SCA2, SCA3, SCA6, SCA7) are caused by CAG trinucleotide expansions in their respective genes. Autosomal dominant cerebellar atrophy 1 (ADCA1), which presents with a range of findings, including ataxia, pyramidal and extrapyramidal signs, and ophthalmoplegia, corresponds to the current classifications SCA1–4. ADCA2, which is similar but includes retinal degeneration, corresponds to SCA7. ADCA3, which involves relatively pure cerebellar signs, corresponds to SCA6 and 7. Clinically, patients diagnosed with OPCA correspond to those with SCA1, SCA2, and SCA3. SCA1 maps to 6p23, SCA2 to 12q24, and SCA3 to 14q24.3-q31. Macular and retinal degeneration are seen predominantly in SCA7, but occasionally in SCA2. Patients with SCA7 have abnormal electroretinograms showing predominantly cone dysfunction. MR imaging shows severe OPCA in SCA2, similar but milder changes in SCA1, and very mild atrophy with sparing of the olives in SCA3. An SCA panel can be ordered when the one of the spinocerebellar ataxias are suspected.

Supranuclear ophthalmoplegia may be accompanied by gaze-evoked nystagmus in patients with SCA1, SCA3, and SCA6, and by rebound nystagmus in SCA1 and SCA3. Impaired saccadic velocity and latency are characteristic of SCA2 and SCA2. In SCA1, saccadic amplitude is significantly increased, resulting in hypermetria. A supranuclear ophthalmoplegia with severe saccadic slowing is highly characteristic of SCA2, which may show selective involvement of vertical saccades, impaired VOR, and gaze-evoked nystagmus. The constellation of impaired VOR, saccadic dysmetria, and slow-wave jerks are common to both SCA3 and Friedreich’s ataxia. The association of these oculomotor disorders with dystonia, spasticity, facial and lingual fasciculations, diplopia, and parkinsonism should suggest the diagnosis of Machado–Joseph disease (SCA3). Many reports have described a striking “ocular stare” or “prominent eyes,” which are thought to result from lid retraction rather than proptosis.

SCA1–4 (previously known as ADCA type I) are associated with optic atrophy and ophthalmoplegia. SCA7 (previously known as ADCA II) is distinguished by the presence of pigmentation macular dystrophy that includes early granularity and mottling, and is later associated with pigment changes that gradually spread to the periphery, with late optic atrophy and attenuation of retinal vessels.

The ADCA type II locus, which corresponds to SCA7, has been mapped to chromosome 3p12-p21. SCA7 (or ADCA type II) is caused by an unstable CAG repeat in the SCA gene. Larger expansions are associated with earlier onset, a more severe and rapid clinical course, and a higher frequency of decreased vision, ophthalmoplegia, extensor plantar responses, and scoliosis. The mutation is highly unstable, with an increase in repeats with paternal transmission correlating with marked anticipation. This instability of transmission is more marked than with other SCA subtypes. A supranuclear ophthalmoplegia is commonly seen in more than half of SCA patients. The responsible gene for SCA7 has been cloned. Molecular testing of DNA from whole blood is now available to detect the SCA7 CAG repeat to confirm the diagnosis genetically.

The fundamental neurologic lesions of the spinocerebellar ataxias are localized to the cerebellum, and the pontine, inferior olivary, arcuate, and pontobulbare nuclei. Cerebellar atrophy fundamentally involves Purkinje cells and predominates in the neocerebellum. CT scanning and MR imaging show the characteristic brainstem and cerebellar atrophy, with the most sensitive diagnostic feature being the diameter of the middle cerebellar peduncle. Intermediate and T2-weighted MR images may show cruriform hyperintensity (“hot cross bun” sign) of the ventral part of the pons, accounted for by demyelination and gliosis of transverse fibers of the pons secondary to atrophy of nuclei pontis.
It is important to remember that several metabolic disorders that present in infancy or childhood (abetalipoproteinemia, hexosaminidase A deficiency, cholestanolosis, the leukodystrophies, [metachromatic, Krabbe’s disease, and adrenoleukodystrophy], and Refsum disease) can be associated with a progressive and unremitting ataxia that can first appear in early adulthood. Of the vitamin deficiencies, vitamin E deficiency is most often associated with the development of progressive ataxia, associated with areflexia, and loss of proprioception and vibration sensation (abetalipoproteinemia or Bassen–Kornzweig disease). Affected patients develop pigmentary retinopathy and progressive gaze restriction. Some patients have vitamin E deficiency without fat malabsorption, inherited in an autosomal recessive manner, with symptoms similar to Freidreich’s ataxia.

**Botulism**

Signs of total (internal and external) ophthalmoplegia, dry mouth, descending paralysis, obtipation, absence of fever, and lucid sensorium, as cardinal symptoms should raise suspicion of botulism. *Clostridium botulinum* produces seven distinct protein toxins, of which A, B, and E are the most commonly responsible for human botulism. The botulism toxin causes neural paralysis of skeletal muscle by disruption of both spontaneous and stimulus-induced release of acetylcholine from the presynaptic nerve terminal and by interfering with exocytosis of vesicle contents. The toxin enters the body via the following four routes: (1) ingestion of preformed toxin, as in the case of food poisoning; (2) toxin production by *Clostridium* spores or bacteria infecting a wound; (3) colonization of the gastrointestinal tract by *Clostridium botulinum*, with subsequent production of toxin; it is by this mechanism that infant botulism and the “infant form of botulism” that affects some adults occurs; and (4) the “hidden” form in which no identifiable route of entry of toxin or bacteria into the body can be identified.

Botulism spores are ubiquitous, and have been isolated from yard and houseplant soil and vacuum cleaner dus. In adults, the disease usually results from ingestion of preformed botulinum toxin in contaminated foods such as poorly sterilized canned goods or raw fish. Infant botulism, first described in 1976, is caused by ingestion of live *Clostridium botulinum* organisms or spores, which subsequently release toxin in the intestine. Most pediatricians advise against feeding honey to infants younger than 1 year of age, as it has been documented as a source of spores causing infant botulism.

Infant botulism was first recognized in 1976 and has since become the most frequently reported form of botulism. Most reported cases have been from North America. A history of honey ingestion or soil eating is frequently obtained. Because *Clostridium botulinum* is ubiquitous and is commonly ingested without adverse effects, a number of host factors may render a particular individual predisposed. Constipation, immune dysfunction, gastric pH, and unusual gut flora, among others, may permit the colonization and germination of *Clostridium* spores and subsequent local production of toxin.

Infant botulism has been described in infants ranging from 10 days to 8.5 months old, but 98% of those affected are between 2 weeks and 6 months old. The earliest clinical sign of disease is usually constipation, which can be present for several days before other signs appear. Bulbar signs later predominate and include impaired sucking with poor feeding, a feeble cry, tachycardia due to loss of vagal tone. Isolated internal ophthalmoplegia may evolve into diffuse ophthalmoplegia with ptosis. Crouch et al reported an infant who had bilateral sixth nerve palsies following resolution of infant botulism. Other signs of cranial nerve palsy include drooling, diminished gag reflex, and facial weakness. Generalized muscular weakness progresses in a descending fashion from the cranial nerves to the limbs. Generalized weakness, hypotonia, hyporeflexia, and cranial nerve weakness constitute the “floppy infant” syndrome. Respiratory arrest and death may follow, but most infants recover completely in 1–5 months.

While mild cases are often managed on an outpatient basis, the age distribution of infant botulism closely mirrors that of the Sudden Infant Death syndrome (SIDS), and botulism toxin has been recovered from 5% of autopsy specimens of infants with the diagnosis of SIDS. Cases of infant botulism may also be mistakenly diagnosed as crib death, failure to thrive, sepsis, dehydration, viral infection, idiopathic hypotonia, poliomyelitis, meningitis, brainstem encephalitis, or other neuromuscular disorders such as myasthenia. To add to the diagnostic quandary, some patients with botulism may give false-positive response to intravenous edrophonium chloride. One important differentiating feature of botulism is the dilated, poorly reactive pupils, which are not seen in ocular myasthenia. The differential diagnosis also includes Reye’s syndrome, Guillain–Barré syndrome, hypothyroidism, tick paralysis, and toxins.

The diagnosis is made when toxin or organisms are recovered from stool samples. However, the level of botulinum toxin is too low to be detected in the sera of patients with infant botulism. Electromyographic (EMG) studies are highly useful in the diagnosis of botulism, with a characteristic EMG pattern that has been given the acronym BSAP, for “brief duration, small-amplitude, overly abundant, motor-unit action potentials.” Fibrillation potentials suggesting functional denervation are observed in about half the cases. Repetitive fast rates of stimulation (20–50 Hz) result in marked incremental response, a finding not present in older
children and adults with botulism, probably due to the large amount of toxin present. Other conditions showing an incremental EMG response, such as Eaton–Lambert (not seen in infants), hypermagnesemia, and aminoglycoside toxicity, can be readily excluded on clinical and laboratory grounds. Logistical problems in terms of application of EMG to the investigation of infant botulism include the need to transport the cumbersome equipment to the intensive care unit and electrical interference there with the EMG recording.

Spontaneous recovery occurs through sprouting of new nerve endings with formation of new myoneural junctions. Treatment of affected patients includes insertion of a nasogastric tube with suction, enemas, antitoxin administration (benefit controversial), and mechanical ventilation, if indicated. The recently introduced botulinum immune globulin (BIG) appears promising. In a recent clinical trial, it reduced the severity of illness and reduced the mean length of hospital stay from 5.7 to 2.6 weeks without complications.19

**Fisher Syndrome: A Variant of Guillain–Barré Syndrome**

The Guillain–Barré syndrome (acute infectious polyneuropathy) consists of progressive, usually symmetric muscular weakness that appears several days after a nonspecific infectious prodrome. Mild sensory disturbances, such as pain and paraesthesias, are commonly present. The paralysis usually affects the lower extremities and then ascends. Cranial nerve palsies may appear at any time during the clinical course. Results of EMG studies are usually consistent with involvement of the lower motor neurons or peripheral nerves.

Fisher syndrome is a variant of Guillain–Barré syndrome with the distinct triad of ataxia, areflexia, and ophthalmoplegia without concurrent peripheral neuropathy. Fisher syndrome constitutes about 5% of all reported cases of Guillain–Barré syndrome. There appears to be a gender predilection, with the male/female ratio being 2:1. Of the 223 cases reported before 1993, the average age was 43.6 years (range, 14 months to 80 years), with 14.3% of these being children.46

Most patients with Fisher syndrome suffer a preceding viral prodrome, usually respiratory, 1–3 weeks prior to onset of the syndrome.66 Most patients reach maximum neurologic deficit within 1 week of onset. Diplopia and ataxia are the most common presenting symptoms. Associated ophthalmoplegia is complete (including the parasympathetic fibers to the pupillary sphincter muscle) in about half of patients with Fisher syndrome,66 but pure external ophthalmoplegia or internal ophthalmoplegia may occur. Isolated ocular motor nerve palsy and combinations of horizontal and vertical gaze palsies may be noted. Internuclear ophthalmoplegia, one-and-a-half syndrome, gaze-evoked lid nystagmus, convergence spasm, and a dorsal midbrain syndrome with upward gaze paralysis, but intact Bell’s phenomenon, have also been reported.16,46,529 The presence of these latter disorders and similar findings pointing to brainstem involvement fuels the controversy about the nature of the disease as a peripheral (infranuclear, due to involvement of sensory fibers in the peripheral nerves and dorsal roots) or CNS (supranuclear) disorder or as a combination of both.529

Other cranial nerves may be affected, the most common being the facial nerve. Dysphasia and dysarthria may result when the lower cranial nerves are involved. Monoparesis, hemiparesis, or quadriparesis have been described. Patients may have sensory symptoms, including paraesthesias, dysesthesia, and headaches. Other symptoms and signs include disturbance of consciousness, seizures, myoclonus, tremors, fever, vomiting, irritability, positive Babinski sign, and respiratory insufficiency. The CSF, if examined 2–3 weeks or later after onset, usually shows mild elevation in protein, with about 10% of cases in the literature showing pleocytosis.

Some authors consider the Fisher variant to be due to pathologic changes exclusively within the peripheral nervous system. This concept is supported by reports of normal MR imaging scans in affected patients.655 While pure cases of Fisher syndrome are apparently attributable to peripheral neuropathy and are not uncommon, overlapping cases occur that bridge the spectrum from the benign Fisher variant to the more virulent Guillain–Barré syndrome. For instance, cases that include limb paralysis do not, strictly speaking, fall within the original definition of the Fisher syndrome and are transitional forms to the Guillain–Barré syndrome. On the basis of current evidence, some authors believe that Fisher syndrome represents an encephalomyeloneuritis.66

The triad of severe external ophthalmoplegia, ataxia, and areflexia in an otherwise alert child is fairly unique. The characteristic history and physical findings are usually sufficient to establish the presumptive diagnosis, but differentiation from posterior fossa tumors may be difficult without neuroimaging. Wernicke syndrome and phenytoin intoxication can show a similar syndrome complex, but these entities can be excluded by the clinical history. Both Fisher syndrome and botulism may show a similar early presentation consisting of extraocular muscle weakness and mydriasis. Other conditions included in the differential diagnosis of Fisher syndrome are brainstem stroke, pituitary apoplexy, cerebral sinus thrombosis, tick fever, and diphtheria.

While some cases may follow a more virulent course, most cases of Fisher syndrome resolve spontaneously within 1–3 months. Corticosteroids as well as plasmapheresis have been used, but there is little evidence to support their efficacy in the limited form of the condition without brainstem signs. Intravenous immunoglobulin may be helpful in severe cases.30
Serological, immunological, and pathological studies all implicated a role for complement-mediated damage to neuronal and Schwann cell membranes in Guillain–Barré syndromes. In vivo and in vitro models of Fisher syndrome have shown that anti-GQ1b ganglioside antibodies target the presynaptic motor nerve terminal axon and surrounding perisynaptic Schwann cells, thereby mediating destructive injury through deposition of membrane attack complex (MAC). The anti-GQ1b antibody has been detected in the sera from patients during the acute phases of Fisher syndrome, Bickerstaff brainstem encephalitis, and Guillain–Barré syndrome with ophthalmoplegia. These cases seem to demonstrate a close relationship between ophthalmoplegia and serum anti-GQ1b antibody. 

It has been hypothesized that ganglioside epitopes on Campylobacter jejuni are the key to the development and characterization of Guillain–Barré syndrome. The presence of these bacterial epitopes in neuropathy patients correspond to autoantibody reactivity. In one study, patients infected with C. jejuni (Asn51) regularly expressed the GQ1b epitope (83%), whereas those with cst-II (Thr51) had the GM1 (92%) and GD1a epitopes. Patients infected with C. jejuni (Asn51) more often were positive for anti-GQ1b IgG (56% vs. 8%), and had ophthalmoplegic signs (64% vs. 13%) and ataxia (42% vs. 11%). Patients who had C. jejuni (Thr51) more frequently were positive for anti-GM1 (88% vs. 35%) and anti-GD1a IgG (52% vs. 24%) and had limb weakness. Thus, the genetic polymorphism of C. jejuni appears to determine autoantibody reactivity as well as the clinical presentation of Guillain–Barré syndrome, possibly through modification of the host-mimicking molecule.

**Bickerstaff Brainstem Encephalitis**

Bickerstaff’s brainstem encephalitis is a clinical syndrome of ophthalmoplegia, cerebellar ataxia, and central nervous system signs. Diagnostic criteria include a progressive, relatively symmetric external ophthalmoplegia and ataxia with disturbance of consciousness or hyperreflexia. Positive anti-GQ1b antibodies support the diagnosis. Conditions that mimic the disorder, including brainstem tumors, must be excluded. There is a clinical continuum between Bickerstaff brainstem encephalitis and Fisher syndrome. However, CNS signs, such as disturbance of consciousness and cogwheel rigidity, are more in keeping with brainstem encephalitis.

In general, Bickerstaff brainstem encephalitis is a disease of the CNS, while Fisher syndrome is primarily a disease of the peripheral nerves. However, some clinical and pathologic overlap is found. It is interesting to note, for example, that one in three patients in the original description of Fisher syndrome had drowsiness, whereas Bickerstaff described four cases of Bickerstaff brainstem encephalitis in which the patients had areflexia. Both conditions have been described following Mycoplasma pneumoniae infection. Treatment with intravenous immunoglobulin or use of plasmapheresis has been reported to produce clinical improvement, although it is unproven that they affect the natural history of this disorder.

**Tick Paralysis**

Tick paralysis should be considered in the differential diagnosis of Fisher syndrome in children in tick-infested areas who develop ophthalmoplegia and ascending paralysis. The diagnosis is confirmed by finding a tick embedded in the skin and observing for signs of improvement after tick removal. No other tests for confirming tick paralysis exist. Tick paralysis is thought to be caused by a toxin secreted in tick saliva that reduces motor neuron action potentials and the action of acetylcholine. Symptoms usually begin 4–7 days after tick feeding. Ascending flaccid paralysis progresses over several hours or days; sensory loss does not usually occur, and pain is absent. When the tick is not removed, the mortality rate resulting from respiratory paralysis is approximately 10%.

**Wernicke Encephalopathy**

Although classically considered an adult disorder, in 2003, an epidemic of Wernicke encephalopathy developed in Israeli infants fed a thiamine-deficient soy-based formula. These infants showed no neurologic signs for the first 6 months on the thiamine-deficient diet. Apathy, vomiting, and diffuse ophthalmoplegia brought these infants to medical attention and helped to establish the diagnosis. Wernicke encephalopathy preferentially affects neurons in particular areas of the nervous system such as the putamen, parts of the thalamus, and the periaqueductal gray matter. Thiamine turnover is higher in these areas and these structures have high rates of oxidative metabolism in neonates, which could make them more vulnerable.

**Miscellaneous Causes of Ophthalmoplegia**

Involvement of the respiratory and renal systems in the child with diffuse ophthalmoplegia should suggest the diagnosis of Wegener granulomatosis. A new autosomal recessive ophthalmoplegic disorder affecting highly inbred Arab families in Israel produces limited upgaze, slow saccades, and impaired...
Transient Ocular Motor Disturbances of Infancy

Healthy neonates may exhibit a variety of benign, transient supranuclear eye movement disturbances. These include horizontal heterophorias, tonic downgaze and upgaze, opso-clonus, skew deviations, and transient idiopathic nystagmus in infants. As each of these disorders may forebode serious neurological disease, especially in older children, their benign nature in healthy neonates must be recognized to avoid unnecessary diagnostic testing.

Transitory Neonatal Strabismus

Several nursery studies have shown that the eyes of otherwise healthy, full-term neonates are commonly misaligned. In one study of 1,219 neonates, 48.6% had orthotropia, 32.7% had exotropia, 3.2% had esotropia, and 15.4% were not sufficiently alert to allow determination of ocular alignment. No cases of congenital esotropia were found in any neonate, supporting the concept that congenital esotropia does not manifest at birth. Follow-up studies of these patients have shown that the vast majority of children with transient heterophorias become orthotropic between 2 and 3 months of age, a stage coincident with development of stereoscopic vision. Unlike exotropia, which may be found transiently in the neonatal period, the finding of large esotropia in the first several weeks of life should not be classified as congenital esotropia (which usually first appears after 6 weeks of age) until other conditions such as sixth nerve palsy and Möbius syndrome are ruled out (Fig. 7.12). It should also be recognized that the eyes of premature infants may transiently display exotropia with limited adduction. These findings have been speculated to result from immaturity of the medial longitudinal fasciculus in the premature infant.

Large convergent movements of the eyes, producing esotropia, are often observed in the first 2 months of life. These convergent eye movements resolve spontaneously, giving way to normal ocular alignment. The fact that these large-angle convergent eye movements are predictive of the normal binocular alignment belies the notion that infantile esotropia results from excessive convergence.

Transient Idiopathic Nystagmus

Good et al described six infants with transient idiopathic nystagmus. Four of these infants had other visual abnormalities, including regressed retinopathy of prematurity, coloboma, and delayed visual maturation, which may have precipitated the nystagmus. They interpreted the transient nystagmus as indicative of a fragile period of postnatal maturation of the ocular motor system. It is also recognized that some infants with delayed visual maturation may exhibit transient nystagmus.

Tonic Downgaze

Tonic downward deviation of the eyes may occur as a transient phenomenon in neonates and does not necessarily indicate underlying neurologic dysfunction. Both eyes are tonically deviated downward while the infant is
awake, but can be maneuvered upward with oculocephalic or vestibulo-ocular stimulation; the condition resolves during sleep, with both eyes returning to the midline. It usually resolves within the first 6 months of life. Two infants who displayed this transient tonic downgaze also showed associated upbeat nystagmus, with complete resolution of both findings within the first few months of life. The authors proposed that immaturity of the vestibular system was the cause. In some cases, these transient episodes of downgaze can be followed by abnormal body movements.813

The benign, transient form of tonic downgaze differs from the “setting sun sign” associated with hydrocephalus by the absence of eyelid retraction. Yokochi described downward deviations of the eyes of neurologically affected infants that were paroxysmal rather than constant, as in the foregoing benign variety. The paroxysms were not associated with seizure activity. He considered this to be a sign found in brain-damaged infants with cortical visual impairment. The paroxysms spontaneously resolved with time in many patients. We examined a blind infant with profound bilateral optic nerve hypoplasia, absent septum pellucidum, and developmental delay who showed sudden episodic downward deviations of the eyes occurring every 1–2 min and lasting 5–10 s (Fig. 7.13). The downward deviation was associated with lid lag. The patient also showed intermittent side-to-side head shaking. Episodic downgaze may be one of the presenting signs of Leigh subacute necrotizing encephalomyelopathy.511 Mak et al. reported a previously healthy infant who, at 6 months of age, showed episodic downgaze with limited horizontal movements that resolved after 5 days, then recurred several times along with other abnormalities before a diagnosis of Leigh disease was made.

It is not clear whether congenital hydrocephalus alone results in tonic downgaze. The setting sun sign, a feature of congenital hydrocephalus (Fig. 7.14), may be considered a combination of lid retraction (Collier’s sign) and tonic downgaze. Acquired hydrocephalus in older patients does not produce tonic downgaze, suggesting a specific susceptibility of the neonatal brain to the mass effect of hydrocephalus on midbrain structures responsible for downgaze or suggesting a higher sensitivity of the prefrontal area in infants to hydrocephalus, leading to more severe upgaze palsy (causing the eyes to deviate downward) than is seen in older patients. Tamura and Hoyt reported 11 premature infants with intraventricular hemorrhages who showed acute tonic downward deviation of the eyes, esotropia, and upgaze palsy. All patients showed associated hydrocephalus, shunting of which resulted in gradual improvement in upgaze, with persistence of the large-angle esotropia. The authors suggested that the gradual recovery of upgaze indicates that the upgaze palsy may not be simply due to the acute effects of the hydrocephalus. Rather, they suggested that the associated intraventricular hemorrhages act as a mass lesion, compressing (and hence paralyzing) the upgaze centers or irritating (and hence stimulating) the downgaze centers within the mesencephalon. They speculated that injury to these mesencephalic structures may contribute to the delay in recovery of upgaze after shunting. We most commonly see tonic downgaze in conjunction with esotropia in infants with periventricular leukomalacia, where it can occur in the absence of intraventricular hemorrhage. As with intraventricular hemorrhage, the tonic downgaze spontaneously resolves, and infants are usually left with an A-pattern esotropia with superior oblique muscle overaction. The telltale ocular intorsion can easily be missed if the retinas are examined in the esotropic position, which places the eyes in the vertical rather than the torsional field of action of the overacting superior oblique muscles. We have proposed that a posterior canal predominance caused by injury to bilateral central brainstem pathways mediating upward pitch could explain this constellation of

Fig. 7.13 Episodic tonic downgaze. Blind infant with profound bilateral optic nerve hypoplasia, absent septum pellucidum, and developmental delay showed sudden episodic downward deviations of eyes occurring every 1–2 min and lasting 5–10 s. These have occurred since birth. Downward deviation was associated with lid lag. Infant also showed intermittent side-to-side head shaking.

Fig. 7.14 Setting sun sign in hydrocephalus. Child presented with pronounced lid retraction and mild to moderate tonic downward deviation of eyes. Disproportionately large head and dilated ventricles on neuroimaging confirmed diagnosis of hydrocephalus.
In congenital hydrocephalus that is not caused by intraventricular hemorrhage, however, the upgaze palsy and/or the setting sun sign responds quickly to reduction of intracranial pressure. For instance, Hoyt and Daroff described a 3-month-old infant with intermittent hydrocephalus secondary to a tumor of the thalamus and septum pellucidum. The infant displayed tonic downgaze and esotropia whenever the ventricular pressure increased; eye movements normalized when the ventricular pressure became normal. Such cases demonstrate that a mass effect, independent of the effect of the hydrocephalus itself, need not be present for tonic downgaze to develop in infants with hydrocephalus.

Children with hydrocephalus are predisposed to esotropia through several different mechanisms: (1) early-onset childhood esotropia, which is more common in neurologically impaired children; (2) unilateral or bilateral sixth nerve palsies; and (3) intraventricular hemorrhage in premature infants, which may involve the thalamus and mesencephalon and produce neuro-opthalmologic signs of a thalamic infarction (tonic downward deviation of the eyes, upgaze palsy, and esotropia). The esotropia in these patients usually persists even after the vertical gaze deficits resolve. Visually significant upgaze limitation can be relieved with bilateral inferior rectus recessions in Parinaud’s syndrome.

Tonic downgaze may be observed in very ill patients with impaired consciousness who have medial thalamic hemorrhage, severe encephalopathy, acute obstructive hydrocephalus, or severe subarachnoid hemorrhage. In this setting, it should be distinguished from V-pattern pseudobobbing, wherein the eyes show an abrupt downward jerk followed by a slow, upward drift to primary position. Keane reported this finding in five patients with acute obstructive hydrocephalus who had arrhythmic, repetitive, downward and inward ocular deviations at a rate of 1 per 3 s to 2 per second. The fast downward movements render the condition similar to ocular bobbing, but it differs by the presence of a V pattern, a generally faster rate, and associated pretectal, rather than pontine, signs. Keane speculated that V-pattern pseudobobbing represents a variant of convergence-retraction nystagmus that signals the need for prompt shunt placement or revision.

### Tonic Upgaze

Tonic upgaze is less common than tonic downgaze. It also tends to be more episodic. In 1988, Ouvrier and Billson described four patients with a new condition they termed “benign paroxysmal tonic upgaze of childhood.” This condition was characterized by onset during infancy of episodic tonic conjugate upward deviation of the eyes that was relieved by sleep. The children had impaired downgaze below the primary position, with downbeating nystagmus on attempted downgaze and apparently normal horizontal movements. The patients were otherwise neurologically intact, with the exception of mild ataxia. Results of metabolic, electroencephalographic (EEG), and neuroradiologic investigations were unremarkable. All eventually improved, with one child showing a favorable therapeutic response to levodopa.

The following year, Ahn et al described three infants who had tonic upgaze with no associated seizure activity or neurologic disease. The vestibulo-ocular reflexes were intact, revealing a full range of vertical movements. These episodes were initially noted in the first month or two of life and were most conspicuous when the infant was ill or fatigued. These episodes diminished with time. Mets described a 9-month-old otherwise healthy infant with large-angle esotropia who displayed extreme sustained spasms of upgaze. This infant was noted to have full vertical range of ocular motion at times and could fixate in primary gaze. No EEG abnormality was found. These episodes resolved at age 3 months, but the esotropia with associated amblyopia required patching therapy and strabismus surgery. Tonic upgaze is not an epileptic phenomenon, and paroxysmal tonic upgaze may be exacerbated by treating coincident epilepsy with valproate.

Phenomenologically, benign paroxysmal upgaze and congenital downbeat nystagmus are closely related conditions. Congenital downbeat nystagmus is distinguishable only by the presence of corrective downward refixational saccades. It is likely that benign hereditary downbeat nystagmus and the syndrome of benign tonic upward deviation of the eyes with ataxia are variants of the same disorder. In several affected children, tonic upgaze has evolved into downbeating nystagmus. We have proposed that, tonic upgaze an anterior canal predominance.

Tonic upgaze is difficult to distinguish from the “overlooking” that was reported by Taylor in patients with neuronal ceroid lipofuscinosis. Instead of looking at the object of regard directly, affected children look above the object. Initially attributed to relative preservation of the inferior visual field associated with certain retinal disorders, it was later reported not to be disease-specific, but rather to represent a sign of bilateral central scotomas (and vision of 20/200 or worse) in children from a variety of causes. Recently, Cruysberg reported that some patients with overlooking display a tonic upgaze and a dystonic neck extension, the two conditions are not always distinct. When not associated with overlooking, tonic upgaze is more often associated with neck flexion than neck extension.

Intermittent episodes of upward ocular deviation may be a manifestation of oculogyric crisis or of a seizure disorder,
typically petit mal. Oculogyric crisis denotes an extreme, episodic upward rotation of the eyes, often obliquely to the right or to the left. The deviation is usually sustained and is often associated with rhythmic jerking or twitching of the eyelid. Each oculogyric movement lasts several seconds, after which the eyes return to the horizontal position before deviating again a few seconds later until the “crisis” passes, typically in 1 or 2 h. Patients may have associated thought disorders. Dopamine-blocking agents (neuroleptics) are the most common cause of drug-induced acute dystonic reactions such as oculogyric crisis, but other drugs have been incriminated, including carbamazepine, lithium carbonate, metoclopramide, and sulpiride, among others. Oculogyric crisis has also been reported after Tensilon administration. Similar eye movements have been observed in patients with various CNS disorders, such as herpetic encephalitis, pantothenate kinase-associated neurodegeneration, and Rett syndrome, and in one patient with cystic glioma in whom the onset of crisis was positional. Oculogyric crisis can be aborted with use of anticholinergics (e.g., Cogentin) and subsequently controlled by reducing the dosage of the offending medication or changing it altogether. Patients with petit mal seizures may show eye movements similar to oculogyric crisis, usually with concurrent eyelid flutter. Eye movement tics (see later in this chapter) may also superficially resemble intermittent episodic tonic upgaze. Barontini concluded that either dystonia or downgaze palsy can underlie the phenomenon of tonic upgaze. Acquired tonic upward deviation is also seen in comatose patients, wherein it indicates a very poor prognosis, or in patients with brainstem disease causing downgaze paralysis.

Cherubism, a rare inherited disorder that involves the facial bones and produces facial fullness because of bony enlargement occurring between 2 and 4 years of age should also be considered in the differential diagnosis of tonic upgaze. This disorder was so named by Jones in 1933 because the marked fullness of the jaws and cheeks and the upward displacement of the eyes in patients were thought to resemble the heavenward gaze and round faces of Renaissance cherubs. Although this lesion was originally considered to be a form of fibrous dysplasia, cherubism was eventually accepted as a clinicopathologic entity, with features identical to giant cell reparative granuloma. This condition can be complicated by proptosis and optic neuropathy.

**Neonatal Opsoclonus**

Opsoclonus denotes bursts of chaotic repetitive back-to-back saccades in different directions (see Chap. 8). Although usually indicative of an underlying viral encephalitis or neuroblastoma, opsoclonus has been reported as a benign transient finding in healthy neonates. It usually resolves in 1–3 months, passing through a phase of ocular flutter. Given the apparent rarity of this observation, it is probably prudent to consider this benign transient variant a diagnosis of exclusion, especially in light of the serious nature of other potentially causative lesions such as neuroblastoma. When opsoclonus accompanies neuroblastoma, it imparts a poor long-term neurological prognosis, but a highly favorable prognosis for survival.

**Transient Vertical Strabismus in Infancy**

A transient vertical deviation of the eyes with or without a horizontal component has been reported in the neonatal period without associated evidence of posterior fossa dysfunction and is referred to as skew deviation. Some infants exhibiting this sign may subsequently develop large-angle esotropia typical for congenital esotropia or nystagmus compensation syndrome. Whether this transient vertical deviation of the eyes is an early manifestation of dissociated vertical divergence and whether it is a reliable premonitory sign for the subsequent development of congenital esotropia is not known.

**Congenital Cranial Dysinnervation Syndromes**

The congenital cranial dysinnervation syndromes comprise a group of disorders characterized by deficient innervation to the extraocular muscles and facial musculature. These congenital neuromuscular disorders result from developmental errors in innervation of the ocular and facial muscles. They result from mutations in a number of genes, including ROBO3, PHOX2A, SALL4, HOXA1, KIF21A, that are essential to the normal development of brainstem motor neurons or axons.

Recognized disorders congenital ptosis, congenital fibrosis of the extraocular muscles, Duane’s syndrome and its variants, Möbius sequence, horizontal gaze palsy with progressive scoliosis, and congenital facial palsy. They present with varying degrees of ptosis and ophthalmoplegia from birth, together with signs of aberrant innervation. Many of these disorders were previously considered to be myopathic in origin. However, the congenital cranial dysinnervation disorders also include sensory disorders due to trigeminal nerve maldevelopment that cause congenital corneal anesthesia.
**Congenital Ptosis**

Our long-standing understanding of congenital ptosis as a primary myopathy has been overturned, as clinical signs of congenital cranial dysinnervation have been demonstrated. The notion of congenital ptosis as a primary myopathy was first challenged in 1996 when Steel and Harrad found an unrecognized form of oculomotor synkinesis in 44% of patients with unilateral congenital ptosis. Affected patients displayed excessive elevation of the ipsilateral eye beneath the ptotic eyelid in upgaze, but no vertical deviation in primary gaze. This upshoot disappeared when the ptotic eyelid was manually elevated. The authors insightfully attributed this phenomenon to a misdirection of levator innervation to the ipsilateral superior rectus muscle. They proposed that manual elevation of the ptotic eyelid reduced innervation to the levator muscles, thereby extinguishing the aberrant superior rectus innervation.

In 2000, Harrad and Shuttleworth described another group of patients with long-standing unilateral ptosis that resolved in upgaze and increased in downgaze, suggesting that superior rectus innervation had become misdirected to a paretic levator muscle. These clinical observations suggest that prenatal and postnatal routing of the superior division of the oculomotor nerve is a delicate process that may be subject to directional modification, perhaps on the basis of the relative innervational recruitment by its two target muscles.

For reasons that are unclear, an inverse Bell’s phenomenon (unilateral or bilateral) is occasionally observed postoperatively following levator resection. This phenomenon reverts to normal within 2 weeks.

Congenital ptosis may be associated with other forms of ocular motor synkinesis. Khan et al described a large family in which two siblings exhibited ptosis with abnormal synkinetic elevation on ipsilateral abduction. One was bilaterally affected, while the other had unilateral findings. A third demonstrated classic bilateral congenital ptosis, while a fourth demonstrated Duane’s syndrome. Its association with congenital fibrosis syndrome is detailed below. Indeed, congenital ptosis can now be viewed as a limited form of congenital fibrosis syndrome selectively affecting the superior division of the third nerve. Several genes for isolated congenital ptosis have now been identified.

**Marcus Gunn Jaw Winking (Trigemino-Oculomotor Synkinesis)**

A normal synkinesis denotes simultaneous contraction of muscles normally innervated by different peripheral nerves or different branches of the same nerve. A pathologic synkinesis occurs when muscles are reinnervated by nerves other than their own following a nerve injury. Pathologic synkinesis may be congenital (Duane’s syndrome, synergistic divergence, Marcus Gunn jaw winking) or acquired (facial synkinesis or oculomotor synkinesis after trauma).

The Marcus Gunn jaw winking (MGJW) synkinesis usually presents as variable unilateral ptosis noted at birth or shortly thereafter. Unlike ordinary congenital ptosis, when the infant nurses, the ptotic lid jerks upward with each sucking movement. In a series of nearly 1,500 cases of congenital ptosis, the Marcus Gunn phenomenon accounted for 80 patients (5%). Of these 80 patients, 42 showed right eye involvement, 35 showed left eye involvement, and three had bilateral synkinesis. No gender preponderance was identified, and only two cases were familial. Fifty-four percent of patients showed amblyopia, and 26% showed anisometropia. Some form of strabismus was found in 56%, including 19 cases of superior rectus palsy, 19 cases of double elevator palsy, and two cases of Duane’s retraction syndrome. The natural history of the disorder remains unsettled, with some authors noting that the synkinetic movement becomes less conspicuous with age, although patients may learn to camouflage the lid excursions.

The pathogenesis of the MGJW synkinesis is controversial. The prevalent concept is that the disorder results from aberrant innervation of the levator palpebrae muscle by a branch of the motor division of the trigeminal nerve that supplies the muscles of mastication, hence the designation *trigemino-oculomotor synkinesis*. However, Sano has presented EMG evidence that the jaw winking phenomenon is a release phenomenon representing an exaggeration of a normally found but clinically undetectable physiologic cocontraction. Utilizing EMG studies of normal subjects, he demonstrated cofiring of the oculomotor-innervated extraocular muscles and the muscles of mastication innervated by the motor branch of the trigeminal nerve. He argues that congenital brainstem lesions may “release” phylogenetically older neural mechanisms, such as synkinetic movements from higher central control, which are similar to other synkinetic movements such as the palmomental and primitive grasp-feeding reflexes.

Muller’s muscle is doubly innervated by an efferent sympathetic nerve and an afferent proprioceptive nerve. Muller’s muscle acts as a serial muscle spindle (similar to that seen in jaw closing periodontal receptors). Stretching of Muller’s muscle has been found to produce involuntary levator muscle contraction (the Hoffman reflex). These proprioceptive fibers function as mechanoreceptors to induce reflex contracture of the levator muscle against gravity as a type of length servomechanism. The central modulation of these levator and jaw closing pathways by motor trigeminal
nucleus may give rise to the innervational crossover that manifests in the form of Marcus Gunn jaw winking.534

Sano672 has classified the trigemino-ocular motor synkinesis into two major groups: (1) external pterygoid-levator synkinesis (the most common type) with lid elevation upon thrusting the jaw to the opposite side (ipsilateral external pterygoid firing), upon projecting the jaw forward (both external pterygoids firing), or upon opening the mouth widely; and (2) internal pterygoid-levator synkinesis (relatively rare) with lid elevation upon teeth clinching.

In the typical case of MGJW, firing of the motor branch of the trigeminal nerve is associated with firing of the oculomotor branch to the levator. A rare variant of this phenomenon, termed the inverse Marcus Gunn phenomenon,504 shows firing of the motor branch of the trigeminal nerve synkinetically, with inhibition of the oculomotor branch to the levator. Here, the affected eyelid falls as the mouth opens or as the jaw moves to the opposite side, without associated activity of the orbicularis oculi.

Pathologic synkineses may cluster together. For instance, the MGJW synkinesis (congenital trigemino-oculomotor synkinesis) has been reported in association with Duane’s syndrome (congenital oculomotor-abducens synkinesis) and with synergistic divergence.120,337 This association generally occurs in the setting of congenital fibrosis syndrome.304,120,337 Other forms of ocular motor synkinesis have also been reported in patients with Marcus Gunn jaw winking. “Eye bobbing” was attributed to coactivation of the superior rectus muscle in one patient with Marcus Gunn jaw winking.603 Trigemino-abducens synkinesis444,466 and pseudo-inferior oblique muscle overaction have also been described.387

A frontalis suspension operation is usually recommended for cases severe enough to come to surgery. Some controversy exists regarding whether to disinsert the ipsilateral levator and whether to also disinsert the contralateral levator and perform a frontalis suspension on the opposite side to achieve a greater degree of symmetry.

**Congenital Fibrosis Syndrome**

Congenital fibrosis of the extraocular muscles (CFEOM) is characterized by the presence of congenital restrictive ophthalmoplegia, fixed downgaze, horizontal strabismus, ptosis, and a compensatory backward tilting of the head.751 In this disorder, the extraocular muscles and the levator muscles are replaced by fibrous tissue to a variable extent.350 The disorder may be unilateral or bilateral and may be clinically limited to specific muscles in a given individual. The resultant ocular motility deficits depend on which of the extraocular muscles are involved. The inferior rectus muscle is most commonly involved, followed by the levator muscle and the lateral rectus muscle. In the presence of ptosis, inferior and lateral rectus muscle involvement may mimic unilateral or bilateral congenital oculomotor palsy. Rarely, all of the extraocular muscles, including the levator, are affected (generalized fibrosis syndrome). Historically, investigators have divided congenital ocular fibrosis into different subtypes that include congenital fibrosis of the inferior rectus with ptosis, strabismus fixus, congenital unilateral enophthalmos with ocular muscle fibrosis and ptosis,362 and the vertical retraction syndrome.

Fixed downgaze and associated ptosis with sparing of pupillary function and similar findings in other family members provide critical clues to the diagnosis. Patients with CFEOM may show rapid convergent movements of the eyes on attempted upgaze, simulating convergence retraction nystagmus.104 The diagnosis of CFEOM should therefore be suspected when “convergence-retraction” nystagmus is accompanied by ptosis rather than lid retraction. Although this phenomenon could theoretically result from the mechanical tethering effect of tight inferior rectus muscles in attempted upgaze, the fact that these convergent movements persist following recession of the inferior rectus muscles suggests that they arise from a supranuclear deficiency of elevation, as suggested by several investigators.1,78,168,262

CFEOM has traditionally been regarded as a primary myopathy localized to the extraocular muscles on the basis of biopsy studies of affected muscles. Both light and electron microscopy studies show replacement of extraocular muscles by dense fibrous connective tissue and collagen.350 Histology of an affected levator showed reduction or absence of striations and Z bands and vacuolation of muscle cells. Muller muscle fibers appeared intact. Anomalous insertions of affected muscles may occur, presumably resulting from a maturational defect at or before the seventh week of gestation.29 Involved eyes may also have anomalous adhesions between the muscles, Tenon’s capsule and globe, and inelasticity or fragility of the conjunctiva so that conjunctival recession may also be necessary.266,487 Like in Duane syndrome, the involved extraocular muscles in congenital fibrosis syndrome are simultaneously tight and hypoplastic. Affected muscles often appear small and atrophic on orbital imaging studies.805

On the basis of the presence of multiple synkinetic eye movements in a patient with CFEOM, Brodsky et al, in 1989, proposed that is caused by failure of normal neuronal connections with the extraocular muscles to become established early in embryogenesis.120 Assaf independently concluded that congenital fibrosis syndrome must arise from a CNS abnormality.120,168 Our subsequent report of additional patients with CFEOM, who displayed both synergistic divergence and MGJW,120,337 provided clear evidence that congenital fibrosis of the extraocular muscles can result from the absence of normal innervation to orbital striated muscles early in development (Fig. 7.15). Unlike the synergistic divergence of Duane syndrome, the paradoxically abducting eye simultaneously abducted and depressed, suggesting that the synergistic divergence was attributable to aberrant innervation of the superior oblique muscle. A primary failure to establish normal neuronal connections with the extraocular muscles and levator muscle...
would predispose to neuronal misdirection, which allows for limited preservation of innervated muscle fibers and replacement of the remaining muscle by fibrous tissue. Clinically, only deficient innervation could explain the superimposition of synkinetic eye movements on a diffuse congenital ophthalmoplegia. Other forms of aberrant innervation have since been documented in CFEOM.

A neuropathologic study by Engle et al. demonstrated that congenital fibrosis of the extraocular muscles is associated with abnormal development of the oculomotor axis, primarily affecting the superior division of the oculomotor nerve, corresponding to alpha motoneurons in the midbrain, the target extraocular muscles, and the levator and superior rectus muscles. This study established that CFEOM can result from the failure of developing cranial nerves to form appropriate neuromuscular connections with their target extraocular muscles, a finding supported by subsequent genetic studies.

Because most patients with CFEOM do not display signs of neuronal misdirection, and because anomalous fibrous bands and adhesions are sometimes discovered to be attached to the globe during strabismus surgery, we now suspect that the genetically determined dysgenesis of CFEOM can directly influence the extraocular muscles, in addition to developing cranial nerves. It is therefore likely that the underlying pathophysiology of congenital fibrosis syndrome must lie along a spectrum from a primary absence of normal innervation to localized orbital dysgenesis of the extraocular muscles.

Neuroanatomic abnormalities are often missed on routine intracranial MR imaging, which frequently shows no overt

Fig. 7.15 Congenital fibrosis syndrome with synergistic divergence (simultaneous abduction during attempted lateral gaze) and Marcus Gunn jaw winking. (a) Bilateral ptosis, exotropia, and fixed downgaze. (b) Retraction of the right upper eyelid with mouth opening. (c) Position of the eyes with eyelids manually elevated. (d) In attempted left gaze, the right eye abducts and depresses. From Brodsky with permission.
structural malformations of the brain. However, high-resolution images of the ocular motor nerve commonly show hypoplasia or absence of the oculomotor nerves and involved extraocular muscles (Fig. 7.16).

To date, three genetic CFEOM loci have been identified and three clinical phenotypes have been delineated. The most common form is CFEOM1, with bilateral nonprogressive ophthalmoplegia, bilateral ptosis, and an infraducted (downward) primary position of each eye with limited supraduction. CFEOM1 pedigrees demonstrate autosomal dominant inheritance with full penetrance and minimal variation in expression. CFEOM1 has been mapped to the centromeric region of chromosome 12. It has now been demonstrated that congenital fibrosis of the extraocular muscles type 1 results from heterozygous mutations in the KIF21A gene encoding a kinesin motor protein. Although the specific function of the KIF21A protein and its stalk are yet to be determined, the mouse ortholog, KIF21a, was found to be an anterograde microtubule-based motor protein expressed predominantly in neuronal tissues. Engle et al have found that human KIF21A is expressed most abundantly in developing neural tissues, suggesting that it plays an important role in neuronal development consistent with the congenital fibrosis of the extraocular muscles 1 phenotype.

CFEOM2 is autosomal recessive, and its gene is localized on chromosome 11q13.1. CFEOM2 patients have bilateral ptosis and restrictive ophthalmoplegia, with eyes partially or completely fixed in an exotropic position. Patients have severely limited ability to depress or adduct either globe. ARIX, previously called PHOX2A, is the gene that is mutated in CFEOM2. ARIX is a transcription factor essential for the development of oculomotor and trochlear nuclei in mice and zebra fish. It is therefore believed that CFEOM2 results from hypoplasia of the oculomotor and trochlear nerve nuclei as a result of mutations in both copies of ARIX.

CFEOM3 is an autosomal dominant disorder with variable expression and probably incomplete penetrance. The gene maps to markers on 16p24.2-q24.3. Severely affected patients have ptosis, with eyes fixed in a downward and exotropic position and bilateral severe restriction of eye movements (a phenotype resembling that of congenital fibrosis of the extraocular muscles 1). Mildly affected patients have normally positioned globes, with limitation of vertical gaze. Moderately affected patients may have asymmetric involvement, with one eye severely affected and the other mildly affected. Mackey and colleagues reported a family that maps to the CFEOM3, with involvement primarily of the vertically acting extraocular muscles. Because the involved extraocular muscles are both tight and hypoplastic, the surgical management of congenital fibrosis syndrome presents a unique set of challenges. Free tenotomies obviate the need for suture placement into the rectus muscles, which can be technically difficult due to severe restriction. Free tenotomies of tight rectus muscles are technically simple and rarely produce surgical overcorrection. The need for resections can be determined by examining the position of the eyes under nondepolarizing paralyzing anesthesias. In our experience, raising the globe does not produce improvement in associated ptosis, so surgical correction of ptosis should be modest to avoid exposure keratopathy. Despite multiple surgeries, some degree of ocular misalignment usually persists.

Congenital Horizontal Gaze Palsy with Scoliosis

In 1974, Dretakis and Kondoyannis described the autosomal dominant syndrome of horizontal gaze palsy and progressive scoliosis. In 2004, Jen et al described 11 patients with autosomal recessive congenital horizontal gaze palsy caused by a mutation of the ROBO3 gene on chromosome 11. Affected children are born with absent horizontal eye move-
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ments and had variable strabismus, horizontal nystagmus, and defective vertical smooth pursuit. Convergence can be preserved, and some people use convergence substitution as a substitute for horizontal gaze. All patients developed progressive scoliosis during early childhood. The disorder is found in both consanguineous and nonconsanguineous families. Heterozygotes were unaffected. This disorder produces a pathognomonic brainstem malformation. MR imaging shows a hypoplastic pons and medulla, with overall diminished anterior–posterior dimension (Fig. 7.17). The ventral surface of the pons is flat. The medulla fans out both dorsally and ventrally in a butterfly configuration. There is a prominent midline cleft in the medulla that extends down to the cervicomedullary junction. Affected patients had electrophysiologic evidence of ipsilateral corticospinal and dorsal column-medial lemniscus tract innervation. In contradistinction to most other congenital cranial dysinnervation disorders, the abducens nerves are normal in size and configuration. ROBO3 mutations may disturb brainstem morphogenesis by failing to promote decussation of long motor and sensory tracts in the pons and medulla. Impaired decussation of pontine ocular motor pathways may explain the absence of horizontal eye movements in this disorder.

**Möbius Sequence**

Möbius sequence is a rare congenital disorder characterized by congenital facial weakness with horizontal gaze palsy or impairment of ocular abduction. Dysfunction of other cranial nerves, orofacial malformations, limb malformations, and musculoskeletal system defects are common associated features, but they are not obligatory for the diagnosis.

Möbius sequence is a sporadic multiple-malformation complex that affects the face and horizontal gaze mechanisms bilaterally. Affecte
difficult in children with Möbius sequence, owing to structural abnormalities of the mandible and palate.\textsuperscript{22}

Cardiovascular abnormalities (most commonly dextrocardia, patent ductus arteriosus, and ventricular septal defects), micrognathia, structural abnormalities of the pinna, and mild mental retardation and autism are also occasionally present.\textsuperscript{16,54,193,403,545,547} Other abnormalities can include an A-shaped mouth, lagophthalmos, a “hidden” smile and laughter, syndactyly, a hypoplastic, asymmetric tongue that cannot be protruded over the lips, and a groove over the midline of the tongue. The ocular abduction deficit may be caused by congenital horizontal gaze paresis, Duane’s syndrome, simple abducens palsy, or congenital fibrosis.\textsuperscript{781}

Children with Möbius sequence have difficulty relating to people in their environment because of an inability to convey their reaction of joy or sorrow. They are often incorrectly assumed to be mentally retarded and are predisposed to social and psychiatric problems.\textsuperscript{21a,547a,555} The successful management of Möbius sequence entails a multidisciplinary approach that includes the medical, speech, education, and mental health disciplines.\textsuperscript{16} Strabismus surgery can restore ocular alignment,\textsuperscript{718,777} and regional muscle transfer and microvascular free tissue transfer have been used to provide innervated dynamic muscle to restore facial movement.\textsuperscript{164,547,742} Because of their orofacial abnormalities, children with Möbius sequence are at higher risk of postoperative respiratory failure following general anesthesia.\textsuperscript{102}

Although Möbius sequence is now classified as one of the congenital cranial dysinnervation disorders, it is more than a cranial nerve or nuclear developmental disorder. Möbius sequence is a rhombencephalic developmental disorder with hypoplasia of the entire brainstem, including the traversing long tracts, and signs of neuronal degeneration and other congenital brain abnormalities.\textsuperscript{782} Neurophysiologic studies suggest dysfunction at infranuclear, nuclear, and supranuclear levels.\textsuperscript{148,779} Aberrant regeneration may contribute to the horizontal conjugate gaze paresis in some cases of Möbius sequence. The associated feeding and respiratory problems, along with poor motor development, are consistent with this hypothesis.\textsuperscript{781} Often, the clinical features (facial weakness and impairment of ocular abduction) are only the most salient clinical features of a more extensive developmental disorder with probably diverse pathogenetic mechanisms.

Neither etiology nor pathogenesis of this syndrome have yet been elucidated and are likely to be diverse in nature.\textsuperscript{780} Two major pathogenetic explanations have been suggested: a primary genetic cause, implying a maldevelopment of the brainstem, and a primary ischemic cause, possibly due to embryological or environmental toxic factors mediating an interruption in the blood supply of the brainstem during early embryonic development.\textsuperscript{781} These postulated pathogenetic mechanisms are based on a few postmortem observations, which include hypoplasia of the cranial nerve nuclei with or without active neuronal degeneration and focal necrosis with neuronal loss, gliosis, and calcifications in the brainstem.\textsuperscript{781} MR imaging shows brainstem hypoplasia when measuring the pons (Fig. 7.17), supporting the hypothesis that Möbius sequence is a developmental disorder of the entire lower brainstem\textsuperscript{604,612,780} with other cranial nerve aplasia.\textsuperscript{225} Absence of the facial nerves despite residual function in some facial muscles suggests that other cranial nerves may aberrantly innervate some of the facial muscles.\textsuperscript{780} The finding of crocodile tears in patients with Möbius sequence also supports this association. A variant of Möbius sequence with normal brainstem anatomy has recently been recognized.\textsuperscript{225}

Some investigators have suggested that ischemia of the lower cranial nuclei due to an insufficient blood supply in the pontine branches is the cause of Möbius sequence.\textsuperscript{80,226} Intrauterine brainstem infarction could result from premature regression or obstruction of the primitive trigeminal arteries before the establishment of a sufficient blood supply from the vertebral arteries, which may explain the variability in clinical expression.\textsuperscript{16} Brainstem calcifications, which have been attributed to vascular insufficiency,\textsuperscript{16,219} are not indicative of a specific mechanism and could equally support a maldevelopmental pathogenesis.\textsuperscript{782} Neuropathologic studies have emphasized the presence of brainstem atrophy and/or necrosis in Möbius sequence.\textsuperscript{188} Patients with Möbius sequence are predisposed to primary respiratory failure and recurrent apnea, which correlates with both tectal necrosis with calcifications and marked brainstem hypoplasia at autopsy. The association of Möbius sequence with thalidomide embryopathy and misoprostol exposure\textsuperscript{191,518,774} demonstrates that early embryonic exposure to teratogens may produce a similar malformation complex.\textsuperscript{143a} Möbius sequence is usually considered sporadic, however, rare instances of autosomal dominant, autosomal recessive, and X-linked recessive inheritance have been reported. Cytogenetic studies have suggested two loci for Möbius sequence: 1p22 and 13q12.2-13.\textsuperscript{782}

**Monocular Elevation Deficiency, or “Double Elevator Palsy”**

“Double elevator palsy” is a descriptive term denoting a congenital deficiency of monocular elevation that is equal in abduction and adduction. Generally speaking, an inability to elevate one eye may occur on a restrictive or paretic basis and may be congenital or acquired. The patient or his family frequently reports that one eye shoots up and disappears under the upper eyelid while, in fact, the contralateral eye is the one with abnormal motility. The patient frequently has associated hypotropia and ptosis or pseudoptosis. The term “double elevator palsy” was originally coined to reflect what was then thought to be the basis for the disorder, namely, con-
genital palsy of the ipsilateral inferior oblique and superior rectus muscles, a concept that has since been abandoned. It has since become apparent that the concomitant limited elevation, very characteristic of double elevator palsy, may result from at least three disparate pathophysiologic disorders, namely, inferior rectus restriction, superior rectus paresis, and a supranuclear disturbance of monocular elevation. In truly paretic cases, dual palsy of the inferior oblique and superior rectus muscles does not occur; paresis of the superior rectus muscle alone (the dominant elevator of the globe) is sufficient to produce the clinical picture. The term monocular elevation deficiency is a more accurate descriptive term.

The monocular elevation deficiencies undoubtedly overlap with the congenital cranial dysinnervation syndromes (discussed below). Several large series have shown that most patients with monocular elevation deficiency have a restrictive abnormality to elevation. Some of these cases represent unilateral inferior rectus muscle fibrosis, which can present with a tight inferior rectus muscle, hypotropia, and secondary ptosis in CFEOM3. Congenital inferior rectus fibrosis and neurogenic double elevator palsy may closely mimic each other because both may exhibit defective elevation associated with ptosis or pseudoptosis. Conversely, a long-standing hypotropia associated with neurogenic double elevator palsy may result in secondary contracture of the inferior rectus muscle and cause a positive forced duction test. Similar cases of inferior rectus tightness may result from perinatal orbital trauma.

The diagnosis of contralateral superior oblique palsy should be considered in any child who has a monocular elevation deficiency, because fixation with the “paretic eye” can produce a contralateral inferior rectus contracture. Other conditions to be considered include orbital blowout fractures and orbital fat adherence syndrome. Patients with inferior rectus restriction due to orbital blowout fracture may also show a component of inferior rectus paresis.

On the basis of studies utilizing scleral search coil techniques, Ziffer et al. suggested the existence of at least three distinct etiologic categories: primary inferior rectus restriction, primary superior rectus palsy, and congenital supranuclear elevation defects. The inferior rectus restriction may be present primarily or may secondarily result from long-standing superior rectus weakness. Examination for the status of Bell’s phenomenon and other reflex upward movements is very useful. An intact Bell’s phenomenon, or the ability to produce an upward movement of the eye with the oculocephalic maneuver, suggests a supranuclear disturbance. An absent Bell’s phenomenon would indicate either inferior rectus restriction or superior rectus palsy. The two can be distinguished by saccadic velocity analysis, forced ductions, and active force generation. If restriction is absent and the eyes are orthotropic in the primary position, a superior rectus paresis is most unlikely, and a supranuclear disturbance is inferred. Scott and Jackson have noted that the appearance of an accentuated lower lid fold on attempted upgaze predicts the presence of an inferior rectus contracture.

While the location of the “lesion” in the restrictive variety of the monocular elevation deficiency is readily apparent, generally pointing to tightness in the inferior rectus muscle complex, the location of a lesion in the other two classes of the monocular elevation deficiency is not as well determined. Cases resulting from isolated superior rectus weakness could theoretically result from disorders, affecting the muscle or its nerve supply anywhere from the superior rectus subnucleus to the orbit. Congenital absence of the superior oculomotor division could produce double elevator palsy with hypotropia and neurogenic ptosis. Hoyt described a patient who developed sudden monocular elevation deficit and features of superior rectus paresis, which he attributed to superior rectus subnucleus infarction precipitated by coexisting polycythemia vera. Mather and Saunders reported a case of bilaterally absent superior rectus muscles.

As oculomotor fascicular fibers destined to the elevators of the eye and eyelid are believed to course laterally in the fascicle as it traverses the midbrain, a midbrain infarction involving a lateral portion of the oculomotor fascicle can cause an acquired unilateral ptosis and elevation deficit. A congenital lesion at this location could theoretically explain the paretic infranuclear form of monocular elevation deficiency. MR imaging has shown hypoplasia of the involved superior rectus muscle in one case, and focal thickening of the inferior rectus in another. However, the absence of these findings on neuroimaging in the great majority of cases support a prenuclear deficit in the unilateral center for upgaze.

Olson and Scott noted that 9 of 31 patients with monocular elevation deficiency had dissociated vertical divergence manifesting in the affected eye. The findings of Bell’s phenomenon, dissociated vertical divergence, normal velocity of upgaze saccades when moving from a downward to primary position, negative Bielschowsky Head Tilt test, and elevation during stage II of general anesthesia provide evidence of a supranuclear etiology.

Supranuclear disturbances of monocular eye movements are rare. The neuroanatomic substrate of unilateral supranuclear upgaze deficiency is controversial. It has been attributed to either lesions of the contralateral pretectum or lesions involving the upgaze efferents from the ipsilateral rostral interstitial nucleus of the medial longitudinal fasciculus. Most reports have been in adults in association with metastatic tumors. Lessell reported a man with bronchogenic carcinoma who developed left monocular elevation deficit, but with orthotropia in primary position and an intact Bell’s phenomenon. A metastatic tumor was found in the right pretectum at autopsy, which was speculated to have caused the double elevator palsy by interrupting axons destined for the ipsilateral superior rectus subnucleus and the contralateral
inferior oblique subnucleus. Ford et al\textsuperscript{274} described a 52-year-old woman who developed right monocular elevation paresis who was demonstrated to have a focal, right-sided tumor of the mesodiencephalic junction in the region of the riMLF. Acquired unilateral double elevator palsy has been described in a child with a pineocytoma.\textsuperscript{570} The most recent evidence incriminates a lesion of the vertical saccadic burst or pause neurons of the riMLF. A genetic factor is suggested by the finding of identical twins concordant for supranuclear double elevator palsy on the same side, with preservation of Bell’s phenomenon.\textsuperscript{62}

The possible neuroanatomic origins of monocular elevation deficit are summarized in Table 7.9. Patients with superior oblique palsy who habitually fixate with the paretic eye may present with limited monocular elevation of the contralateral (hypotropic) eye due to inhibitory palsy of the contralateral antagonist.\textsuperscript{290} This so-called “fallen eye syndrome” may lead to a contralateral inferior rectus contracture and thereby cause a monocular elevation deficiency. The correct diagnosis may be inferred by the three-step test and the comparison of ductions to versions. Cases of vertical retraction syndrome, wherein congenital unilateral restriction of elevation is associated with retraction of the globe and narrowing of the palpebral fissure,\textsuperscript{683} have been speculated to arise from a vertical innervational misdirection similar to that observed in Duane’s syndrome and in some cases of congenital fibrosis syndrome.\textsuperscript{291}

The association of an isolated monocular elevation deficiency with congenital ptosis in general, and MGJW in particular, implies that aberrant misdirection may play a role in the pathogenesis of some cases of double elevator palsy.\textsuperscript{619} Undoubtedly, a subgroup of patients with monocular elevation deficiency fall into the classification of congenital cranial dysinnervation syndromes (discussed below). This view is supported by reports showing that the superior rectus muscle itself may be involved in the aberrant phenomenon. For example, Oesterle et al\textsuperscript{603} described a 9-month-old infant with congenital ptosis without jaw winking who showed an up-and-down movement of the left eye synchronous with jaw movements of the jaw. A 5-year-old girl with left ptosis, jaw winking, and left double elevator palsy showed up-and-down movements of the left upper lid and the left eye synchronous with chewing. The eye movements persisted after levator excision and fascia lata sling procedures. The authors speculated that the up-and-down eye movements probably represented aberrant innervation of the superior rectus muscle in a manner analogous to the abnormal innervation of the levator muscle in MGJW.

Surgical treatment consists of inferior rectus recession (in cases with a positive forced duction test),\textsuperscript{690} partial or full tendon width transpositions of the horizontal rectus muscles (in cases with a negative forced duction test),\textsuperscript{141,227,349,441} or innervation surgery with large recession of the contralateral superior rectus muscle (in cases with a negative forced duction test and some residual supraduction).\textsuperscript{620} Newer modifications of this procedure may include posterior fixation sutures to the transposed muscles and placement posterior fixation sutures on the normal superior rectus muscle.\textsuperscript{709}

Inferior rectus recession alone or in combination with other procedures ameliorates the restrictive variety of double elevator palsy. Treatment of neurogenic double elevator palsy includes conventional vertical rectus muscle surgery (recess and/or resect) and vertical transposition of the tendons of the medial rectus-lateral rectus superiorly (Knapp procedure).\textsuperscript{135} The pseudoptosis disappears on correction of the vertical deviation, and any residual true ptosis can be addressed after ocular alignment is optimized.\textsuperscript{542}

### Brown Syndrome

Brown syndrome can be distinguished from double elevator palsy by its increasing limitation of elevation in the adducted position.\textsuperscript{808a} Brown syndrome must also be distinguished from the much less common inferior oblique palsy by the presence of little or no associated superior oblique overaction, a Y-pattern producing exotropia in extreme upgaze, and a positive forced duction test. Brown syndrome results from a congenital or, less commonly, an acquired dysfunction involving the trochlear-superior oblique tendon complex.\textsuperscript{808a} Either form may be constant or intermittent (Fig. 7.19). Intraoperative forced duction testing can help distinguish an inferior rectus restriction from a severe Brown syndrome. Retropulsion of the globe into the orbit while performing forced supraductions reduces or eliminates an inferior rectus restriction, but exacerbates tightness due to Brown syndrome. Pulling on the globe does the opposite. Many acquired and some congenital cases of Brown syndrome improve spontaneously so that a conservative approach is reasonable. It has recently been argued that congenital superior oblique palsy with misinnervation to the medial or inferior rectus muscle can produce a motility pattern that is indistinguishable from Brown’s syndrome due to a tight superior oblique tendon.\textsuperscript{447}

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**Table 7.9** Neuroanatomic differential diagnosis of monocular elevation deficiency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Absence or hypoplasia of the superior rectus</td>
<td>Absence of muscle innervation</td>
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<tr>
<td>(e.g., Crouzon’s disease)</td>
<td></td>
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<tr>
<td>Inferior rectus contracture (e.g., congenital</td>
<td>Inferior rectus contracture</td>
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<tr>
<td>fibrosis syndrome, “fallen eye syndrome”)</td>
<td></td>
</tr>
<tr>
<td>Lateral oculomotor fascicular lesion</td>
<td>Lateral oculomotor fascicular lesion</td>
</tr>
<tr>
<td>Superior division oculomotor paresis</td>
<td>Superior division oculomotor paresis</td>
</tr>
<tr>
<td>Superior rectus myoneural junction disease (e.g., myasthenia gravis)</td>
<td>Superior rectus myoneural junction disease</td>
</tr>
<tr>
<td>Superior rectus subnucleus lesion</td>
<td>Superior rectus subnucleus lesion</td>
</tr>
<tr>
<td>Supranuclear lesion</td>
<td>Supranuclear lesion</td>
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</table>
Although classically viewed as a restriction syndrome, Neugebauer and colleagues have argued that Brown syndrome may be a congenital cranial dysinnervation syndrome.\textsuperscript{577} Using high-resolution dynamic MR imaging, Kolling and colleagues demonstrated absence of the fourth nerve within the orbit and hypoplasia of the superior oblique muscle on the affected side in patients with Brown syndrome.\textsuperscript{447} They have suggested that reinnervation of a paretic superior oblique muscle by branches from the medial or inferior rectus muscles can produce a motility pattern that is indistinguishable from Brown’s syndrome due to a tight superior oblique tendon.\textsuperscript{447}

Treatment is undertaken for persistent cases with significant strabismus in the primary position and/or a significant compensatory anomalous head position. Superior oblique weakening (tenotomy or placement of a silicone spacer to lengthen the tendon)\textsuperscript{818} with or without inferior oblique weakening, is the treatment of choice in persistent congenital or idiopathic acquired cases with symptomatic diplopia or marked compensatory chin elevation. Local corticosteroid injections around the trochlea may be helpful in acquired inflammatory cases. The occurrence of Brown’s syndrome in multiple siblings\textsuperscript{331} and in monozygotic twins\textsuperscript{617} supports a genetic basis in some cases. Causes of acquired Brown syndrome include trauma, a rheumatoid nodule in the vicinity of the trochlea, peribulbar anesthesia, blepharoplasty, pansinusitis, frontal sinus osteoma, metastatic lesions, localized inflammation (orbital pseudotumor), surgical manipulation in the area of the trochlea, and surgical tucking of the superior oblique tendon.

**Other Pathologic Synkineses**

Physiological synkineses are well-recognized. Opening the mouth causes the eyes to simultaneously open, a reflex that is useful in the ocular examination of children. In the less known \emph{oculo-auricular phenomenon}, horizontal gaze evokes a synkinetic retraction of the external ear muscles.\textsuperscript{808} Curling of both auricles during strong lateral gaze is said to be present in 40\% of the normal population.\textsuperscript{265,808} This reflex is seen more easily in people who have prominent ears.\textsuperscript{765}

As discussed in Chap. 6, other forms of ocular motor synkineses can occur in isolation or cluster together. A trigeminino-abducens synkinesis may occur after trauma, and facial synkineses is a common finding after facial nerve palsy. It should be noted that various forms of aberrant innervation have been reported in the thalidomide embryopathy, especially Duane’s retraction syndrome and aberrant lacrimation\textsuperscript{544} (crocodile tears). Platysma-levator synkinesis has been documented in a child with congenital third nerve palsy, demonstrating the potential for aberrant regeneration from a portion of the facial nerve.\textsuperscript{102}

Rarely, deglutition-trochlear synkinesis may be noted\textsuperscript{526} with the affected patient showing torsional diplopia associated with swallowing. This phenomenon suggests a synkinetic movement coupling the trochlear nerve with the bulbar musculature that is innervated by the trigeminal, facial, and hypoglossal nerves. Boehme and Graef described a 10-year-old boy with a right-sided Horner’s syndrome and a paresis of the recurrent laryngeal nerve, following neuroblastoma resection, whose right pupil distorted into an oval shape when he swallowed.\textsuperscript{77} They postulated that aberrant vagal sprouts had established connections with the cervical sympathetic chain.

Some phenomena resemble synkinetic movements, but are difficult to explain on the basis of aberrant reinnervation. In some patients, voluntary gaze may evoke such phenomena as vertigo, tinnitus, blepharoclonus, eyelid nystagmus, eyelid closure, facial twitching, arm movements, or seizures.\textsuperscript{226,693,789,790} The pathogenesis of these “synkinetic” movements is unclear, but has been speculated to involve ephaptic transmission.\textsuperscript{893} Gaze-evoked upper lid jerks (lid nystagmus) may also be seen in patients with Fisher’s syndrome.\textsuperscript{666} and in patients with midbrain pseudomyasthenia (e.g., due to mesencephalic astrocytoma).\textsuperscript{114}

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**Fig. 7.19** Intermittent Brown syndrome: Teenager complained of intermittent diplopia. On attempted gaze up and to his left, full ocular ductions and versions were noted on some trials (a), but intermittently, right eye failed to elevate in adduction (b)
Internuclear Ophthalmoplegia

The hallmark of internuclear ophthalmoplegia (INO) is weakness or absence of adduction in one or both eyes on lateral gaze, with nystagmus in the abducting eye.\textsuperscript{381,706,834} Despite this adduction limitation, the eyes remain orthotropic in the primary position. The adduction weakness may be profound and quite noticeable on testing of ocular ductions and versions or may be so subtle as to be discernible only by noting slow adducting saccades in the affected eye. Refixation from abduction to primary position causes the contralateral eye to momentarily overshoot the target.\textsuperscript{707} The slow, floating nature of the adducting saccades can be effectively elicited by having the patient fixate an optokinetic nystagmus target moving temporally with respect to the eye with limited adduction, which elicits a dysconjugate horizontal nystagmus of greater intensity in the abducting eye.\textsuperscript{707}

Convergence is usually preserved, except in rostral cases that simultaneously affect the medial rectus subnucleus. However, decreased convergence in the setting of bilateral INO with multiple sclerosis may be due to central scotomas caused by optic atrophy, as opposed to a primary convergence disorder. Older children may complain of diplopia. A skew deviation often accompanies unilateral INO, while vertical upbeat nystagmus in upgaze often accompanies bilateral INO. Unlike most forms of skew deviation in which the lower eye is ipsilateral to the lesion, the higher eye is usually on the same side of the lesion in patients with INO. As INO resolves, the clinical picture evolves from absent or decreased adduction to slow adduction to normal-appearing adduction with retention of the abducting nystagmus (i.e., abducting nystagmus is the last to resolve).

Internuclear ophthalmoplegia signifies intrinsic brainstem disease involving the pons or midbrain.\textsuperscript{706} It results from injury to axons that originate from interneurons in the abducens nucleus and project via the medial longitudinal fasciculus to the contralateral medial rectus subnucleus of the oculomotor nuclear complex. A number of mechanisms have been suggested to explain the dissociated nystagmus in the abducting eye.\textsuperscript{836} One popular explanation suggests that increased innervation to the medial rectus to overcome the adduction weakness is accompanied, under the influence of Hering’s law of equal innervation, by a commensurate increase in the innervation to the normal lateral rectus muscle of the contralateral eye. While increased innervation to the paretic medial rectus muscle would improve adduction, the increased innervation to the normal lateral rectus of the other eye would result in adducting saccadic overshoot followed by backward post-saccadic drift. This mechanism is supported by the observation that abducting nystagmus may also be noted in patients with adduction weakness resulting from medial rectus muscle recession.\textsuperscript{786}

Other mechanisms invoke the possibility that the abducting nystagmus may result from: (1) increased convergence tone to improve adduction of the weak eye; (2) interruption of descending internuclear neurons that run in the medial longitudinal fasciculus from the oculomotor internuclear neurons to the abducens nucleus; (3) associated injury to fibers other than those of the medial longitudinal fasciculus; and (4) an associated gaze-evoked nystagmus, with the component of the nystagmus expected in the adducted eye being dampened by the coexisting adduction paresis.\textsuperscript{481,834}

In unilateral cases, diplopia in the primary position is often vertical rather than horizontal and is attributable to a concurrent skew deviation. It can be eliminated with two to three prism dipters of vertical prism incorporated into glasses. Nystagmus and oscillopsia may complicate bilateral cases. The oscillopsia is a result of deficient vertical vestibulo-ocular reflex and pursuit movements or the abduction nystagmus. The role of strabismus surgery in selected patients has been recently analyzed.\textsuperscript{683}

A lesion, encompassing both the medial longitudinal fasciculus and the ipsilateral PPRF or the abducens nucleus, results in an ipsilateral horizontal gaze palsy and an INO. The only preserved horizontal movement is abduction of the contralateral eye. This constellation of findings is called the “one-and-one-half syndrome.” Bilateral INO with unilateral abducens paresis gives a similar motility deficit. The one-and-one-half syndrome has a similar spectrum of causes as INO.

In premature infants, one occasionally notes large-angle exotropia with decreased or no response of the medial rectus to vestibular manipulations with rotation or caloric. This has been interpreted as possible bilateral INO, suggesting a maturational delay in the development of the medial longitudinal fasciculus. Such exotropia has a good prognosis for spontaneous ocular alignment as the medial longitudinal fasciculus matures, compared to the constant large-angle exotropia of infancy that shows no evidence of adduction weakness.\textsuperscript{385} This latter variety is usually observed in the setting of neurologic disease, but a subset is seen in otherwise healthy infants in a manner analogous to congenital esotropia. Duane type 2 syndrome, medial rectus entrapment in a nasal orbital wall fracture with associated paresis, myasthenia gravis, and Fisher syndrome may produce a similar motility pattern and must be excluded.

Causes of INO in infants and children include demyelinating disease, stroke, brainstem tumors (particularly pontine glioma),\textsuperscript{180} vasculitis,\textsuperscript{439} inborn errors of metabolism, parainfectious encephalitis, structural malformations (Chiari malformation),\textsuperscript{816} drug intoxication,\textsuperscript{218,644} \(\text{B}_12\) deficiency,\textsuperscript{13} and trauma. Bilateral INO may be accompanied by exotropia, bilateral ptosis, and supraduction deficits in the midline mesencephalic cleft syndrome.\textsuperscript{311,465} Another increasingly
Cyclic, Periodic, or Aperiodic Disorders Affecting Ocular Structures

A number of heterogeneous ocular disorders have in common a cyclic, periodic, or aperiodic pattern, that is, an involuntary process that repeats over time (Table 7.10). A major lesson to be learned from these cyclic phenomena is the importance of observing certain ocular disorders over time. The nature of the cyclic phenomenon and the duration of a complete cycle define each disorder.

Cyclic esotropia is a relatively rare condition that is also referred to as alternate day, circadian, or clock-mechanism esotropia. The designation “circadian,” which denotes a 24-h cycle, is a misnomer because the usual cycle duration is 48 h. The typical case shows a 24-h period of manifest esotropia measuring 40–50 prism diopters, alternating with a 24-h period of normal ocular alignment (Fig. 7.20). Less common are cycles of 24, 72, or 96 h in duration. The esotropia is nonaccommodative and nonparalytic, with normal eye movements in both eyes when straight and also when esotropic. On days when the eyes are crossed, diplopia is rare, fusional amplitudes are defective or absent, and sensory anomalies are frequent. Whether other cyclic phenomena occur in association with this condition is debatable. Friendly et al monitored numerous psychological and physiologic functions and found no associated cyclical phenomenon. In contrast, Roper-Hall and Yapp described cyclical changes in behavior, frequency of micturition, and EEG activity.

Cyclic esotropia may first appear in infancy, but the diagnosis may be delayed months to years, with the average age at diagnosis ranging from 2 to 4 years, although some cases may occur abruptly in adulthood. Generally, the condition occurs spontaneously without apparent cause, but may be precipitated by strabismus surgery, retinal reattachment surgery, ocular trauma, optic atrophy, or CNS disease. The natural history of this condition is not definitively known, but the cyclicity is thought to diminish with time, leading to a constant esotropia after several months to years. The mechanism of cyclic esotropia remains unknown, and no correlative abnormalities of the hypothalamic pituitary axis have been found. Some cases are associated with neurologic disease. One case was triggered by traumatic sixth nerve palsy, and one by surgery for intermittent exotropia. These reports suggest that patients

Table 7.10 Cyclic, periodic, or aperiodic disorders affecting ocular structures

<table>
<thead>
<tr>
<th>Disorder</th>
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<tr>
<td>Alternating anisocoria</td>
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<tr>
<td>Cyclic esotropia</td>
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<tr>
<td>Cyclic superior oblique palsy</td>
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<tr>
<td>Cyclic vertical deviation</td>
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<tr>
<td>Migrating pupil</td>
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<tr>
<td>Oculomotor palsy with cyclic spasm</td>
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<tr>
<td>Periodic alternating esotropia</td>
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<tr>
<td>Periodic alternating gaze deviation</td>
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<tr>
<td>Periodic alternating lid retraction</td>
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<tr>
<td>Periodic alternating nystagmus</td>
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<tr>
<td>Periodic alternating skew deviation</td>
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<tr>
<td>Periodic head turns in congenital nystagmus</td>
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<tr>
<td>Periodic mydriasis</td>
</tr>
<tr>
<td>Ping-pong gaze</td>
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<tr>
<td>Rhythmic pupillary oscillations (periodic pupillary phenomenon)</td>
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Fig. 7.20 Cyclic esotropia. Patient presented with history of intermittent esotropia but was found on further followup to have cyclic esotropia. She showed orthotropia (a) and esotropia (b) alternating daily.
with cyclic esotropia are basically strabismic with cycles of remission. This abolition of cyclic esotropia after visual improvement appears analogous to previously reported cases of periodic alternating nystagmus that resolved after visual rehabilitation by removing a cataract or clearing a vitreous hemorrhage. It is therefore advisable to provide maximal optical/refractive correction prior to considering extracocular muscle surgery. The treatment of cyclic esotropia consists of strabismus surgery to correct the maximum deviation that stops the overt cycles. Richter likened the effect of surgery to “removing the hand of the clock without altering its motor.”

Cyclic esotropia has been reported in the aftermath of cataract, retinal detachment, intracranial surgery, intermittent exotropia, infantile esotropia, and accommodative esotropia. Cyclic esotropia should not be confused with periodic alternating esotropia. The latter is a rare condition with cycles of similar duration to periodic alternating nystagmus (about 200 s). The few reported cases occurred in association with congenital periodic alternating gaze deviation. Such patients probably had the neuroanatomic substrate of periodic alternating nystagmus, but with superimposed saccadic palsy leading to absent fast phases of nystagmus.

Periodic alternating gaze deviation (PAGD) is a rare disorder consisting of a slow, conjugate horizontal deviation of the eyes from one side to the other. It may occur at any age (some cases have been reported in infancy) and is associated with concurrent, controversial, cyclic face turning to maintain fixation. During a complete cycle, the eyes rotate conjugately toward one side for 1–2 min, usually with compensatory head turning to the opposite side; return to the midline for a changeover period lasting 10–15 s; then conjugately deviate to the other side for 1–2 min, with compensatory head turning to the side opposite the direction of ocular rotation. The patient may be orthotropic or esotropic. During eye closure, the alternating turning of the head ceases, even though the eyes continue the rhythmic movement. While the eyes are deviated, they exhibit abnormal voluntary movements, convergence, optokinetic nystagmus, and oculocephalic responses, but all of these normalize during the changeover phase. Caloric testing can override the eye and head movements, and the cycling stops during sleep.

Periodic alternating gaze deviation may occur on a congenital basis or may be acquired. Most documented cases reported so far have been due to posterior fossa abnormalities. It has been reported in association with pontine vascular lesions, Arnold–Chiari malformation, Dandy–Walker malformation, congenital hydrocephalus, occipital encephalocoele, cerebellar medulloblastoma, spinocebellar degeneration, and Joubert’s syndrome with cerebellar vermis hypoplasia. In congenital or early onset PAGD, cerebellar vermis atrophy is the most common neuroradiologic abnormality.

The duration of a complete cycle of PAGD (3–4 min) is similar to that of periodic alternating nystagmus (PAN), suggesting that the two conditions may have a similar neuroanatomic substrate, the difference being an added saccadic palsy in the case of PAGD. This concept is supported by the findings in a patient with recurrent cerebellar medulloblastoma who sequentially demonstrated PAN, bilateral gaze palsy, PAGD, and then resumption of PAN.

When encountered in a comatose patient, PAGD is usually considered a sign of bilateral cerebral hemispheric dysfunction with a relatively intact brainstem. In this setting, the total duration of the abnormal movements is usually short, a few hours to days, disappearing a few hours before death.

Ping-pong gaze superficially resembles PAGDs, but the movements are much faster, although some authors have used the two terms interchangeably. It consists of conjugate horizontal ocular deviations that alternate rapidly every few seconds. Ping-pong gaze is usually seen in comatose or semicomatose patients and typically denotes cerebellar or bilateral cerebral hemispheric lesions, but a relatively intact brainstem. Ping-pong gaze has been speculatively ascribed to damage of the descending supranuclear inhibitory input on the horizontal gaze centers.

Periodic alternating skew deviation is a rare condition in which the patient develops right hypertropia lasting one to several minutes, alternating with left hypertropia in a cyclic fashion. In some patients, the condition may be aperiodic or intermittent. Downbeat nystagmus may also be present. In one patient, a focal lesion affecting the interstitial nucleus of Cajal was demonstrated with computed tomography. In contrast to seesaw nystagmus, periodic alternating skew deviation has slower movements, larger excursions, and no torsional component. Periodic eye movement disorders with a cycle duration of about 200 s, which include PAN, PAGD, and periodic alternating skew deviation, may have similar pathophysiologic mechanisms and have been reported to occur in combinations in the same individual.

One case of cyclic superior oblique palsy developed in a 10-year-old patient following trauma to the left trochlear area. Typical left superior oblique palsy alternated daily with orthotropia. A patient with cyclic vertical deviation of an unspecified nature, with a cyclic duration of 48 h, has been reported following craniofacial surgery. Other cyclic ocular motor disorders include paroxysmal ocular tilt reaction and oculomotor palsy with cyclic spasm. In patients with oculomotor palsy with cyclic spasm, the pupil may reportedly be the only structure to cycle although, more commonly, the extraocular muscles and levator muscle are also involved in the cyclic spasms.

Cyclic or alternating phenomena may affect the pupils. Keane described a patient with traumatic oculomotor palsy in whom the ipsilateral pupil, although unreactive to light, showed continuous rhythmic involuntary oscillations.
He speculated that dysfunction of the central parasympathetic nervous system may have been responsible. *Alternating anisocoria* is a rare condition characterized by alternating pupillary dilatation, with the dilated pupil showing little or no light reactivity in some cases, but normal reactivity in others.\(^{121}\) This may occur in otherwise neurologically normal children.

**Fig. 7.21** Congenital PAGD. Two-year-old girl with Joubert syndrome displayed PAGD with cycle duration of about 200 s. During complete cycle, (a) eyes rotated conjugately to right over 90 s, usually with compensatory head turning to opposite side, (b) returned to midline for a changeover period lasting seconds, then (c) conjugately deviated to other side over 90 s, with compensatory head turning to side opposite direction of ocular rotation. (d) MR imaging showed profound cerebellar vermis hypoplasia.
but a similar phenomenon has been observed in a quadriplegic patient with a posttraumatic syringomyelic cyst. The pathophysiology of this phenomenon is unclear, but it may be due to either episodic oculosympathetic spasm producing alternating Claude Bernard–Horner’s syndrome or episodic oculosympathetic interruption producing Horner’s syndrome. Some other pupillary disorders have been intermittent rather than rhythmic and include intermittent mydriasis, cyclic sympathetic spasm with concentric dilatation lasting 40–60 s, and “tadpole pupils,” in which the sympathetic spasm is sectoral.

Conditions with cycle duration of a few minutes sometimes become apparent when the clinician notices a reversal of a previously noted finding – for example, observation of conjugately turned eyes to the right in a patient whose eyes were previously noted to be conjugately turned to the left brings forth the diagnosis of PAGD. Conditions with a cycle duration of 24 h or longer cannot be definitively diagnosed from data collected during a single office visit. For instance, a patient with cyclic esotropia may be initially evaluated on a “crossed” day and be labeled as congenital or acquired esotropia. If the subsequent visit occurs on a “crossed” day, it may only consolidate the earlier false diagnosis. If it occurs on a “straight” day, the clinician may suspect spontaneous resolution or an accommodative element with variable angle and either question the observation of esotropia in earlier visits or correctly suspect cyclic esotropia. Conversely, initial evaluation of a patient with cyclic esotropia on a “straight” day may lead to missing the diagnosis, dubbing the condition pseudostrabismus.

Cyclic phenomena in children are not limited to the neuro-ophthalmologic disorders discussed here, but involve other organ systems as well. Other biologic phenomena, such as sweating, salivation, and pulse rate, also have intrinsic periodicity, as do many manifestations of psychiatric dysfunction. Periodicity appears to be the norm in many biologic phenomena, and a normal person displays a complex array of biorhythms involving the various body systems. Numerous periodic or rhythmic disorders have been described – for example, periodic recurrence of fever, swelling of joints, fluctuations of circulating blood cells (periodic hematopoiesis), and edema. Accumulating evidence points to the existence of a biologic clock mechanism that keeps time with extraordinary accuracy and is independent of internal and external stimuli.

**Ocular Neuromyotonia**

Myotonia denotes delayed muscle relaxation after sustained contraction as a result of muscle membrane dysfunction. In contrast, neuromyotonia or pseudomyotonia represents delayed muscle relaxation as a result of impulse-induced repetitive discharge in a peripheral nerve. Neuromyotonia describes neuromyotonia accompanied by fibrillations, fasciculations, myokymia, or sustained contraction of a muscle group. Ocular neuromyotonia describes sustained contraction of one or more extraocular muscles due to involuntary firing of the supplying oculomotor nerve.

Ocular neuromyotonia is a relatively rare ocular motility disorder that manifests with brief paroxysmal monocular deviations with associated diplopia. Episodes generally last 10–60 s (range, 5 s to 3 min) and may recur 20 or more times per day. Some episodes occur spontaneously, while others are triggered by gaze in the direction of the involved muscle. Between attacks, affected patients usually show normal ocular motility, although some may show subtle evidence of aberrant innervation manifesting as minimal lid retraction in downgaze. The paroxysms result from tonic involuntary contraction of extraocular muscles innervated by the third (all muscles supplied by the nerve or any combination thereof), fourth, or sixth cranial nerves. Spontaneous discharges from axons with unstable cell membranes are presumed to underlie this condition. In some cases, ocular neuromyotonia may coexist with primary aberrant regeneration.

Histopathologic studies of peripheral nerves in nonocular cases of neuromyotonia have shown segmental demyelination as well as axonal degeneration, sprouting, and remyelination. Most patients have a history of brain irradiation, typically for the treatment of tumors of the skull base, such as pituitary tumors or craniopharyngiomas. Idiopathic cases with no specific cause have been reported. The interval between radiotherapy and onset of neuromyotonia may be months to years. Two cases have been reported in teenagers following radiation therapy for paranasal lesions. A favorable response to membrane-stabilizing medications, such as carbamazepine is reported in many patients, supporting pathoetiology consisting of spontaneous or impulse-induced repetitive discharge of hyperexcitable trigger zones in ocular motor nerves. In some instances, the neuromyotonia has not reocurred on cessation of the medication. Some cases may remit spontaneously.

Several conditions not associated with radiation therapy may come to be classified as ocular neuromyotonia. Adie’s pupil and superior oblique myokymia are two common forms of ocular neuromyotonia seen in neuro-ophthalmologic practice.

**Ocular Motor Adaptations and Disorders in Patients with Hemispheric Abnormalities**

Cerebral hemispheric abnormalities are often associated with ocular motor abnormalities that may be subtle or profound depending upon the size, location, and other characteristics of the lesion. These are reviewed in detail elsewhere.
Children with congenital hemianopsia develop a compensatory saccadic strategy, wherein they overshoot the intended visual target then “find it” as the eyes drift back. Some patients with congenital homonymous hemianopsia have been noted to also show concurrent exotropia, usually also of early onset. Some investigators have suggested that the exotropia in these patients is a compensatory phenomenon for the hemianopic field defect, essentially allowing the patient to have panoramic vision. For this to occur, anomalous retinal correspondence has to coexist, otherwise the patient would be diplopic. Some investigators raise the possibility that the exotropia in such patients is an epiphenomenon, possibly reflecting the type of strabismus one sees in many children with neurologic disease.

It is not clear whether the concurrent exotropia in these children simply represents strabismus precipitated by infantile neurologic disease, or develops as a physiological compensatory phenomenon leading to the development of anomalous retinal correspondence and panoramic vision, or exists as a combination between these two mechanisms. The fact exotropia is so common in these children, who often show an uncanny ability to navigate through visual space without difficulty despite their homonymous hemianopia, suggests that the exotropia serves an important compensatory function. Therefore, the clinician should understand the potentially devastating sensory implications of performing strabismus surgery to straighten the eyes.

**Eye Movement Tics**

Tics are quick, jerky, sudden, and repetitive movements of circumscribed groups of muscles without apparent cause or purpose. They occur frequently in children and most often resolve spontaneously. Tics most commonly affect facial musculature, but may rarely affect the extraocular muscles, causing eye movement tics. It is important to recognize eye movement tics as such and not confuse them with more serious disorders. The few cases of eye movement tics reported to date have been mostly associated with facial tics, but isolated ocular tics may occur and may thus mimic nystagmus. Frankel and Cummings reported eye rolling tics in a group of patients with Tourette syndrome. The tics consisted of eye rolling, gaze abnormalities, staring, or forced gaze deviations resembling oculogyric crises. Two of the cases described a corneal sensation preceding their tics. All of these children also had blepharospasm, and most were taking neuroleptic or other medications. Neuroleptics have been implicated in the pathogenesis of a variety of movement disorders, including tics and oculogyric crisis. Binyon and Prendergast reported three cases with conjugate eye movement tics: one was associated with Tourette’s syndrome, one was associated with neurological and behavioral disorders, and one was isolated. The latter resolved spontaneously. Shawkat reported opsoclonus-like ocular tics associated with facial tics in an otherwise healthy child that resolved spontaneously. Affected children are sometimes able to imitate their tics in the clinic on request, which is a useful indicator that consciousness is not impaired during the tics, allowing the examiner to rule out epilepsy.

**Eyelid Abnormalities in Children**

### Congenital Ptosis

As detailed above, congenital ptosis occurs most frequently as a congenital cranial dysinnervation disorder. Because congenital ptosis can also be the presenting sign of several other neuro-ophthalmologic disorders (Table 7.11), however, specific attention to ocular motility, pupillary examination, and coexisting neurologic signs is imperative. Congenital ptosis must also be differentiated from pseudoptosis due to ipsilateral hypotropia, enophthalmos, or contralateral lid retraction. Motility abnormalities may include congenital oculomotor nerve palsy and double elevator palsy. The latter is a reason to be conservative with ptosis correction to prevent corneal exposure postoperatively due to absent Bell’s phenomenon. Pupillary abnormalities associated with unilateral ptosis may include a large unreactive pupil due to oculomotor palsy or a miotic pupil either due to Horner syndrome or to congenital oculomotor palsy with aberrant regeneration involving the pupil. Causes of pupillary abnormalities associated with bilateral early-onset ptosis include Fisher’s syndrome and botulism.

Rarely, a cerebral hemispheric lesion causes unilateral or bilateral ptosis (termed cerebral ptosis) in the absence of other neurological signs. Lowenstein et al described two children with hemispheric arteriovenous malformations.

**Table 7.11 Differential Diagnosis of Congenital Ptosis**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Blepharophimosis syndrome</td>
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<td>Cerebral ptosis</td>
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<td>Congenital fiber-type disproportion</td>
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<tr>
<td>Congenital fibrosis syndrome</td>
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<tr>
<td>Congenital myotonia</td>
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<tr>
<td>Horner syndrome</td>
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<tr>
<td>Hypotropia with pseudoptosis</td>
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<tr>
<td>Marcus Gunn jaw winking</td>
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<tr>
<td>Microphthalmia, enophthalmos</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Myotubular myopathy</td>
</tr>
<tr>
<td>Oculomotor nerve palsy</td>
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and contralateral ptosis that progressed over several years. In both cases, the ptosis resolved following resection of the arteriovenous malformation. One should consider the rare possibility of cerebral ptosis in the child with progressive nonmyasthenic ptosis, especially when a history of seizures or recurrent unilateral headaches is obtained.

The finding of unilateral congenital ptosis with lid swelling should suggest the diagnosis of dural arteriovenous fistula. When accompanied by supraduction deficit, bilateral internuclear ophthalmoplegia, and exotropia, bilateral ptosis should suggest the possibility of midline menencephalic cleft malformation. Tatli et al reported bilateral ptosis with lower extremity muscle weakness and dysautonomia as probable paraneoplastic effects of neuroblastoma in a 28-month-old girl. An extensive workup for myasthenia gravis was negative, and no paraneoplastic autoantibodies were identified.

**Excessive Blinking in Children**

The spontaneous blink rate in infants under 18 months of age is low, ranging from 2 to 5 blinks per minute, whereas in older children, it is about 10, reaching approximately 20 blinks by the age of 20 years and remaining relatively constant throughout adulthood. Benign tics, (blinking eyes, twitching mouth, movements of head, jerking shoulders or other body parts) are common in children, with a prevalence as high as 12% between the ages of 6 and 12 years. Benign tics involving the eyes, may manifest as excessive intermittent blinking without associated ocular or systemic disorders. Eye winking or blinking tics in children represent exaggerated contractions of the orbicularis muscle. The tics usually increase in frequency when the child is bored, anxious, or tired. Most these tics are benign and transient, improving spontaneously with time, without any discernible causation. Unlike essential blepharospasm of adults, there is little, if any, functional visual impairment.

Although tics have been thought to result from an underlying psychological conflict, recent evidence suggests that they may be of organic origin but triggered or exacerbated by stress. Elston et al described a family in which different members in three generations suffered eye-winking tics, excessive blinking, and/or blepharospasm. The proband in that study had eye-winking tics in childhood, then developed excessive blinking evolving to blepharospasm by the age of 21 years. They also described five patients with adult-onset blepharospasm, or Meige’s syndrome, who had a history of excessive blinking dating back to childhood. They speculated that eye-winking tics, excessive blinking, and blepharospasm may represent age-dependent manifestations of a common pathophysiologic disorder.

Frequent eye blinking may be a manifestation of ocular surface, tear film, or eyelid disorders at any age. It may also accompany lacrimal drainage obstruction. Children with congenital glaucoma are classically described as presenting with the triad of epiphora, photophobia, and blepharospasm, but may also show frequent blinking, as do children with significant intraocular inflammation. Excessive blinking and blepharospasm also occur in conditions with damage to the basal ganglia, such as Wilson disease and Huntington disease.

Seizure activity is associated with a variety of neuro-ophthalmologic signs and symptoms that include nystagmus, gaze deviations, spasm of the near reflex, hemianopsia, cortical blindness, as well as a variety of eyelid signs. Lid signs may consist of eyelid nystagmus or eyelid fluttering resembling tics and spells of eyelid spasms. For instance, Cogan et al described a 7-year-old girl with methylmalonic aciduria and homocystinuria who exhibited spells of fluttering of the eyelids and elevation of the eyes. The EEG showed 2.5-s polyspike and wave discharge during the spells, characteristic of petit mal seizures. Excessive blinking and eyelid myoclonia has been reported in association with typical absence seizures, and this condition has been reported in monozygotic twins. Finger waving and rapid eyelid blinking is a feature of photoconvulsive epilepsy.

Eyelid myoclonia may occur on eye closure in association with electrical status epilepticus without altered consciousness. Patients with occipital lobe epilepsy may exhibit a variety of neuro-ophthalmologic manifestations, including elementary visual hallucinations, ictal or postictal amaurosis, eye movement sensations, eye and/or head deviation, visual field deficits, and early forced blinking or eyelid flutter. Seizure activity may also be associated with abnormal eye movements such as gaze deviations (usually to the contralateral side) and nystagmus. The terms “lid nystagmus,” “upper lid jerks,” and “lid hopping” have all been applied to a neuro-ophthalmologic phenomenon in which a series of rapid, rhythmic, jerky movements of the upper lids occurs alone or in conjunction with specific movements of the eyes or head. Most previously reported cases have been associated with posterior fossa disease and can be subdivided into lid nystagmus evoked by convergence and lid nystagmus evoked by horizontal gaze. Children have been described with signs and symptoms of myasthenic ophthalmoplegia in whom gaze-evoked lid hopping signaled the presence of intrinsic midbrain tumors. Other rare causes of lid nystagmus include the lateral medullary syndrome, pretectal lesions, and Fisher syndrome. While horizontal eye movements in myasthenia gravis may be accompanied by occasional twitching or fluttering movements of the upper lids, lid nystagmus is uncharacteristic of neuromuscular disease and should prompt neuroimaging. Lid nystagmus would appear to necessitate a dissociation between the output of the levator and the...
superior rectus subnuclei within the oculomotor nuclear complex. Convergence-evoked lid nystagmus often signifies a structural lesion within the posterior fossa. Howard377 described a patient with convergence-evoked eyelid nystagmus without ocular upbeating nystagmus, who had a large vascular lesion distorting the blood supply to the pontomesencephalic and pontomedullary junctions. Safran et al1864 described two similar patients with convergence-evoked eyelid nystagmus. Patient 1, a 29-year-old man, developed a cerebellar syndrome after sustaining severe head injuries. Patient 2, a 12-year-old girl, had a tumor of the anterior cerebellar vermis. Treatment with corticosteroids (patient 1) and surgery (patient 2) led to gradual resolution of the eyelid nystagmus, which the authors attributed to cerebellar dysfunction.

The cause of tic disorders may lie in the dopaminergic system of the brain, as well as in genetic and other biological factors.406 Coats et al171 found the most common etiologies of excessive eye blinking to be anterior segment or lid abnormalities in children. Occasionally, children show frequent eye blinking as a manifestation of Tourette syndrome.486 Some children may exhibit lower eyelid pulling as a transient behavior lasting weeks to months.187 These children are otherwise healthy, and the condition is thought to initially be triggered by ocular irritation, but then develops into a “bad habit.” This functional disorder is readily distinguishable from eye poking (oculodigital sign) encountered in children who are blind secondary to congenital retinal disease (i.e., Leber congenital amaurosis, retinopathy of prematurity, retinal dysplasia)394 and vigorous eye rubbing seen in patients with Down syndrome.

Eyelid myokymia may occur alone or in association with facial myokymia. Facial and eyelid myokymia are characterized by unilateral involuntary fine rippling movements, spreading across the surface of affected muscles. Facial myokymia has been reported in association with multiple sclerosis, Guillaumin–Barré syndrome, Bell’s palsy, rattlesnake bites, brainstem tumors, and others. The clinical features of facial myokymia are sufficiently distinctive to avoid confusion with other facial dyskinesias such as essential blepharospasm, tardive dyskinesia, facial tics, focal seizures, aberrant regeneration of the facial nerve, hemifacial spasm, and benign facial fasciculations. Some cases of facial myokymia have occurred in association with spastic paretic facial contracture, which is characterized by tonic spasm of the paretic facial muscles, with typical prominence of the nasolabial fold and deviation of the nose toward the affected side. We have examined a patient with diffuse disseminated encephalomyelitis who showed left facial myokymia, spastic paretic facial contracture, and one-and-one-half syndrome and who also showed scattered lesions in the brainstem on MR imaging.

Gilles de la Tourette syndrome is a bizarre but relatively common disorder that comprises multiple involuntary motor tics and obscene utterances. There is a predilection for whites and for boys (male-to-female ratio ranges from 3:1 to 5:1). The condition is familial in about one-third of cases, appears to be transmitted as an autosomal dominant trait, and has been mapped to the long arm of chromosome 18.

Symptoms usually appear between ages 5 and 10 years, with presenting features consisting of multifocal tics of the face and head. In addition to clonic motor tics (most commonly blinking and facial twitching) and vocal/phonic tics seen in all patients, many patients exhibit one or more dystonic tics that may include oculogyric deviations, blepharospasm, and dystonic neck movements.398 The globes may also show dystonic tics. For example, Frankel and Cummings276 reported eye rolling tics in a group of patients with Tourette syndrome who also had blepharospasm. The motor tics are followed by vocal tics such as grunting, sneezing, coughing, barking, coprolalia (compulsive monosyllabic swearing), and echolalia. Tiqueurs may be able to voluntarily suppress the tics, but a resulting mounting tension eventually leads to further discharge of tics. Patients may show associated obsessive-compulsive traits, self-mutilation, attention-deficit disorders, learning disabilities, and serious psychiatric illness. Haloperidol and pimozide are useful in controlling the symptoms.

Epileptic disorders and their treatment may cause eye rolling or eyelid myoclonia.188 When accompanied by absence spells, eyelid myoclonia is highly suggestive of Jeavon’s syndrome (i.e., eyelid myoclonia and absences). In this condition, there is marked jerking of the eyelids with upward deviation of the eyes, associated with spike-wave discharges that are often irregular, immediately after eye closure and invariably evoked by intermittent photic stimulation. This diagnosis is likely when the eyelid myoclonia is combined with photosensitivity and pathognomonic when it also occurs after eyelid closure (in some cases, it can look like the child is purposefully closing the eyes to initiate a seizure). EEG shows characteristic eye closure-related discharges and photosensitivity. Rhythmic or random closing of the eyes is often seen in other forms of idiopathic generalized epilepsy, with absences or the eyelid jerking that may occur at the opening or the initial stage of the discharges in typical absence seizures of childhood or juvenile myoclonic epilepsy.

Toxicity from the antiepileptic drug clobazam in a 4-year-old boy has been reported to cause episodes of eye rolling, ataxia, and back arching, which were nonepileptic.50,188 Chung et al found ictal eye closure to be a reliable indicator of psychogenic nonepileptic seizures.165

The workup of tics is conservative, consisting mainly of observation, unless otherwise dictated by the presence of associated clinical findings. Explanation and reassurance of patients and their families is helpful in steering them away from becoming too focused on the tics. Neuroleptics and other drugs should be reserved for severe cases. The long-term prognosis of tics is good, with about two-thirds of cases spontaneously remitting.186
Hemifacial Spasm

Hemifacial spasm is primarily a disorder of middle-aged and older individuals, but a variety of cases have been reported in childhood. Hemifacial spasm is characterized by involuntary, intermittent unilateral twitching of the muscles innervated by the facial nerve, almost uniformly including the orbicularis oculi. They differ from tics in several ways, including the inability of the patient to suppress the twitches or initiate them, and the absence of compulsion to make them. In about half the patients, a particular position of the head (most commonly, the contralateral lateral decubitus position) diminishes or halts the spasms. The patient may hear ipsilateral clicking sounds if the stapedius muscle is involved.

Hemifacial spasm should be differentiated from blepharospasm and facial myokymia. Essential blepharospasm consists of bilateral, localized, repetitive spasms of the orbicularis oculi muscle that, in severe cases, leads to visual impairment. The rare case of bilateral hemifacial spasm can be distinguished from essential blepharospasm because the bilateral contractions do not occur synchronously. Essential blepharospasm is not seen in children, but excessive blinking due to tics or blepharospasm due to ocular disorders, such as congenital glaucoma, may bear superficial resemblance to essential blepharospasm. Facial myokymia consists of continuous, fascicular ripping movements of the face that usually begin in the orbicularis muscle. It is not affected by voluntary or reflex activity of the face. The most common causes include multiple sclerosis and brainstem glioma.

Most adult cases of hemifacial spasm are caused by vascular compression of the facial nerve at the root exit zone of the brainstem.297,806 The offending vessels are usually arterial, most commonly the anterior or the posterior inferior cerebellar artery or the posterior inferior cerebellar artery.667 This neurovascular compression theory was challenged by an MR imaging/MR angiography study that concluded that the development and severity of hemifacial spasm were not associated with a specific blood vessel or multiple neurovascular contact points.367 “Cross talk” between the sensory and motor branches of the seventh nerve has been suggested as an underlying pathophysiology. Congenital or acquired cholesteatoma is the most common associated tumor. Vascular malformations of the posterior fossa have also been implicated. Rare familial cases suggest a component of genetic transmission. Friedman et al278 described a family in which hemifacial spasm occurred in five members through three generations. Aside from neurovascular compression,490,540 a variety of rare causes of hemifacial spasm have been identified in children. These include venous sinus thrombosis,271 masses of the fourth ventricle,271 ganglieneuroma,706 pilocytic astrocytoma,378,667 congenital or acquired cholesteatoma,630 tuberculous meningitis,670 thickening of the arachnoid membrane,443 and possible intrauterine facial nerve injury.831 The diagnosis of epilepsy should also be considered, as hemifacial spasm has been reported as part of a seizure phenomenon.21,41,356 The presence of hemifacial spasm in an infant should therefore be considered an ominous sign.

Langston and Tharp370 described a case of infantile hemifacial spasm beginning at 6 weeks of age. Surgical exploration at 5½ years of age revealed a ganglieneuroma of the fourth ventricle. Flueler et al271 described three infants who presented with the onset of hemifacial spasm in the first year of life. One patient had occlusion of the straight sinus and large collateral vessels at the base of the brain, supporting the concept of vascular compression of the facial nerve at its exit from the brainstem as a mechanism for the production of hemifacial spasm. Each of the other two patients had an intrinsic mass compressing the fourth ventricle: one was located in the lower pons and extended into the cerebellar vermis and right cerebellar peduncle; the other involved the cerebellar vermis and right middle cerebellar peduncle. Interestingly, hemifacial spasm has been described in some cases of Joubert syndrome, which includes cerebellar vermis aplasia or hypoplasia.438 Unlike the usually benign nature of the late childhood and adult variety, it appears that early-onset hemifacial spasm should raise suspicion of an underlying CNS malignancy. Neuroimaging is therefore warranted in cases of hemifacial spasm with onset in the first 2 years of life. In older children with typical, isolated, hemifacial spasm, neuroimaging should be obtained when atypical features (headaches, facial pain, cranial neuropathy, cerebellar dysfunction) are present.36

In the toddler with apparent hemifacial spasm, the diagnosis of accommodative esotropia should also be considered.122 In this setting, a young child may have to exert a hemifacial contraction to close one eye to prevent diplopia. For this reason, a cycloplegic refraction should be included in the diagnostic evaluation of hemifacial spasm.122 Both botulinum injection and surgical decompression of the facial nerve have been used with good results in both adults and children.153,704 Microvascular decompression of the facial nerve is considered the definitive treatment by some authors. Jho and Jannetta492 described improvement of hemifacial spasm with microvascular decompression of the facial nerve in two children and eight adults who had the onset of hemifacial spasm before the age of 20.

Eyelid Retraction

The margin of the upper eyelid is normally located 1–2 mm below the upper corneoscleral limbus. Upper eyelid retraction is more commonly considered in the adult age group, where it occurs most commonly in patients with thyroid eye disease, dorsal midbrain syndrome, trauma, proptosis,
and seventh nerve palsy, amongst other conditions. SCAs, such as Machado–Joseph disease, are known to produce a peculiar “ocular stare” that is has been attributed to lid retraction rather than proptosis.

The causes of eyelid retraction in children are heterogeneous (Table 7.12).729 Graves orbitopathy is rare in children. When it occurs, it is less severe than in adults,317,766,827 and most cases require no treatment.228 Most children are clinically hyperthyroid at the time of diagnosis.228 Exophthalmos is notably less common in the prepubescent group, presumably because there is room for the orbit to grow and produce a physical decompression. In our experience, diplopia is rare, and orbital fat expansion is more common than extraocular muscle enlargement on imaging studies. Compressive optic neuropathy is rare.228 Secondhand smoke has been implicated as a possible pathogenetic factor.152 Unless specific clinical or neuroimaging findings suggest the diagnosis of Graves orbitopathy, neurological causes should be primarily considered.

Bilateral lid retraction in dorsal midbrain syndrome is attributable to disruption of inhibitory fibers from the posterior commissure to the central caudate nucleus.182 Rarely, patients with medial midbrain lesions demonstrate a “plus minus lid syndrome” characterized by ipsilateral ptosis (from injury to the oculomotor fascicle) and contralateral lid retraction (from disruption of bilateral inhibitory fibers to the central caudal nucleus). When the ptosis resolves, the ptotic lid can assume a retracted position.283,287

Lid retraction in children is often intermittent, as in aberrant reinnervation associated with congenital oculomotor palsy or the MGJW phenomenon. Cases of neuromyotonia affecting only the levator muscle would also be expected to show isolated intermittent lid retraction. Cases of oculomotor palsy with cyclic spasm show intermittent momentary elevation of the eyelid on the affected side, but careful scrutiny of the ocular alignment and the mandatory pupillary involvement in the cyclic process confirm the diagnosis.499 A single case of posttraumatic, bilateral, pupillary-involving oculomotor palsy has been reported, wherein the patient showed bilateral nonsynchronous episodic eyelid retraction not associated with eye movement or pupillary changes.467 Patients with unilateral inferior rectus restriction and alternating fixation may show intermittent contralateral eyelid retraction, which occurs as a result of Hering’s law when the restricted eye takes up fixation.

Healthy infants also frequently display eyelid retraction to darkness, which resembles the setting sun sign (Fig. 7.22). Eyelid retraction to darkness can be elicited by turning off the

<table>
<thead>
<tr>
<th>Table 7.12 Causes of eyelid retraction in children</th>
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<tr>
<td>Setting sun sign/hydrocephalus/dorsal midbrain syndrome (Collier sign)</td>
</tr>
<tr>
<td>Congenital, cryptogenic</td>
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<tr>
<td>Oculomotor palsy with aberrant innervation</td>
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<tr>
<td>Oculomotor palsy with cyclic spasm</td>
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<td>Marcus Gunn jaw winking</td>
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<tr>
<td>Eyelid retraction to darkness (normal in first year of life)</td>
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<tr>
<td>Neuromyotonia</td>
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<tr>
<td>Graves disease/hyperthyroidism</td>
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<td>Familial periodic paralysis</td>
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<td>Orbital hemangioma</td>
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<td>Optic nerve anomalies with vertical nystagmus</td>
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<td>Contralateral ptosis with compensatory superinnervation of both levators (fixation duress)</td>
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<tr>
<td>Myasthenia gravis</td>
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<td>Hepatic cirrhosis</td>
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<td>Cushing syndrome</td>
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<td>Levator muscle fibrosis</td>
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<tr>
<td>Inferior rectus muscle restriction with fixation duress</td>
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<tr>
<td>Iatrogenic after surgical repair of ptosis</td>
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<tr>
<td>Eyelid scarring (e.g., after inflammation from herpes zoster)</td>
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<tr>
<td>Claude Bernard syndrome (sympathetic irritation)</td>
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<tr>
<td>Volitional lid retraction</td>
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<tr>
<td>“Startle” reflex to dimming light in infants</td>
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</tbody>
</table>

Fig. 7.22 Pseudo-setting sun sign. Healthy infant showed eyelid retraction immediately after room light was turned off (a) that resolved when ambient illumination was restored (b)
room lights while observing the palpebral fissures. It can be a clinically useful sign that an apparently blind infant has at least light perception vision. The phenomenon, which appears to be limited to the first year of life, disappears when ambient illumination is restored and is thought to represent a primitive startle reflex.

**Apraxia of Eyelid Opening**

Apraxia of eyelid opening is a nonparalytic motor disorder of the eyelids. It is characterized by the inability to volitionally initiate eyelid opening despite intact reflex lid elevation, lack of concurrent orbicularis oculi muscle contraction, and intact ocular motor nerves. Affected patients open the eyes manually or may employ a head thrusting movement to do so.\(^{484}\) It may be differentiated from blepharospasm by the absence of Charcot’s sign (orbicularis contraction forces the eyebrows to a level lower than the superior orbital margin). The condition usually appears in older patients with extrapyramidal disease, but may be seen in patients with unilateral or bilateral hemispheric dysfunction. It may respond favorably to Botulinum injections.\(^{418}\)

**Pupillary Abnormalities**

**Congenital Bilateral Mydriasis**

Congenital mydriasis is a rare defect that was first described by White and Fulton in 1937.\(^{302}\) Lindberg and Brunvand described a 12-year-old girl with congenital bilateral mydriasis in association with aeurysmal dilatation of a persistent ducus arteriosus.\(^{496}\) They attributed these findings to a hypoplastic or aplastic sphincter and ciliary body because there was also absent accommodation. Khan et al reported two patients with dilated pupils with hypoplasia of the iris, Moyamoya angiopathy, dolichoectatic internal carotid arteries, and patent ductus arteriosus. The mechanistic link between the ocular and cardiac defects is unclear.\(^{433}\)

**Accommodative Paresis**

A recent report described five children with a syndrome of benign transient loss of accommodation. No child had other ocular, neurological, or systemic abnormalities that could be associated with accommodative paralysis.\(^{18}\) All had preserved pupillary responses to light and near, and preserved convergence. All did well with bifocals, and accommodation returned to normal in 3–14 months in all cases. Similar cases of isolated accommodative paresis in otherwise healthy young patients have been previously reported.\(^{303,222}\) Idiopathic paralysis of the near vision triad has also rarely been described.\(^{149}\) Organic causes of accommodative paresis include head/neck trauma, pharmacologic agents, systemic diseases (diphtheria, diabetes mellitus, decompression sickness), neuromuscular disease (myasthenia gravis, myotonic dystrophy, botulism, tetanus), neurologic diseases (dorsal midbrain syndrome, encephalitis, Wilson disease, hemispheric hematoma, oculomotor nerve palsy, Adie tonic pupil), ocular disease (uveitis, trauma, metastasis, glaucoma), and presbyopia. Isolated accommodation palsy can also be functional in origin. Accommodative paresis can be one of the earliest symptoms of dorsal midbrain syndrome, resulting from either hydrocephalus or compression by an extrinsic tumor such as a solid pineal tumor.\(^{592}\) Blurred vision and isolated accommodative palsy have been reported in patients with symptomatic pineal cysts,\(^{86}\) which are usually considered to be an incidental radiologic finding (1.2–2.4% of all MR studies).\(^{301,477,677}\) Accommodative paresis is a common component in children with Down syndrome, leading to the frequent need for bifocals. The extra accommodative effort exerted by these patients may explain the development of esotropia and the common undercorrections experienced after strabismus surgery for this condition.

**Adie Syndrome**

Isolated internal ophthalmoplegia is commonly due to trauma or pharmacological dilatation of the pupil or is a feature of Adie syndrome. Adie syndrome is rare in childhood,\(^{498}\) having an average age of onset of approximately 32 years and a predilection for females. It is characterized by unilaterally or bilaterally enlarged, tonic pupils that show markedly slow constriction to either light or near stimulation, followed by a very slow, tonic, redilatation. Patients with Adie’s syndrome also show regional corneal hypesthesia due to interruption of fibers of the ophthalmic division of the trigeminal nerve as they traverse the ciliary ganglion.

The light-near dissociation found in Adie syndrome differs in pathophysiology from that seen in mesencephalic disease; it may be attributed to either diffusion of acetylcholine from partially innervated or reinnervated ciliary muscle to the supersensitive pupillary sphincter muscle\(^{143}\) or by aberrant misdirection to the pupillary sphincters of nerve fibers that originally synapsed in the ciliary muscle.\(^{744}\) An accommodation paresis may also be associated, which is understandable if one considers that the ciliary ganglion has 30 times more neurons destined for the ciliary muscle than for the iris sphincter. Following acute onset, most of the sprouting new axons arise from accommodative neurons, but many of
these end up in the iris sphincter (i.e., aberrant regeneration). Hence, although the pupils tend to be large at presentation, they become smaller with the passage of time and may eventually be confused with Argyll Robertson pupils if the examiner is not aware of their earlier dilated status.

With the slit lamp, segmental vermiform movements of the iris and sectoral palsy are seen. Sectoral palsy produces shifting of the iris stroma toward the area of active contraction, a phenomenon known as “iris streaming.” An associated sectoral palsy of the ciliary muscle causes lenticular astigmatism that may blur vision during near tasks. The iris vermiform movements noted at the slit lamp represent normal contractile activity of those iris sectors still innervated by light-responsive neurons. Citing two young adults who were found to have long-standing miotic pupils in association with typical features of Adie’s syndrome, Rosenberg has argued that some cases of Adie syndrome primarily present with miotic pupils in a manner analogous to primary aberrant regeneration of the oculomotor nerve. However, the observation of Adie syndrome with dilated pupils in children as young as 4 years (with subsequent development of miosis) argues against this hypothesis.

Because oculomotor palsy rarely presents with isolated mydriasis, it is important to look closely for an exophoria that increases in adduction and for alternating hyperphorias in vertical gaze to rule out subclinical oculomotor nerve palsy. It is now recognized that cholinergic supersensitivity of the iris sphincter may also develop in oculomotor palsy with pupillary involvement. Other clinical signs usually attributed to postganglionic damage (light-near dissociation, sectoral sphincter palsy) can also be seen, so it is important to differentiate Adie pupil from an early or resolving oculomotor nerve palsy.

One case of Adie syndrome involved a 4-year-old boy who developed bilateral consecutive, idiopathic Adie syndrome over a follow-up period of 6 years. At the age of 4 years, he was diagnosed with right Adie syndrome and was found to have ambylophia, because the associated accommodative difficulty unmasked his latent hyperopia. Examination at age 10 revealed additional myotonic involvement of the left pupil and absent or sluggish deep tendon reflexes.

Two children with unilateral congenital tonic pupils were found to have ipsilateral orbital neural-glia hamartoma. Two children with Adie pupil have recently been found to have an endodermal cyst of the intracranial oculomotor nerve. Toxic pupils have also been described in a child with neuroblastoma and attributed to a paraneoplastic process. Lambert et al reported bilateral tonic pupils in two infants with a congenital neuroblastoma, Hirschsprung disease, and central hypoventilation syndrome. Children with congenital hypoventilation syndrome tend to have miotic pupils with light-near dissociation, convergence insufficiency, and other defects in autonomic control such as absence of normal variability in heart rate. Whether the tonic pupils result from result from a paraneoplastic disorder or from the effects of a generalized neurocrisopathy is unclear. Recently, a case of reversible posterior leukoencephalopathy was reported in association with an Adie’s tonic pupil in a 9-year-old boy following measles vaccination. Botulism should also be considered in the differential diagnosis of bilateral tonic pupils. In this setting, the tonic pupils may persist as a chronic condition.

Thompson classified patients with tonic pupils into three general categories on the basis of their underlying pathophysiologic disorders: (1) Local pathologic disorders within the orbit that involve the ciliary ganglion (e.g., inflammatory processes such as herpes or sarcoid, trauma). These conditions are commonly unilateral. (2) Neuropathic conditions causing diffuse peripheral or autonomic neuropathy. These include syphilis, diabetes, Guillain–Barré syndrome, Ross syndrome, and several hereditary neuropathies, such as Shy–Drager and Charcot–Marie–Tooth diseases. These conditions are typically bilateral. The presence of Adie-like pupils in an infant younger than 1 year of age should raise the possibility of familial dystonia (Riley–Day syndrome), Cryptogenic tonic pupils, or true Adie syndrome, begins unilaterally, but eventually at least 20% of patients develop the syndrome bilaterally. In addition to the ocular signs, the deep tendon reflexes, especially the knee and ankle jerks, may be diminished or absent. Adie syndrome bears some resemblance to Ross syndrome, which is a rare, presumably degenerative peripheral neuropathy characterized by the triad of unilateral or bilateral tonic pupil, hyporeflexia, and segmental anhidrosis. The recent demonstration of subclinical segmental hypohidrosis in patients with Adie syndrome suggests that the two conditions may be related.

The diagnosis of Adie syndrome can be confirmed by demonstrating constriction of the dilated pupil in response to a dilute solution of pilocarpine (0.125%), which confirms the presence of pupillary supersensitivity due to parasympathetic denervation. This supersensitivity may not be demonstrable acutely, with some acute cases failing to constrict even to strong solutions of pilocarpine, making a differentiation from pharmacologic blockade difficult.

Pharmacological misadventures are a common cause of isolated pupillary dilation, resulting from instillation of mydriatic agents, exposure to certain plants that contain belladonna or atropine-like alkaloids (e.g., jimsonweed), or exposure to certain perfumes or cosmetics. The mydriatic pupils associated with ophthalmoplegic migraine, oculomotor palsy with cyclic spasm, botulism, Fisher syndrome, and the dilated pupil accompanying the dorsal midbrain syndrome do not usually cause a diagnostic problem due to the other associated features of these disorders. Various infectious diseases have been associated with pupillary mydriasis or tonic pupils, including herpes zoster, measles, diphtheria, syphilis, pertussis, scarlet fever, smallpox, influenza, and
hepatitis, but a history of an infectious illness is usually present. Chickenpox may produce a tonic pupil in children, which may present during the incubation period, the active disease stage, or during convalescence. The mydriasis and decreased accommodation in the setting are presumed to reflect direct infectious or inflammatory involvement of the ciliary ganglion; however, the coexistent iridocyclitis with iris stromal vasculitis and sphincter necrosis could also contribute in some cases. The finding of mutton-fat keratoprecipitates and/or sectoral iris stromal atrophy would favor the latter mechanism.

Traumatic injury, either to the iris sphincter or to the ciliary nerves (e.g., panretinal photocoagulation, orbital surgery), may also produce pupillary mydriasis or tonic pupils. Some children may present with isolated episodic unilateral or bilateral mydriasis accompanied by head pain; these may represent a variant of ophthalmoplegic migraine or represent a migraine equivalent and are usually self-limited.

Horner Syndrome

Horner syndrome results from a lesion affecting the sympathetic supply to the eye and may be encountered at any age (Fig. 7.23). The clinical features found on the affected side include the following: (1) 1–2 mm of miosis, with greater anisocoria in dim illumination and a dilation lag. The miosis results from denervation of the sympathetically innervated pupillary dilator muscle. Oculosympathetic denervation of the pupillary dilator muscle can be demonstrated by dimming the ambient light and observing an immediate but transient increase in anisocoria, because the affected pupil does not dilate as rapidly as the normal pupil (dilation lag). (2) Mild upper lid ptosis measuring 1–2 mm (due to denervation of the sympathetically supplied superior tarsal muscle) and corresponding elevation of the lower eyelid (upside-down ptosis) due to denervation of the lower eyelid retractors.

The upside-down ptosis may be confirmed by matching the lower limbus to the lower lid margin in each eye; more scleral showing would be found on the normal side. The resulting narrowing of the palpebral fissure leads to an apparent enophthalmos. (3) Anhidrosis if the lesion is proximal to the carotid bifurcation. Lesions distal to the carotid bifurcation do not affect sympathetic innervation of facial sweat glands. Both acquired and congenital Horner’s syndrome rarely causes Harlequin syndrome, a neurocutaneous phenomenon in which one half of the face fails to flush during thermal or emotional stress as a result of damage to vasodilator sympathetic fibers. In some cases, however, this condition cannot be attributed to straightforward sympathetic injury. Some children show a different pattern of scalp hair growth, with straight hair on the affected side.

Congenital or perinatal Horner syndrome results in failure of the iris to become fully pigmented, resulting in heterochromia, with the ipsilateral iris appearing lighter in color. Iris heterochromia takes several months to develop and may be difficult to detect in infants who normally have lightly colored irides. Wallis et al reported the unusual case of a 20-month-old boy with congenital Horner syndrome, with the darker iris on the affected side attributable to concomitant Waardenburg syndrome. Much less commonly, heterochromia may also follow acquired lesions in adults. Subtle iris heterochromia can sometimes be made more visible by examining the child in sunlight. Some congenital cases may present with ipsilateral facial flushing. Patients with acute Horner syndrome may also exhibit decreased Schirmer response, transient myopia, transient hypotony, and transient conjunctival hyperemia. The last three signs are seen only in acquired cases.

The location of the causative lesion along the sympathetic pathway may be inferred clinically and confirmed pharmacologically and/or neuroradiologically. For instance, the combination of Horner syndrome and ipsilateral abducens palsy implicates a lesion in the cavernous sinus. Mesencephalic lesions, involving the trochlear nucleus or fascicles before decussation in the superior medullary velum and adjacent sympathetic fibers, may produce an ipsilateral Horner syndrome and contralateral superior oblique muscle paresis. Pharmacological testing consists of topical instillation of autonomically active drugs to confirm oculosympathetic paralysis (cocaine test) and to distinguish a preganglionic from a postganglionic lesion (hydroxyamphetamine test). However, a preganglionic congenital Horner syndrome may show a false-positive hydroxyamphetamine test because of transynaptic degeneration.

Recently, apraclonidine 0.5% has been touted as a diagnostic test for Horner syndrome on the basis of its alpha-2

Fig. 7.23 Congenital Horner syndrome. Note right upper lid ptosis, right miosis, and mild heterochromia. Right lower lid shows mild reverse ptosis, covering more of cornea than its left counterpart.
inhibitory effects in normal eyes and weak alpha-1 adrenergic/excitatory effects in Horner eyes. Apraclonidine makes the Horner pupil dilate and the normal pupil constrict slightly. The reversal of anisocoria is more obvious with the room lights on. Apraclonidine is reported to be safe and effective in the pediatric population because it does not cross the blood–brain barrier, thereby reducing the incidence of centrally mediated effects. However, a recent report documenting CNS and respiratory depression in three children (one requiring intubation) suggests that its use in children should probably be avoided.

Iris pigmentation, which occurs within the first year of life, requires sympathetic stimulation. Interestingly, Mindel et al reported a 21-year-old woman with neurofibromatosis type I who had a unilateral congenital Horner syndrome with heterochromia. The patient showed symmetric Lisch nodules, which are melanocytic hamartomas, in both eyes, suggesting that, unlike iris pigmentation, the formation of Lisch nodules is not influenced by sympathetic innervation of the iris. Other causes of heterochromia, such as iris nevus or melanoma, neurofibromatosis, hemosiderosis, hemochromatosis, Waardenburg syndrome, Fuch heterochromic iridocyclitis, and essential iris atrophy, should be excluded.

Most cases of congenital or early acquired Horner syndrome are of a benign nature. Rarely, congenital Horner syndrome may occur as an autosomal dominant disorder. Hageman et al reported a Dutch family with five cases of congenital Horner syndrome spanning five generations. A history of perinatal trauma, such as brachial plexus injury (Klumpke paralysis), neck or cardiothoracic surgery, carotid dissection, peritonsilar lesions, and surgical or nonsurgical intraoral trauma, may be elicited in many cases, but some cases remain cryptogenic despite extensive investigations. Permanent postganglionic Horner syndrome can develop in children with a middle ear infection. Brachial plexopathies caused by forceps injury at birth are the putative cause in some cases.

MR angiography has recently brought to light the association of congenital Horner syndrome with agenesis of the ipsilateral internal carotid artery. Congenital Horner syndrome has also been reported with hemifacial atrophy, synergistic divergence, basilar impression and Chiari malformation, cervical vertebral anomaly and an enterogenous cyst, and viral infections such as congenital varicella or cytomegalovirus infections, and PHACE syndrome. In acquired pediatric Horner syndrome, it is important to look for Lisch nodules and café au lait spots, because schwannomas, plexiform neurofibromas, or malignant peripheral nerve sheath tumors may affect the sympathetic tract in neurofibromatosis 1. A case of congenital postganglionic Horner syndrome and fibromuscular dysplasia of the ipsilateral internal carotid artery incited speculation that prenatal or neonatal cervical trauma might have been responsible for both findings.

Congenital tumors, including neuroblastoma of the neck, chest, or abdomen have been reported to underlie some cases of congenital Horner syndrome. Most reported cases of neuroblastoma occurred in the neck, where they are frequently mistaken for infectious adenitis, or in the mediastinum, but three patients with abdominal neuroblastoma have also been described. Because the cervical sympathetic chain does not descend to the abdominal level, the Horner syndrome in these cases was probably caused by metastatic cervical lesions or a second (undiagnosed) primary lesion. Cervical neuroblastoma causing Horner syndrome can be associated with other paraneoplastic disorders such as cerebellar degeneration.

Other systemic clues to the presence of neuroblastoma may be present. Nonophthalmologic symptoms of neuroblastoma include pain (due to primary tumor, bone marrow involvement, or abdominal distension), watery diarrhea (due to paraneoplastic secretion of a vasoactive intestinal peptide), and acute cerebellar encephalopathy, which may be related to antineural antibodies such as anti-Hu, formed in response to the tumor that react to the normal cerebellum. There is an unusually high rate of spontaneous regression in the neuroblastoma of young infants, even in the disseminated form. Asymptomatic infants may have biologically favorable tumor with higher rate of spontaneous regression. Horner syndrome acquired in early life may be very difficult to distinguish from congenital cases, but close scrutiny of previous photographs may be helpful.

In a large retrospective study, Mahoney et al found responsible mass lesions in six of 56 children. Two cases with congenital Horner syndrome were caused by mass lesions (neuroblastoma in one case, neurofibroma in the other). They recommended that the brain, neck, and chest MRI with and without contrast, as well as urinary catecholamine metabolite testing, be performed in any child without a surgical history. This study found direct imaging to be more sensitive than urine testing in this setting. Gibbs and colleagues reported a 2-year-old child with congenital Horner syndrome who was healthy until the age of 2 years, when a remote neuroblastoma of the adrenal gland was diagnosed. They argued that both congenital Horner syndrome and neuroblastoma may represent widespread dysgenesis of the sympathetic system. The rare occurrence of underlying tumors, especially neuroblastoma, in a few congenital cases justifies thorough neurodiagnostic evaluation. Mahoney et al recommended palpation of neck, axilla, and abdomen, spot urine for homovanillic acid and vanillylmandelic acid as a ratio of creatinine (which can be falsely negative in patients with small neuroblastomas), and MR imaging of the brain, neck, and chest, with and without contrast (abdomen is unnecessary because the cervical sympathetic chain does not descend to this level).
carotid artery, we believe that MR angiography should also be included in the evaluation. While it has been suggested that a history of forceful manipulation of the neck during birth may reduce the need for extensive systemic evaluation, the possibility of carotid dissection should now be considered and evaluated by MR angiography in this setting.

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