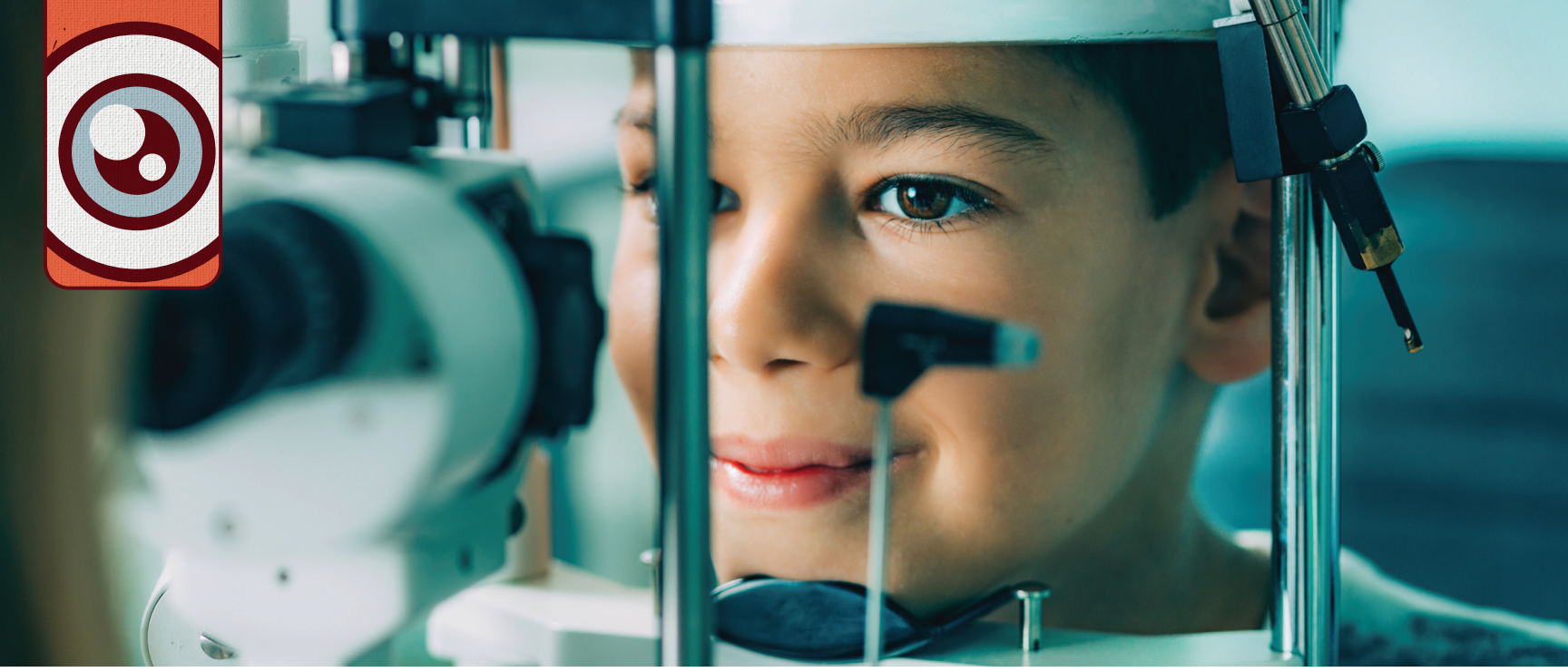

RARE ANTERIOR SEGMENT DISEASES IN CHILDREN

A rundown of conditions to watch out for when examining pediatric patients.

BY AMY WATERS, OD, FAAO

Certain anterior segment diseases are found more commonly in childhood than adulthood. As an optometrist, it's important to be familiar with the signs and symptoms of these vision- and life-threatening conditions, many of which are associated with systemic diseases, so that treatment can begin as early as possible.

This article describes some of the rare conditions you may encounter during an optometric examination and explains what next steps to consider.

PEDIATRIC THYROID EYE DISEASE

Graves disease, an autoimmune condition caused by the presence of autoantibodies in thyroid cells, is less common in children than adults; still, children make up an estimated 2.5% of patients with this disease (approximately 0.8 cases per 100,000 children).[1,2] Thyroid eye disease is typically less severe when it occurs in childhood, especially young children.

The hallmark ophthalmologic signs of Graves disease are lid retraction, proptosis, and strabismus (Figure 1). When you discover these signs in pediatric patients, they should be urgently referred for thyroid labs and autoantibody studies. Proptosis can be unilateral or bilateral; cases of unilateral proptosis should receive imaging to rule out a mass. CT scans are often performed initially, because they can often be obtained more readily on an emergent basis; however, MRI scans may be more beneficial in differentiating causation.[1,2]

Children with Graves disease should receive a thorough ocular evaluation to rule out ocular involvement and secondary effects, such as exposure keratopathy, optic nerve compromise, and strabismus. Children with suspected Graves ophthalmopathy should also be referred to a pediatric oculoplastic surgeon due to long-term complications associated with the disease. An MRI may be warranted in some cases to evaluate the possible involvement of extraocular muscles and the risk of optic nerve compromise.[1,2]

RHABDOMYOSARCOMA

Rhabdomyosarcoma is a rare malignancy occurring almost exclusively in children and adolescents. Of the two main subtypes (embryonal and alveolar) that affect pediatric patients, embryonal involves the head and neck more frequently and is the most common type for orbit involvement. The incidence is

approximately 4.5 cases per 1 million children, and it is more common in boys than girls.[3-5] Some studies have found that minor trauma may precede diagnosis.[3-5] In cases with orbital involvement, the superior location presents most frequently, but it can occur in any location, including inferiorly (Figures 2 and 3). Orbital rhabdomyosarcoma usually presents as a rapidly growing mass with proptosis and lid edema.[3-5]

Prompt imaging and treatment is essential to manage disease progression. As with proptosis, CT scans are often considered first-line due to availability, although MRI's may be more helpful for differential diagnosis and staging. Urgent referral to pediatric ophthalmology is also indicated. Multiple specialists, including pediatric oculoplastic surgeons and pediatric oncologists, are often required for long-term care.[3-6]

Due to typical early diagnosis and treatment advances, orbital rhabdomyosarcoma is associated with better outcomes than many other locations; children with isolated orbital rhabdomyosarcoma have an estimated 97% 5-year survival rate.[3-5]

Figure 1. A young patient with Graves disease with bilateral proptosis (A) and lid retraction (B).

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a rare condition that can present anywhere in the body, and isolated lesions are associated with better outcomes than multisystem involvement. LCH has an incidence of approximately four to nine cases per 1 million children, and there is much debate as to whether the condition represents a malignancy or an inflammatory condition. Biopsy is required for definitive diagnosis. For certain high-risk sites, including the eye, guidelines recommend treatment with chemotherapy due to the potential for central nervous system involvement.[7-8]

In ocular cases of LCH, the most common location for the lesion is the superior temporal orbit. It typically presents as a slow- or fast-growing swelling of the upper lid that can be associated with mild pain and proptosis. Differential diagnosis includes dacryoadenitis, periorbital and orbital cellulitis, rhabdomyosarcoma, and other masses. On imaging, a hallmark symptom of LCH is an osteolytic lesion, often causing destruction of the superior orbital rim. When isolated lesions in the orbit are diagnosed early and treated promptly, children often have good outcomes, both visually and systemically; however, reoccurrence of the disease has been noted.[7,8] In cases of new onset orbital masses of unknown etiology in children, CT scans are often first-line due to increased availability on an urgent basis, but an MRI scan may give more information to help in differential diagnosis.

AT A GLANCE

- Certain anterior segment diseases present more commonly in childhood than adulthood.
- With the advances in genetic testing, causes can now be identified for more than 50% of cases of developmental anterior segment conditions.
- Knowing the proper next steps to take in such situations could make a crucial difference to the life and visual outcomes of the patient.

MAC SPECTRUM DISORDERS

Microphthalmia, anophthalmia, microphthalmia, and uveal coloboma (MAC) are three related developmental disorders of the eye that have been characterized as a spectrum. The more severe the disease symptoms, the more likely it has a genetic cause; suspicion or diagnosis of any of these conditions warrants prompt genetic testing.[9,10]

Anophthalmia and Microphthalmia

Anophthalmia is characterized by the absence of normal ocular structures such as the optic pit; microphthalmia, in contrast, usually presents as a smaller than normal eye. In some

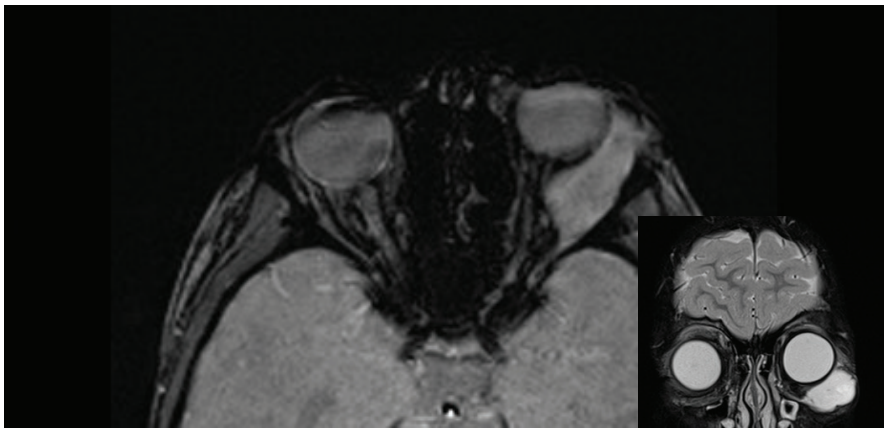

Figure 2. MRI of an infraorbital rhabdomyosarcoma with posterior extension in the patient's left eye. Note the globe displacement.

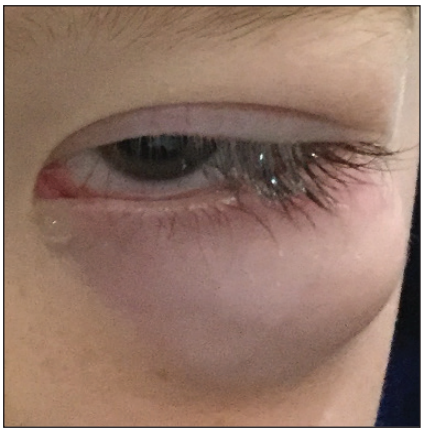

Figure 3. Photograph of the left eye described in Figure 2, showing presentation and atypical inferior location.

cases of simple microphthalmia, the eye appears structurally normal other than size. More severe cases can have other structural abnormalities, such as anterior segment dysgenesis, cataracts, or colobomas. The most severe cases of microphthalmia and anophthalmia are frequently associated with systemic syndromes.[9,10]

Rubella, cytomegalovirus, and toxoplasmosis are known infectious causes of these diseases, but most cases have a genetic cause. In severe cases, referral to an ocularist is warranted for conformers or prosthesis to maintain normal growth of the orbit. In unilateral cases that affect vision, protective eyewear is essential to shield the normal seeing eye. Axial length is beneficial in the diagnosis of suspected microphthalmia.[9,10]

Uveal Coloboma

Uveal coloboma is a congenital anterior segment developmental anomaly that is typically diagnosed in infancy and is characterized by incomplete closure of the embryonic optic fissure. Most cases are sporadic and may be caused by de novo genetic mutations. The incidence of uveal coloboma is approximately two to 14 cases per 100,000 children. The most common location is inferior nasal, but any ocular structure can be affected, including the eyelid and iris.[11,12]

Because of the high incidence of systemic associations, a careful history and genetic evaluation is warranted if anophthalmia, microphthalmia, or uveal coloboma is suspected. Up to two thirds of children with ocular coloboma may have systemic associations, the most common being CHARGE syndrome. CHARGE hallmark findings include coloboma, heart defects, atresia of the choanae, reduced physical growth, mental development delays, genital anomalies, and ear malformations. Because systemic associations can be associated with morbidity, early diagnosis and treatment is key, and coloboma may be the presenting sign of the syndrome. The incidence of CHARGE syndrome is approximately one case per 100,000 children and has been strongly associated with the *CHD7* gene. Coloboma can also occur without systemic associations or it can be inherited in autosomal dominant, autosomal recessive, or x-linked patterns.[11,12]

In unilateral cases of uveal coloboma, amblyopia can develop and should be treated. Patients with retinal involvement may have poorer visual outcomes, especially with macular involvement. Patients with posterior segment involvement are at higher risk for retinal detachment and should be educated and monitored closely.[13]

PAX6-ASSOCIATED DISORDERS

More than 500 distinct mutations have been associated with the *PAX6* gene, which encodes a protein that plays a critical role in the formation of the eyes. Such mutations can affect multiple structures of the eye and cause a variety of disorders, including microphthalmia, aniridia, and anterior segment dysgenesis, among other conditions.[10,14,15]

Aniridia

Aniridia is a disorder that involves partial or complete absence of the iris structures. Approximately two thirds of patients with this disorder have a family history; other cases are caused by sporadic mutation. It has been highly associated with *PAX6* genetic abnormalities and has 100% penetrance (meaning all individuals with the causative mutation will show symptoms) with variable expression; therefore, each patient suspected of having aniridia should undergo genetic evaluation. Aniridia can be associated with Wilms tumor, a renal malignancy (or nephroblastoma) caused by mutations of the *WT1* gene. Genetic evaluation should include verification of whether abnormalities are present in regions associated with Wilms tumor.[9,12,13]

Children with aniridia often have other structural abnormalities, including foveal hypoplasia, corneal disease, progressive corneal changes, limbal stem cell insufficiency, cataracts, and lens

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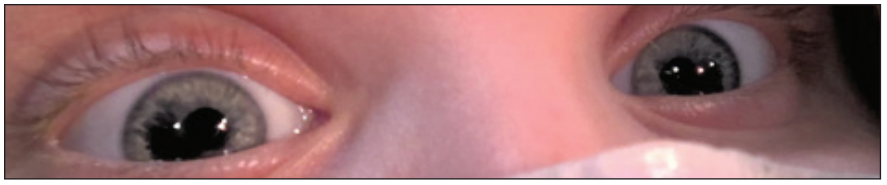

Figure 4. Bilateral anterior segment dysgenesis with greater involvement in the temporal iris of each eye.

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dislocation. Vision is universally reduced, and nystagmus is typical. Glaucoma and keratitis can also develop with increasing age. MRI abnormalities and auditory deficits are high in patients with *PAX6*-related aniridia. Aniridia can also be an indication of Gillespie syndrome and WAGR syndrome.[10,14,15]

Anterior Segment Dysgenesis

Anterior segment dysgenesis describes a heterogenous group of rare *PAX6*-associated disorders that can be mild to severe in appearance. Patients tend to present with unique anterior segment disease, and many developmental abnormalities of the anterior segment are first noted in childhood. Iris structures alone or multiple anterior segment structures can be affected (Figure 4). Patients with anterior segment dysgenesis are at higher risk for glaucoma. Studies have estimated that up to 50% of patients with anterior segment dysgenesis develop glaucoma.[15,16] If glaucoma is suspected, referral to a pediatric glaucoma specialist is recommended.

VIGILANCE IS KEY

As optometrists, we may not encounter these rare diseases frequently, but we must be ready when they do present and require further evaluation. Knowing the proper next steps to take in such situations could make a crucial difference to the life and visual outcomes of the patient. ■

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