Pediatric Diagnoses
You Don’t Want to Miss

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Learning Objectives

Upon completion of this module, the reader should be able to:

• Identify eye findings that indicate a child may be a victim of physical or sexual abuse
• Consider the implications of pigmented fundus ocular lesions and *Toxoplasmosis* scars in infants
• Describe the potential systemic significance of unusual eye movements and incomitant acquired strabismus in children
• Identify the types of optic nerve hypoplasia and recognize their potential central nervous system and endocrine implications.
• Consider the potential for associated systemic findings with periorcular port-wine stains and capillary hemangiomas.

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Introduction

Certain eye findings alert the savvy ophthalmologist to the presence of systemic disease in children. This Focal Points module highlights a collection of distinct clinical features that call the practitioner to initiate further investigation (Table 1). These features include ocular
findings related to child abuse, unusual eye movements, fundus findings with systemic significance, acquired cranial nerve palsies, optic nerve abnormalities, and birthmarks that are more than skin deep.

Is This Child Safe? Evidence of Child Abuse

The ophthalmologist may be the only health care provider encountering a child who is a victim of abuse. Alternatively, certain eye findings solidify the clinical suspicion of abuse when found in conjunction with other systemic features. When abuse is suspected, referral to the appropriate child protection agency is crucial.

**Table 1. Pediatric Eye Findings and Their Clinical implications**

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Sexually Transmitted Infections

Chronic follicular conjunctivitis not responsive to topical medications in a child raises the possibility of infection with *Chlamydia trachomatis*. Associated findings include watery discharge and a palpable preauricular node. Enzyme-linked immunosorbent assay (ELISA) or immunofluorescent antibody testing of conjunctival secretions is diagnostic. Chlamydia ocular infection occurs by direct or indirect contact with infected genital secretions. Neonatal chlamydia infection results from passage through an infected birth canal. Chlamydia infection in older children is a sign of sexual activity and probable sexual abuse. Treatment for chlamydia infection is systemic erythromycin or azithromycin. Treatment failure occurs in up to 20% of infected individuals so patients should be re-evaluated following treatment.

Lice and nit infestation of the eyelashes in children is not just lousy. Because only pubic lice are trophic for eyelashes, pediatric eyelash pediculosis strongly suggests sexual activity and likely sexual abuse. Ocular treatment involves mechanical removal of lice and nits and suffocation of remaining organisms and eggs with a bland ophthalmic ointment for 7 to 10 days. If necessary, the pubic area should be treated with a lice shampoo. Re-treatment in 7 to 10 days is advised. Contaminated clothing and linens should be cleaned with very hot water or dry-cleaned.

Unusual Eye Movements

Nystagmus in children often accompanies strabismus or is found in association with selected syndromes. Nystagmus is most often horizontal and comitant. A few unusual disturbances of ocular motility deserve increased notice.

Downbeat Nystagmus

Downbeat nystagmus is unusual in children. It is typically worse on lateral gaze and can reflect pathology at the cervicomедullary junction. The Chiari I malformation, increasingly recognized as a source of headache in children, involves herniation of the cerebellar tonsils into the foramen magnum. Eye movement disorders arise from cerebellar ectopia and lower brainstem distortion. Eye findings are frequently intermittent and include acquired esotropia and oscillopsia, typically associated with downbeat nystagmus. Associated features include...
occipital headache that worsens with Valsalva, ataxia, vertigo, disequilibrium, or dysphagia. Posterior fossa decompression can result in improvement in symptoms.

**“Setting Sun” Sign**

An infant with “setting sun” sign demonstrates lid retraction and a tonically downward deviation of the eyes. Mid-dilated pupils that constrict to light but not to accommodation to a near target and convergence retraction nystagmus are associated findings.

This exaggerated form of dorsal midbrain syndrome occurs in infantile hydrocephalus because the posterior commissure is stretched by an enlarged third ventricle or suprapineal recess. An enlarged head size, dilated scalp veins, and tense and bulging fontanelle are additional signs of hydrocephalus and/or shunt failure. Urgent neuroimaging is recommended. Other entities in the differential diagnosis include Marcus Gunn jaw-winking ptosis, neonatal thyroid eye disease, and cranial nerve III palsy with aberrant regeneration. Occasionally the “setting sun” sign in infants is benign without associated hydrocephalus. In these infants, versions are full and lid retraction is absent. Benign tonic downgaze often dissipates by 6 months of age.

**Opsoclonus and Opsoclonus-Myoclonus-Ataxia Syndrome**

Opsoclonus is a striking ocular motility disorder characterized by bursts of multidirectional high amplitude saccades.

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a constellation of opsoclonus, tonic muscle spasm, and inability to control trunk and limb movement. OMAS often presents in the second year of life. Speech problems, irritability, vomiting, sleep disturbance, and lethargy are also features of OMAS. Importantly, neuroblastoma is present in 50% of children with OMAS. The syndrome is a manifestation of the paraneoplastic syndrome that can occur with neuroblastoma. Neuroblastomas associated with OMAS tend to be more mature, with favorable histology, and prognosis for treatment is excellent. OMAS symptoms respond to steroids, immunosuppressants, and biologic agents, although a relapsing and remitting course is common. Despite control of OMAS manifestations with medications, affected children have long-term sequelae with delay in the areas of motor function, sleep, behavior, and speech.

**Congenital Ocular Motor Apraxia**

Infants with congenital ocular motor apraxia (COMA) seem blind for the first several months of life. Horizontal (but not vertical) voluntary saccade initiation is impaired and saccadic amplitude is decreased. Because pursuit in young infants is actually a series of hypometric saccades, young infants with COMA cannot follow an object of interest. Once head control is mastered, infants use a bizarre head thrusting behavior to redirect their gaze. Head thrusts recruit the vestibulo-ocular reflex to drive the eyes opposite to the direction of the head thrust, allowing the gaze to fall on the object of regard. Parents describe their child as looking out the sides of the eyes. With time, the head thrusts become more subtle and act to initiate saccades rather than recruit the vestibulo-ocular reflex. Most children with congenital COMA show some degree of delayed motor, speech, or cognitive development. COMA may be a feature of several neurometabolic diseases, most notably ataxia telangiectasia (Louis-Bar syndrome) and Joubert syndrome.

**Voluntary Nystagmus**

The child with voluntary nystagmus should not mislead the savvy ophthalmologist. Actually, the entity is saccadic oscillation rather than true nystagmus. Voluntary nystagmus is horizontal and comitant, often associated with convergence, and cannot be sustained for greater than 30 seconds. The patient experiences oscillopsia and decreased vision during the episodes. The only treatment necessary is reassurance as to the benign nature of the child’s unique trick.

**Fundus Findings With Systemic Significance**

The posterior segment generally yields scant diagnostic findings in children, as it is usually normal in appearance. Sometimes, however, findings in the posterior segment lead to diagnoses that are life altering.
Toxoplasmosis

Congenital *Toxoplasma gondii* infection occurs in 1 in 1,000 to 1 in 10,000 live births. Ocular involvement occurs in 80% of those infected and presents with atrophic scar(s) with a predilection for the macula. Cytomegalovirus and lymphocytic choriomeningitis virus are other considerations in this setting. Recognition of toxoplasmosis in infancy is critical, as treatment with pyrimethamine, sulfadiazine, and leucovorin for up to a year dramatically decreases the incidence of recurrent macular disease and subsequent neurologic and cognitive complications for both severe and more mildly affected infants. Children with congenital toxoplasmosis should be followed into adulthood, as disease reactivation can occur throughout childhood. Acquired toxoplasmosis infection can occur in older children following exposure to unwashed contaminated vegetables, cat feces, and undercooked contaminated meat.

Pigment Abnormalities

When observing the hypoplastic fovea of a child with oculocutaneous albinism, the clinician should remember two systemic associations. Children with albinism, particularly those who have Puerto Rican ancestry, are very likely to have Hermansky-Pudlak syndrome (Figure 2), a disorder of lysosome-related organelles found in platelets, pulmonary cells, and melanocytes. Absence of dense bodies on whole-mount electron microscopy of platelets is diagnostic. Hypopigmentation results from a reduced melanin production in melanosomes. Systemic complications, including bleeding, pulmonary fibrosis, and colitis, arise from poor platelet aggregation and/or accumulation of ceroid-like substance in many tissues.

Another systemic syndrome associated with albinism, Chédiak-Higashi syndrome, is much more rare than Hermansky-Pudlak syndrome and has no ethnic predilection. The disease involves defects in synthesis and maintenance of storage/secretory granules in various types of cells including melanocytes. Melanosomes in Chédiak-Higashi syndrome are reduced in number and large in size. The function of immune cells is severely impaired and patients are susceptible to pyogenic infections and lymphoma-like conditions that can be life threatening. Hematopoietic stem cell transplantation has been a successful treatment for some.

Pigmented ocular fundus lesions (POFLs) present as multiple, bilateral, pigmented lesions of the retinal pigment epithelium. Most lesions are less than 0.5 disc diameters in size with a hypopigmented tail at one edge (Figure 3). The presence of multiple POFLs should alert practitioners to possible familial adenomatous polyposis (FAP), an autosomal dominant cancer predisposition syndrome involving hundreds to thousands of precancerous colonic polyps. Gardner syndrome is FAP with POFLs and extracolonic manifestations, including polyps of the gastric fundus and duodenum, osteomas of the skull, thyroid cancer, and soft tissue tumors. POFLs are congenital and are therefore the earliest phenotypic marker of Gardner syndrome. POFLs differ from congenital hyper trophy of the retinal pigment epithelium (CHRPE) in their bilaterality and more widespread distribution.

Figure 2 Young woman with Hermansky-Pudlak syndrome. (Courtesy of C. Gail Summers, MD.)

Figure 3 Pigmented ocular fundus lesions (POFL) associated with Gardner syndrome. (Courtesy of Elias Traboulsi, MD.)
The presence of 3 or more POFLs in an individual from an at-risk family indicates that the individual has the FAP gene mutation. FAP diagnosis is crucial because, if left untreated, hundreds to thousands of precancerous colonic polyps become evident by age 19 and colon cancer is inevitable. Prophylactic colectomy prevents the development of colon cancer in patients with FAP and Gardner syndrome.

Double Take: Acquired CN III, IV, and VI Palsies

Acutely acquired incomitant pediatric strabismus should heighten the ophthalmologist’s attention because of the possible systemic implications. Because of the distinct anatomic features of cranial nerves III, IV, and VI, the systemic implications of the acutely acquired palsy depend on the cranial nerve(s) involved. Most concerning to parents is the possibility of an intracranial mass lesion. Other causes of acute cranial nerve palsy in children include inflammation, elevated intracranial pressure, and trauma, with myasthenia gravis also being in the differential diagnosis. Careful history taking and skilled observation identifies possible associated neurologic features including headache, nausea, lethargy, and focal neurologic deficits.

Third Nerve Palsies

The majority of third nerve palsies in children are congenital. Trauma accounts for most acquired third nerve palsies in children. Damage to the nerve can occur anywhere from the nucleus to the orbit. Although traumatic palsies vary from partial to complete, pupillary involvement is usually present. In a complete third nerve palsy, the affected eye is exotropic and usually slightly hypotropic. The lid is ptotic and the pupil is fixed and mid-dilated. The exotropia worsens on attempted adduction of the affected eye.

Nontraumatic causes of acquired third nerve palsies are relatively rare. Ophthalmoplegic migraine involves headache followed within 4 days of onset by palsy of one or more of cranial nerves III, IV, or VI. The third cranial nerve is most frequently involved and the palsy is usually complete. Ophthalmoplegia usually resolves within 3 to 4 days. Ophthalmoplegic migraine is a diagnosis of exclusion once parasellar, orbital fissure, and posterior fossa lesions have been eliminated by neuro-imaging. Acute bacterial meningitis accounts for most cases of infectious third nerve palsy secondary to inflammation of the nerve within the subarachnoid space. Children may present with lethargy, headache, and neck stiffness. Vascular causes of third nerve palsies are very rare in children. Subarachnoid hemorrhage is invariably present. Intracranial neoplasm accounts for roughly 10% of acquired third nerve palsies and many different neoplasms have been associated with acquired third nerve palsy in children. Notable exceptions include medulloblastoma and astrocytoma, suggesting that the midline location of the third nerve is protective. Myasthenia gravis can mimic a third nerve palsy and should be considered in the differential diagnosis in a child with a painless, pupil sparing third nerve palsy. The strabismus is usually observed to vary throughout the day and the associated ptosis should improve following sleep.

Third nerve aberrant regeneration occurs a few weeks to months following oculomotor nerve injury. Aberrant regeneration most frequently results from palsies caused by trauma, tumors, or aneurysms, but can also occur in congenital palsies. Several patterns in the affected eye exist, including eyelid elevation on attempted downgaze or on attempted adduction, globe retraction with vertical eye movement, and constriction of the pupil with adduction.

Fourth Nerve Palsies

Most “acquired” childhood fourth nerve palsies are not truly acquired but represent a decompensation of a congenital palsy. The remainder of acute fourth nerve palsies is nearly entirely traumatic in origin. A unilateral fourth nerve palsy involves a hypertropia that is worse in contralateral gaze and ipsilateral head tilt. A head tilt away from the side of the palsy is typical. Amblyopia is rare because a compensatory head posture is usually adopted to allow development of single binocular vision. Signs of a decompensated congenital palsy include long-standing head tilt, generous vertical fusional amplitudes, and facial asymmetry. Very rarely is a fourth nerve palsy in children due to neoplastic, vascular, or neurologic etiology.

Sixth Nerve Palsies

Sixth nerve palsies are the most common acquired cranial nerve palsy in childhood. Unilateral or bilateral abduction deficits and an esodeviation worse at distance than at near are characteristic. Patients often have a face turn toward the side of the palsy. Isolated sixth nerve palsies can occur in children following immunization or a viral infection. Such benign palsies are large, isolated, and appear acutely. Benign sixth nerve palsies generally resolve over 8 to 12 weeks, but can recur. Nonisolated
sixth nerve palsies are worrisome for intracranial pathology and associated signs include optic nerve edema or atrophy, facial palsy, headache, nausea and alterations of gait, coordination, or mental state. Sixth nerve palsy following trauma is relatively common, either from direct injury or elevated intracranial pressure.

Although series differ in the relative percentage of pediatric patients with benign vs non-benign palsies, all new sixth nerve palsies should be evaluated by neuroimaging even if they appear isolated. Trauma and neoplasms are the most common causes of acquired sixth nerve palsies in children. Juvenile pilocytic astrocytomas and medulloblastomas account for majority of brainstem tumors in children. Juvenile pilocytic astrocytomas in general tend to have a more benign course and prognosis and are slower-growing tumors while medulloblastomas tend to grow more rapidly, are more malignant, and have a poorer prognosis. Both tumors can present with elevated intracranial pressure with hydrocephalus and sixth nerve palsies due to downward displacement of the brainstem, thereby placing the sixth nerves on stretch. Etiologies of intracranial hypertension include posterior fossa tumors, neurosurgical trauma, shunt failure, pseudotumor cerebri, and venous sinus thrombosis. Optic nerve swelling or atrophy is frequently associated. Infection and inflammation, such as meningitis and Lyme disease, can also present with acquired sixth nerve palsies in children and lumbar puncture with examination of spinal fluid may be necessary.

Trauma is the most common cause of multiple acquired cranial nerve palsies occurring in children. Any inflammatory, infectious, or neoplastic disease involving the brainstem, orbital apex, skull base, or cavernous sinus can also involve multiple cranial nerves. Neuroimaging is urgent.

The development of strabismic amblyopia in young children in association with third, sixth, and multiple cranial nerve palsies is common. Early intervention is most successful, but can be challenging with large breaks in treatment occurring while attention is directed to the primary disease. It is crucial for the ophthalmologist to remain involved in the care of the patient following diagnosis and to educate parents regarding the fragility of the developing visual system.

Did That Nerve Look Funny?

The optic nerve in a fussy child zooms from view, leaving the ophthalmologist wondering “was that nerve normal?” Several optic nerve abnormalities have systemic implications for children.

**Optic Nerve Hypoplasia**

Children with optic nerve hypoplasia may present with unilateral or bilateral signs of vision impairment. The condition is sporadic and the etiology unclear, although young maternal age, prima gravida, smoking, and fertility or antidepressant medications are possible risk factors. The hypoplastic nerve is usually one-fourth to one-third of normal size, grey or pale, and surrounded by a halo of increased or decreased pigment. The major retinal vessels are often tortuous or abnormal (Figure 4).

Optic nerve size and color do not correlate directly with function; visual acuity depends on the relative preservation of macular neurons and can range from 20/20 to no light perception.

Septo-optic dysplasia (de Morsier syndrome) describes optic nerve hypoplasia in association with midline brain abnormalities, absence of the septum pellucidum, and agenesis or thinning of the corpus callosum. While corpus callosum hypoplasia is highly correlated with subsequent developmental delay, the absence of the septum pellucidum has no developmental consequences for children with septo-optic dysplasia. Nearly half of children with septo-optic dysplasia have cerebral hemispheric abnormalities including schizencephaly, cortical dysgenesis, periventricular leukomalacia, and porencephaly.

Neurohypophyseal abnormalities, particularly posterior pituitary ectopia, present in 6% to 64% of children
with optic nerve hypoplasia and are associated with deficiencies in growth, thyroid, corticotropin, and antidiuretic hormones. Hypothyroidism can be manifested as prolonged neonatal jaundice and poor growth, and is highly correlated with adverse developmental consequences. Growth hormone deficiency may not be evident until age 3 to 4 years when prolactin levels fall. Hypocortisolism places children with septo-optic dysplasia at risk for sudden death during a febrile illness. Diabetes insipidus is also possible due to lack of a vasopressin hormone. All children with optic nerve hypoplasia should receive an endocrine evaluation and neuroimaging with attention to the posterior pituitary.

Optic nerve hypoplasia can involve only part of the optic nerve. Segmental optic nerve hypoplasia, typically superior, with a corresponding visual field deficit can present in infants of insulin-dependent diabetic mothers (Figure 5). Patients typically have no other intracranial or systemic abnormalities and visual acuity is good.

### Periventricular Leukomalacia

Periventricular leukomalacia is a perinatal ischemic injury that occurs primarily in premature infants and produces an excavated optic nerve that appears glaucomatous (Figure 6). Intraocular pressures are normal. Periventricular leukomalacia affects oligodendrocytes in the periventricular area. Retrograde trans-synaptic degeneration produces a nerve with an abnormally large cup and a thin neuroretinal rim. Cerebral palsy is a frequent comorbidity. It is important for the ophthalmologist to distinguish this nonprogressive cupping from glaucoma. Because measurement of intraocular pressure in the

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**Figure 5** Segmental optic nerve hypoplasia. **a.** Optic nerves with inferior segmental optic nerve hypoplasia. **b.** Visual fields demonstrating superior visual field deficit. Child was the 10 lb, 10 oz product of a pregnancy complicated by maternal diabetes. Vision is normal.
office is challenging, the diagnosis of glaucoma in children is made in conjunction with other suggestive findings including an increasingly myopic refractive error, an enlarged corneal diameter, and a cupped optic nerve. A history of light sensitivity and tearing also suggests glaucoma. Sometimes an exam under sedation or general anesthesia is necessary to obtain a comprehensive glaucoma evaluation in young children. Careful follow-up is essential in suspected or confirmed pediatric glaucoma.

Birthmarks That Are More Than Skin Deep

Cutaneous vascular malformations frequently appear in the head and neck region. When present around the eye, they can jeopardize vision through induced amblyopia or glaucoma. The import of these lesions does not stop at the eye, however.

**PHACES Syndrome**

Ophthalmologists frequently assess and treat amblyopia associated with periorcular capillary hemangiomas. Facial cutaneous hemangiomas vary in size. Careful observation demonstrates that larger hemangiomas localize to one or more distinct facial segments (Figure 7). Extra

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*Figure 6* Excavated optic nerve associated with periventricular leukomalacia. (Reprinted, with permission, from Brodsky MC. Congenital optic disc. In: David Taylor, Craig S. Hoyt, eds. *Pediatric Ophthalmology and Strabismus*, 3rd ed. London: Elsevier Ltd.; 2005:628.)

*Figure 7* Diagram of segmental patterns of facial capillary hemangiomas. (Reprinted, with permission, from Haggstrom AN, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics*. 2006;117:699.)
care is needed in the assessment of larger, periocular segmental hemangiomas because of the potential for associated ocular and systemic abnormalities. The neurocutaneous syndrome PHACES (OMIM 606519) describes patients with segmental hemangiomas who exhibit associated structural abnormalities of the brain parenchyma, cerebral vasculature, heart, eyes, and chest wall (Posterior fossa malformations, Hemangiomas, Arterial abnormalities, Cardiac defects, Eye abnormalities, and Sternal or ventral defects). PHACES affects up to one-third of patients with segmental hemangiomas. PHACES is non-familial, shows a strong female preponderance and, in contrast to localized hemangiomas, affects more full term than preterm infants.

Ophthalmologists are likely to encounter patients with PHACES because the large majority of affected individuals have cutaneous hemangiomas that involve the superotemporal S1 segment (Figure 8). Large facial hemangiomas involving the S1 segment confer high risk for ipsilateral arterial cerebrovascular anomalies. Arterial dysplasia, aberrant origin or course of the principal cerebral arteries, hypoplasia, and absence of vessels are the most common vascular anomalies. A progressive cerebrovasculopathy has been reported in PHACES syndrome, which can cause ischemic stroke or seizure.

Beta-blockers have recently shown great promise in the treatment of capillary hemangiomas. Propranolol should be used with extreme caution in the treatment of hemangiomas in infants with PHACES, however, because the potential for hypotension and decreased perfusion through aberrant or stenotic vasculature can have a catastrophic consequence.

PHACES-associated ocular abnormalities are relatively rare and include morning glory disc anomaly, retinal vascular abnormalities, persistent fetal vasculature, optic nerve hypoplasia, cataract, microphthalmos, Horner syndrome, coloboma, sclerocornea, and peripapillary staphyloma.

The posterior fossa abnormalities associated with PHACES include cerebellar hypoplasia or dysgenesis and Dandy-Walker complex. Coarctation of the aortic arch is the most frequent cardiac abnormality. Ventral or midline defects include sternal clefts, supraventricular raphe, and thyroid abnormalities. Both the cardiac and midline defects are more commonly seen with S3 involvement.

In addition to a complete ophthalmologic examination, infants with PHACES should have a thorough examination by a primary care doctor familiar with its diagnostic criteria as well as brain, cerebrovascular, and cardiovascular imaging.

**Port-Wine Stain**

Port-wine stains are vascular birthmarks comprised of superficial and deep capillary malformations that produce a reddish or purplish discoloration to the skin. These stains occur most commonly on the face, but do not follow the segmental pattern of distribution that is seen in larger capillary hemangiomas. A port-wine stain involving the distribution of the ophthalmic division of the trigeminal nerve with upper lid involvement places a child at increased risk for glaucoma. Additionally, 10% to 20% of people with port-wine stain have Sturge-Weber syndrome (encephalotrigeminal angiomatosis), a sporadic congenital syndrome in which the facial port-wine stain is associated with ipsilateral pial vascular abnormalities and a high incidence of glaucoma (up to 70%). The onset of port-wine stain–associated glaucoma is bimodal. Glaucoma appearing in infancy is caused by structural outflow abnormalities, whereas that occurring in older children and adolescents is caused by increased episcleral venous outflow pressure.

![Figure 8](image-url) Infant with segmental hemangioma involving S1 distribution, before (a) and after (b) treatment with propranolol. Child also had an ipsilateral morning glory disc anomaly and ipsilateral cerebral vascular abnormalities and was diagnosed with PHACES.
Since the mid-1990s, pulse dye laser has been used to reduce the visible color of port-wine stains by obliterating the superficial portion of the birthmark. Because laser treatment reduces the degree of collateral venous outflow, it has been theorized that the risk of glaucoma could increase, although that has never been reported. Further, retrospective comparison of patients with Sturge-Weber who did and did not receive laser treatment suggests no increased glaucoma risk.

Conclusion

Children benefit from the care of ophthalmologists who attend to the significance of unusual features found during the ocular examination. Recognition of these important findings alerts ophthalmologists to the necessity for additional testing and consultation from other medical or surgical specialists. Familiarity with these findings and their broader significance aids the comprehensive ophthalmologist in providing quality care to pediatric patients.

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Clinicians’ Corner

Clinicians’ Corner provides additional viewpoints on the subject covered in this issue of Focal Points. Consultants have been invited by the Editorial Review Board to respond to questions posed by the Academy’s Practicing Ophthalmologists Advisory Committee for Education. While the advisory committee reviews the modules, consultants respond without reading the module or one another’s responses. –Ed.

1. How long do a baby’s retinal hemorrhages persist after vaginal delivery?

Dr. O’Hara: Retinal hemorrhages occur in approximately one-third of neonates after vaginal delivery. Babies born via vacuum delivery have a much higher incidence of retinal hemorrhages; over 75% of these neonates will have retinal hemorrhages. The retinal hemorrhages seen in babies born via vacuum-assisted vaginal delivery are usually more severe than those encountered in non-vacuum-assisted births. It is important to note that retinal hemorrhages can also occur after Cesarean section birth, but the incidence is less than 10% in that group.

Most retinal hemorrhages associated with normal births resolve within 3 weeks. The more severe hemorrhages seen in vacuum-assisted births may take up to 2 months to clear. This information becomes important in discussions surrounding the timing and differential diagnosis of retinal hemorrhages associated with shaken baby syndrome. I quote the study by Hughes et al when discussing the timeline of retinal hemorrhages associated with birth. (See “Suggested Reading.”)

Dr. Weiss: Retinal hemorrhages due to the trauma of the birthing process are normally present in newborns with reported prevalences ranging from 10% to 30%. The hemorrhages tend to be intraretinal with the variable presence of white-colored centers but can be subretinal or preretinal in location. In general, the hemorrhages fade and then disappear over a few weeks without sequelae. On occasion there can be a vitreous hemorrhage of varying extent that takes up to 6 months to resorb. Delayed resolution of a vitreous hemorrhage can be amblyogenic, directly related to visual deprivation, or indirectly related to axial elongation with unilateral high myopia. Of particular note, neither retinoschisis cavities nor circumferential folds centered on the macula occur as a result of birth trauma. The presence of these findings should prompt an evaluation for nonaccidental trauma.
2. **In a young child with suspected toxoplasmosis, what is the work-up and when would you start systemic treatment?**

**Dr. O’Hara:** The diagnosis of toxoplasmosis is primarily a clinical one. The usual findings are focal retinochoroiditis with vitritis. Many times, the retinochoroiditis is adjacent to or at the edge of a previously noted scar. When the vitritis is particularly severe, one can see the characteristic “headlight in the fog” appearance. In less characteristic cases, serological testing via indirect fluorescent antibody or enzyme-linked immunosorbent assay (ELISA) on undiluted sera can be helpful. Even weakly reactive results are significant, but false positives do occur. Polymerase chain reaction (PCR) testing of intraocular fluid can also be helpful. However, this should not be attempted until tumor has been ruled out as a possibility.

Toxoplasmosis affecting the eye is often congenital in origin. If the patient is immunocompromised, systemic treatment is warranted. However, if the patient is immunocompetent, treatment is not warranted unless vision is threatened as most infections are self-limited. My indications for treatment would be significant vitritis or active lesions adjacent to the optic nerve or within the temporal vascular arcades.

If treatment is warranted, several different regimens have been used. I start with the classic “triple” therapy involving the use of pyrimethamine, sulfadiazine, and prednisone. Under this regimen, patients are also given folinic acid because of the risk of bone marrow suppression associated with pyrimethamine. The prednisone is very helpful in quieting the vitritis but should be started at least one day after antibiotic therapy is initiated with the other two agents, and it is tapered after 1 to 2 weeks. Clindamycin can be added as a fourth agent if triple therapy fails to quell the infection or trimethoprim/sulfamethoxazole can be substituted for triple therapy if pyrimethamine, sulfadiazine, or clindamycin is not tolerated. Treatment usually takes a month.

**Dr. Weiss:** Presumably toxoplasmosis in this young child is suspected because of finding a chorioretinal lesion on routine examination or because of posterior uveitis. My work-up would vary depending on the age of the child, activity of the disease, and past medical history. If this child is less than 1 year of age, I would recommend serologic testing to confirm the diagnosis, neurologic evaluation including lumbar puncture, brain computed tomography (CT) scan, and assessment of hepatic function. If this was a healthy older child with an inactive chorioretinal scar or active chorioretinitis, I would recommend a comprehensive evaluation by the child’s primary care physician, serologic testing to confirm the diagnosis and brain CT if there were developmental or learning issues. If this child had a history of malignancy, organ transplantation, corticosteroid usage, or immune deficiency, I would aggressively pursue serologic testing of the serum and cerebrospinal fluid, neurologic examination to include brain CT scan and lumbar puncture, complete blood count, serum immunoglobulins, serum alanine aminotransferase, direct and indirect bilirubin, and T-cell subsets.

Treatment recommendations would also vary according to the age of the child, activity of the disease, and past medical history. If this was an infant with a congenital infection, I would recommend pyrimethamine, sulfadiazine, and leucovorin for 1 year. The same treatment regimen would be recommended for the older child with active chorioretinitis or the immune-suppressed child but the duration of treatment would be limited to 1 to 2 weeks beyond the resolution of the inflammatory signs in the immunocompetent child and 4 to 6 weeks in the immunologically deficient child. In the older child, one could consider oral Bactrim. Corticosteroids could be added if there was inflammation of the posterior pole that encroached on the optic nerve or macula.

3. **A child is seen with multiple small, pigmented spots bilaterally. There is no family history of Gardner syndrome. What evaluation is recommended?**

**Dr. O’Hara:** Any bilateral presentation of focal pigmented retinal lesions should raise suspicion of Gardner syndrome. This is especially true if the lesions have the characteristic halo of depigmentation with a “comet tail.” Although Gardner syndrome is inherited in an autosomal dominant manner and a family history of familial adenomatous polyposis would be expected, one cannot rule out spontaneous mutation of the APC gene. Also, one cannot always depend on the reliability of a family’s
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medical history. Because of this, further evaluation should be undertaken.

The focal pigmented lesions associated with Gardner syndrome do not usually increase in number over a lifetime and are usually present in early childhood. Therefore, serial retinal examinations are not helpful. The child should be referred for molecular testing for a mutation on the APC gene. Although polyps usually appear in individuals with Gardner syndrome in the teenage years, other extracolonic tumors and abnormalities can also occur. Therefore, colonoscopy alone is not a reliable method of ruling out Gardner syndrome.

Dr. Weiss: Assuming the pigmented spots are consistent with grouped pigmented fundus lesions, I would be concerned that this child has Gardner syndrome and is at high risk for colon cancer by age 45. The lack of a family history does not exclude the diagnosis of Gardner syndrome but rather indicates this child has a de novo mutation of the APC gene. First, I would inquire about a family history of cancers, especially of the colon, brain, thyroid, and liver. Then I would refer this child for mutational analysis of the APC gene and recommend a consultation with a gastroenterologist. If gene testing is positive, I would emphasize the need for clinical screening by the primary care physician for brain tumors (glioma, medulloblastoma) and hepatoblastoma on a yearly basis.

4. A mother reports new onset of ptosis in her 1-year-old child, and when you lift the lid, the eye is exotropic and the pupil is fixed and dilated. What do you do next? How would this differ if these findings were noted in these clinical scenarios: immediately after birth and in an 8-year-old child who had a severe headache earlier in the day?

Dr. O’Hara: The above scenario describes the sudden onset of a complete one-sided CN III palsy in a 1-year-old child without other neurologic findings. This is an unusual presentation. The differential diagnosis would certainly include neoplasm, infection, inflammation or trauma (to include nonaccidental trauma). Although extremely rare in this age group, intracranial cerebrovascular malformations must be considered. Myasthenia can be ruled out by the pupillary involvement. A careful history must be taken to determine antecedent infections, symptoms of active infection, and past trauma. After a full eye exam, an MRI/MRA would be my first step in the work-up of this patient.

The differential diagnosis and work-up changes when the scenario switches to a complete congenital CN III palsy. Intrauterine insult, primary midbrain anomaly, or perinatal trauma are the usual causes. Extent of work-up would be dictated by the other findings on physical exam. In this case, a consultation with the child’s pediatrician would guide the next step.

The third scenario is similar to that of the 1-year-old child except that the 8-year-old has history of a severe headache prior to the onset of the complete third nerve palsy. The same differential diagnostic considerations would pertain to this child with the addition of ophthalmoplegic migraine. My diagnostic approach would be the same, realizing that a negative MRI/MRA does not exclude ophthalmoplegic migraine, but thickening and gadolinium enhancement of the third nerve in the subarachnoid region helps establish this diagnosis.

Dr. Weiss: The physical findings in this child are consistent with an acquired oculomotor paresis. First, I would inquire about an antecedent history of head trauma, recent neurosurgical procedure, febrile illness, vesicular (herpes zoster) or pigmented (café-au-lait) skin rash, emesis, limb weakness (Weber syndrome), and changes in mental status or activity level (chronic subdural hematoma). Family history of arteriovenous malformation or intracranial hemorrhage would be relevant. Then I would do a comprehensive eye examination including assessment of the orbit and conjugate eye movements and an abbreviated neurologic examination focusing on the cranial nerves and central nervous system long tracts. If there were no signs of orbital or cavernous sinus involvement, I would recommend a neurologic evaluation and brain MRI with contrast to exclude an intracranial mass (brain stem tumor, neurolemmoma, arachnoid cyst, infectious or carcinomatous meningitis, intracranial bleed, or infiltrative process). If there were concerns about an AVM, or vascular anomaly, I would advise radiology to proceed with an MR angiography. The presence of isolated orbital signs (conjunctival chemosis, proptosis, vascular congestion) would prompt me to proceed with a CT of the orbit and brain.
Dr. Weiss: My indications for treating infantile periocular hemangioma are primarily induced astigmatism and ptosis with deprivation amblyopia. Our non-ophthalmologic colleagues are primarily treating to suppress the growth of unsightly and potentially disfiguring tumors of the face, including the periorbital area. This recent trend of pre-emptive treatment has been prompted by the therapeutic efficacy and low incidence of potential complications of beta-blockers compared to oral corticosteroids. In our geographic region, oral propranolol has become the preferred treatment option for many pediatricians, dermatologists, and ophthalmologists.

5. What are your indications for treating infantile periocular hemangiomas?

Dr. O’Hara: My indication for treating infantile periocular hemangiomas is vision loss from amblyopia. The most common causes of amblyopia in periocular hemangiomas are ptosis and anisometropia. I do not treat for cosmetic reasons. This is sometimes difficult for parents to understand as they are devastated by the appearance of their child and alarmed by the sometimes dramatic growth of the lesion. I spend a great deal of time discussing the risk/benefit ratio for treating these lesions. I reassure the parents that this is a self-limited condition and that the lesion will eventually stop growing and then slowly regress, fully or partially, over several years. It is helpful to show parents pictures of children who had infantile periocular hemangiomas to demonstrate how the lesion changes in appearance over time and to prepare them for what to expect with their child.

My personal guidelines on when to treat an amblyogenic capillary hemangioma are twofold. If the anisometropia is greater than 2 diopters of hyperopia or astigmatism and not amenable to patching and refractive correction, I will treat. If the ptosis is such that the lid cannot clear the pupil, I will treat. If the ptosis is borderline, I will attempt part-time patching of the uninvolved eye. Close follow-up is necessary in the proliferative phase and I usually see these children monthly. My preferred medical treatment is beta-blocker therapy.

Dr. Weiss: I have used topical beta-blockers for the treatment of small superficial tumors of the eyelid and

If the patient was a newborn, I would perform a comprehensive eye and limited systemic examination, and recommend a neurologic consultation and brain MRI in view of the high likelihood of a structural brain malformation. I would also carefully evaluate the cerebellar vermis to exclude Joubert syndrome, in which oculomotor paresis is well described.

In the 8-year-old with severe headache, I would consider ophthalmoplegic migraine and Tolosa-Hunt syndrome, but first, I would recommend a brain MRI scan to exclude an intracranial bleed, dural fistula, cavernous sinus thrombosis, tumor, and infiltrative process of the meninges.

6. What is your current protocol for the use of beta-blockers for treatment of hemangiomas in early childhood?

Dr. O’Hara: The use of beta-blockers in the treatment of capillary hemangiomas is rapidly evolving since its introduction in 2008. Several case studies have documented the effectiveness of both systemic and topical beta-blockers. Ongoing clinical trials will further refine treatment strategies.

My personal strategy is to have the child undergo cardiac evaluation with electrocardiogram, echocardiogram, and a full physical examination. While the child is on therapy, I co-manage with the child’s pediatrician who will monitor heart rate, blood pressure, electrolytes, and blood glucose levels. This may be excessive, but I feel it is necessary until more is known about the effects of long-term topical or systemic beta-blocker therapy on infants in this setting. I will then begin a topical beta-blocker. Topical timolol in either solution or gel will be applied to the lesion twice daily. If there is insufficient response after 1 month of therapy, I will initiate systemic beta-blocker therapy. The usual protocol is to increase the dose of propranolol over a 2-week period to 2 mg/kg/day, divided into 3 doses. This is continued until the lesion is no longer in the proliferative phase. Propranolol is then tapered off over a 2-week period.

Dr. Weiss: I have used topical beta-blockers for the treatment of small superficial tumors of the eyelid and
observed good responses. Although systemic complications have not been reported with topical propranolol, such complications are a potential risk owing to absorption across the thin skin of infants. For larger more extensive tumors of the eyelid and orbit I have found oral beta-blockers to be a better treatment option. Propranolol has a rapid onset of effect that persists on maintenance doses (0.5 to 2.0 mg/kg) and has been shown to be relatively safe. Owing to its blockade of the beta-adrenergic receptor, propranolol treatment can cause bradycardia, hypotension, and bronchoconstriction and blunt the catecholamine response to hypoglycemia. Therefore, children for whom oral propranolol is recommended need a baseline cardiac evaluation including echocardiogram and electrocardiogram. Some clinicians have children on treatment wear a digital blood pressure device to monitor for episodes of hypotension. The current literature indicates that the benefits of oral propranolol exceed the potential risks. Prospective trials to evaluate the relative risks and benefits of oral propranolol versus systemic corticosteroids at our institution have stalled owing to patient preference for oral propranolol.

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