PEDiatric UVEITIS: CHALLENGING FOR OPHThALMOLOGISTS, PATIENTS, AND PARENTS

Management of these complicated diseases differs between pediatric and adult patient populations.

BY LISA J. FAIA, MD, AND KIMBERLY A. DRENSER, MD, PhD

Managing uveitis in children can be daunting. Difficult examinations, anxious parents, delays in diagnosis, and high morbidity make it especially challenging. Although uveitis is less common in children than in adults, a higher percentage (40% in children, 20% in adults) presents in the form of posterior uveitis, which can be more devastating than more anterior disease.

When the disease has such an early onset, the stakes are higher. Some of the biggest mistakes, aside from not delivering timely and proper treatment, are thinking that these diseases affect only the eyes, that they will “burn out,” and that local therapies will be sufficient. In this article, we briefly describe the etiology, diagnosis, treatment, and complications of pediatric uveitis, and we explore how these aspects compare with those of uveitis in adults.

As in adults, uveitis in childhood appears to have a slight female predominance. Smith et al showed the breakdown for pediatric uveitis anatomically as 30% to 40% anterior uveitis, 40% to 50% posterior, 10% to 20% intermediate, and 5% to 10% panuvesis. This is different from the situation for adults, in whom 70% of cases are anterior in origin, followed by posterior and panuveitis and then intermediate uveitis. As stated above, with a higher prevalence of posterior uveitis, the visual consequences can be more severe in the pediatric population.

THE ROOT OF THE DISEASE

The differential diagnosis of pediatric uveitis is extensive. As in adults, classification starts by determining infectious versus noninfectious uveitis and by anatomic location. In the pediatric population, it is also helpful to note age, with the following delineations: infancy (0 to 2 years), toddler-school age (2 to 10 years), and adolescence (10 to 20 years).

Toxocarasis (Figure 1) rarely presents in adults. Other diagnoses seen in children but rarely, if at all, in adults include juvenile idiopathic arthritis (JIA), tubulointerstitial nephritis and uveitis (TINU), leukemia, retinoblastoma, juvenile xanthogranuloma (JXG), and Blau syndrome.

AT A GLANCE

- Pediatric uveitis is an uncommon but potentially blinding condition with a higher rate of complications and vision loss than uveitis in adults.
- Diagnosis requires a good history, a thorough review of systems, a complete examination, and a focused laboratory workup.
- Treatment options and escalations are similar to those for adults, with the exception that long-term oral corticosteroid use is not recommended in children.
- Complications, including amblyopia, can be more devastating in the pediatric population and result in severe vision loss in 25% to 30% of pediatric uveitis patients.
Of noninfectious causes, JIA—arthritis of unknown etiology in children less than 16 years of age—is the most common systemic association of pediatric uveitis.\(^6,5\) It has an estimated incidence of approximately 4.9 to 6.9 per 100,000 person-years and an estimated prevalence of 13 to 30 per 100,000 person-years. Other autoimmune causes include juvenile sarcoidosis and Blau syndrome, which can also present with joint and eye involvement. These two conditions tend to present with granulomatous ocular inflammation and can have posterior segment involvement, which is atypical in JIA-related uveitis. Uveitis develops in 60% to 80% of Blau patients at about 4 years of age.\(^5\) TINU can be autoimmune, but it can also be drug-related, idiopathic, or due to infectious causes.\(^7\) TINU has been estimated to account for 1% to 2% of all uveitis seen in tertiary referral centers.\(^8\)

For uveitis determined not to be autoimmune, other etiologies to consider include infectious, masquerade, and traumatic. The Table above right provides a brief list of these etiologies for uveitis in children. Infectious causes of uveitis in children account for 6% to 33% of all cases of pediatric uveitis and can be caused by reactivation of congenital infections or acquired infections.\(^9\)

As stated above, it is imperative to distinguish early between infectious and noninfectious causes of uveitis, as the treatment pathways are very different. Toxoplasmosis is the most common infectious cause of uveitis in the pediatric population, occurring in approximately 60% of cases.\(^2\) Other infectious causes include viral agents, such as varicella zoster virus, cytomegalovirus, Rubella (associated with Fuchs heterochromia), and infections such as toxocariasis, which are caused by parasites.

Masquerade syndromes, such as leukemia, retinoblastoma, and JXG, can resemble intraocular inflammation. The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies in children less than 15 years of age.

---

**TABLE. ETIOLOGIES OF PEDIATRIC UVEITIS**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
<th>Masquerade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>JIA</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>Blau syndrome</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>HSV</td>
<td>TINU</td>
<td>JXG</td>
</tr>
<tr>
<td>VZV</td>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Behçet disease</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Pars planitis</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>VKH</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Sympathetic ophthalmia</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyme</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; JXG, juvenile xanthogranuloma; TB, tuberculosis; TINU, tubulointerstitial nephritis and uveitis; VKH, Vogt-Koyanagi-Harada disease; VZV, varicella zoster virus.
Children can present with unilateral or bilateral symptoms with or without conjunctival injection with the appearance of iridocyclitis with a pseudohypopyon or a spontaneous hyphema.

Retinoblastoma is the most common primary cancer to affect the eyes of children, with 250 to 300 cases per year in the United States and 6000 to 8000 per year worldwide. Patients can present either with true inflammation secondary to tumor necrosis or with tumor cells being mistaken for inflammatory cells (Figure 2). In a case series reported by Stafford and colleagues, nearly 40% of patients with retinoblastoma were initially misdiagnosed as having uveitis.

JXG is predominantly a skin disorder of the young, characterized by multiple cutaneous papules. Extracutaneous lesions can involve the eye, and patients can present with heterochromia iridis. Young infants presenting with unilateral heterochromia iridis, spontaneous hyphema, secondary glaucoma, and ocular inflammation should be suspected of having JXG.

Traumatic uveitis can develop after blunt ocular trauma. Severe inflammation after minor trauma may signal the presence of an underlying predisposition, such as human leukocyte antigen B27 (HLA-B27) disease. Rosenbaum et al analyzed the records of 496 patients seen in the uveitis clinic of a tertiary referral center to evaluate the role of nonpenetrating trauma in initiating uveitis. They found that 4.8% of patients suspected that their intraocular inflammation was related to previous nonpenetrating trauma.

When no systemic cause for uveitis is found, a diagnosis of idiopathic uveitis is made. In a multicenter series of pediatric uveitis by Smith et al evaluating 527 pediatric uveitis patients, the leading diagnoses were idiopathic uveitis (28.8%), JIA-associated uveitis (20.9%), and pars planitis (17.1%). BenEzra et al found that 25.4% of 821 children and adolescents with uveitis had idiopathic disease. Idiopathic uveitis should be considered only when all other causes for uveitis have been ruled out.

**MAKING THE DIAGNOSIS**

In evaluating a child with uveitis, a complete ophthalmic examination is required. If a good examination cannot be completed in clinic, an examination under anesthesia may be required, especially if additional testing, such as fluorescein angiography, must be obtained. Along with a complete examination, an extensive history with review of systems is needed to better direct laboratory testing. Previous infectious exposures, pets, travel, and review of systems should be elicited. The review of systems and onset of symptoms may be more difficult to obtain in children than in adults, especially in children who cannot communicate, as the ophthalmologist must rely on the parents. Children also tend to adapt more readily and do not report problems at initial onset, presenting only after vision loss has occurred.

Just as in adults, there is no one formula for obtaining laboratory testing or diagnostic imaging for pediatric uveitis. Again, the review of systems must always be taken into account. Most patients with uveitis are assessed for, in the least, sarcoidosis, syphilis, and tuberculosis (TB).

Testing for TB can be performed via skin testing (purified protein derivative) or by a serum interferon gamma assay such as the QuantiFERON-TB Gold (Quiagen). Syphilis testing includes both nontreponemal testing such as rapid plasma reagin and the Venereal Disease Research Laboratory and treponemal testing such as fluorescent treponemal antibody absorption test or *Treponema pallidum* particle agglutination.

Testing for sarcoidosis includes obtaining chest x-ray, angiotensin-converting enzyme (ACE) serum level, and lysozyme level. ACE levels tend to be elevated in the pediatric population in general compared with the adult population, so elevated ACE alone may not be diagnostic of juvenile sarcoidosis; this is why chest x-ray and lysozyme level are helpful. Although computed tomography (CT) of the chest is often obtained looking for sarcoidosis in older patients, it should probably not be used as a screening tool in pediatric patients because of the radiation dose.
Other testing is directed by the history and examination. For example, a child with chronic bilateral anterior uveitis would have antinuclear antibodies (ANA) testing because JIA is a likely diagnosis, and a teenager with severe acute anterior uveitis in one eye would be given HLA-B27 blood test.

For most cases of anterior uveitis, the ophthalmologist may start with complete blood count with differential, ANA, urinalysis, and HLA-B27, adding ACE, chest x-ray (and CT chest), and serum lysozyme, should juvenile sarcoidosis be suspected. For intermediate uveitis, one would order the above and, again, follow clues from the review of systems. A history of camping or hiking in endemic areas would prompt testing for Lyme disease. Testing for TB and syphilis are a must. For adolescents presenting with intermediate uveitis, although it would be early, magnetic resonance imaging could be obtained to look for multiple sclerosis if the review of systems leads one to suspect that disease. For posterior uveitis, noninfectious causes can begin with the above workup. Should infectious etiologies be considered, ordering toxoplasmosis IgM and IgG and toxocariasis IgM and IgG antibodies can be helpful. When vasculitis is a concern, additional testing for myeloperoxidase and proteinase 3 can be ordered.

**EARLY TREATMENT KEY**
Evidence suggests that early, aggressive therapy improves ocular outcomes. Immunomodulatory therapy has been associated with a reduced risk of complications, and control of inflammation within 3 years has been associated with better visual outcomes. These benefits, though, must be weighed against the possible side effects of systemic immunosuppression. In treating a child with uveitis, the ophthalmologist should use an approach similar to that used in adults and start with topical therapies if possible.

Although topical therapies may be enough for anterior uveitis, stronger medications are usually required for intermediate, posterior, and panuveitis, and parents should be made aware of this from the beginning. Should these topical therapies not be enough, if the child is cooperative, regional or intravitreal injections can be given. If this cannot be done in clinic, an examination under anesthesia with concurrent treatment is recommended.

Please note, the fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb) and the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) are available and have been studied for adults, but these medications do not currently have safety information available for use in children.

Systemic steroids would be the next step, but, unlike in adults, their long-term daily use in children is not recommended. Long-term steroid use has been associated with growth retardation.

Steroid-sparing immunosuppression can be considered, with the help of a pediatrician or pediatric rheumatologist. The current approach includes corticosteroids to treat acute inflammation, with rapid establishment of steroid-sparing medications (antimetabolites, T-cell inhibitors, alkylating agents, biologics) such as methotrexate, cyclosporine, mycophenolate mofetil, or cyclophosphamide. Biologics are also an option for control, but long-term use of these medications in such young patients has been a concern—especially with parents.

There are relatively few medications with specific indications for pediatric uveitis. Methotrexate has been approved for use in children with JIA. Adalimumab (Humira, Abbvie) is approved for JIA in patients over age 4 years. Safety and efficacy of many newer therapies are not well established in children.

**BEWARE OF POTENTIAL COMPLICATIONS**
Unlike adults, children with delays in diagnosis, even after treatment begins, may develop amblyopia. The most common causes of vision loss in children with uveitis are cataracts, band keratopathy, glaucoma, and cystoid macular edema (CME). Severe vision loss occurs in 25% to 30% of these pediatric patients, placing quite a long-term burden not only on the patient but also on parents and society. For adults, the main causes of vision loss in uveitis are macular pathology (CME, ischemia, and epiretinal membrane) and glaucoma.

**TAKE SPECIAL CARE**
Uveitis, especially with a delay in diagnosis and undertreatment, can be devastating in children and adults alike. The approach to discovering the underlying etiology for uveitis requires a proper review of systems and complete examination, and both of these may be more challenging in the pediatric population.

(Continued on page 71)
Another difference between adult and pediatric uveitis lies in the differential diagnoses, although treatment and escalation occur in a similar fashion in both.

When it comes to treatment, an important takeaway point is that low-dose long-term corticosteroid therapy may be an option for adults, but it is not so in children. Complications that result in vision loss are similar in both groups, but cataracts are much more problematic in children.

When we are faced with uveitis in a child, we should make all efforts to obtain control of the disease early to prevent possible future unnecessary vision loss, with its additional burdens to the patient, parent, and society.