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Uveitis in Children

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Abstract

Purpose of review—This review provides updates on novel risk markers for the development of pediatric inflammatory uveitis and a severe disease course, on treatment of refractory disease, and on the measurement of visual outcomes.

Recent findings—There are several new genetic markers, biomarkers and clinical factors that may influence a child's uveitis disease course. It is important to identify children at risk for poor visual outcomes and who are refractory to traditional therapy. Racial disparities have recently been reported. We describe agents of potential benefit. In addition, we discuss the importance of patient reported outcomes in this population.

Summary—Uveitis can lead to vision threatening complications. Timely and aggressive treatment of children identified to be at risk for a severe uveitis course may lead to improved outcomes.

Keywords

uveitis; juvenile idiopathic arthritis

Introduction

A. Pediatric non-infectious uveitis

Non-infectious pediatric uveitis is an inflammatory eye disease that can lead to ocular complications and vision loss. It is most often associated with juvenile idiopathic arthritis (JIA), but can be observed in other autoimmune conditions like Behcet's disease or sarcoidosis. Idiopathic uveitis, uveitis without associated systemic illness, is at least as common as JIA-associated uveitis (JIA-U). Classification is often by anatomic location with anterior uveitis (AU) being the most common manifestation. Ocular complications are reported in up to 50% of children, vision loss (visual acuity (VA) of 20/50 or worse) in 25–40%, and legal blindness in (VA of 20/200 or worse) in up to 25% [1*–5]. A chronic course with remission and relapses is characteristic, and many children require long-term

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Conflicts of Interest: The Effects of Youngsters' Eyesight on Quality of Life (EYE-Q) has a license through Emory University but the authors have not received any royalties.

immunosuppressive therapy. This review focuses on 1) risk factors for uveitis and severe disease, with an emphasis on anterior uveitis, 2) treatment related factors, and 3) measurement of visual outcomes.

A. Risk factors for uveitis development

Similar to other autoimmune diseases, the etiology of uveitis is multifactorial and can include genetic predisposition, environmental triggers, immune system activation, and clinical risk factors.

Genetics—Most genetic studies in pediatric uveitis focus on non-Hispanic White (NHW) children with JIA. Associations are reported with polymorphisms of HLA class II genes wherein HLA-DR1 has a protective effect, and there is an increased predisposition in children who carry the HLA-DRB1*11, HLA-DRB1*13 and HLA-B27 alleles [6–10].

In a cohort of 107 NHW children with oligoarticular and polyarticular rheumatoid factor (RF) negative JIA, Angeles-Han examined differences between 60 children with JIA, 47 with JIA-U, and 373 NHW controls. [11*]. Compared to controls, children with JIA-U who carried both HLA-DRB1*11 and *13 had a 9 fold increased odds of developing uveitis (OR, 9 [95% CI 2.8–29], p = <0.001). When compared to children with JIA alone, those with JIA-U had an 8 fold increased odds (OR, 8.6 [95% CI, 1.0–74.4]), p = 0.042), but lost its statistical significance after Bonferroni's correction.

Marrani reported on the association of NOD2/CARD15 gene in 25 Italian patients with autoimmune chronic uveitis, (18 children - 10 JIA and 8 idiopathic, and 6 adults) and 25 age and sex-matched controls. [12*]. The variant P268S/SNP5 was found in 17 uveitis cases (15 heterozygous and 2 homozygous) which was statistically different from controls (OR, 4.03 [95% CI 1.2–13.5], p = 0.04).

Further investigation of genetic variants in larger uveitis cohorts is warranted to further elucidate genetic predisposition.

Clinical risk factors—Approximately 10–20% of children with JIA are at risk for uveitis. Those with positive antinuclear antibodies (ANA), are young at arthritis diagnosis (≤ 6 years old), have oligoarticular or polyarticular RF negative JIA, and early in their disease course (≤ 4 years) are considered high risk. Current screening guidelines recommend monitoring these children every 3–4 months [13]. In 287 children with JIA, 18% with uveitis, Angeles-Han confirmed that oligoarticular JIA category (OR 4.64 [95% CI 2.21–9.75]), and younger age at JIA diagnosis (OR 0.91, [95% CI 0.84–0.99]) increases odds of uveitis [1*]. In addition, 86% developed uveitis during the first 4 years from JIA diagnosis, confirming the importance of frequent screening during this timeframe.

Biomarkers—Potential biomarkers have been examined for early detection of JIA-U, as indicators of active disease, and for targeted therapy [14].

Hasnoot confirmed the elevated ESR as a predictor of uveitis in oligoarticular and polyarticular RF negative JIA [15*]. Ayuso described the histopathologic and

immunohistochemical findings of iris specimens of children who underwent elective trabulectomy and peripheral iridectomy [16**]. They examined 31 eyes of 25 patients and 6 controls with glaucoma but no uveitis. Similar to earlier histologic studies of enucleated eyes and an iridectomy sample in JIA-associated uveitis, plasma cells were abundant [17–19]. These findings may have implications for treatment strategies targeted to B cells such as rituximab therapy.

Walscheid reported an increase in the S100 subtypes S100A8/A9 and S100A12 levels in both serum and aqueous humor (AqH) of children with autoimmune uveitis [20**]. There were 79 patients with oligoarticular JIA-U (89 serum and 17 AqH samples), 24 with idiopathic AU (23 serum and 12 AqH), and 24 controls (17 serum and 16 AqH). Since elevations occur in active arthritis and active uveitis regardless of etiology, S100A8/A9 and S100A12 are likely not disease-specific, but rather a general indication of ongoing inflammation associated with activated neutrophils. Elevated serum S100 levels, which are phagocyte-specific, may be a potential biomarker for ocular inflammation in inactive arthritis.

Another study examined AqH fluid and paired serum of 21 children with JIA-U, 15 with chronic AU, 29 with non-infectious intermediate uveitis or panuveitis, and 8 non-inflammatory controls [21**]. Samples consisted of AqH fluid from 73 children and paired serum from 66. Of 51 soluble mediators analyzed, there were decreased intraocular levels of IL-29/IFN-λ1 in JIA-U but not in serum, thus indicating a potential difference in local mechanisms. Schmeling reports increased anti-dense fine speckled 70 kDa antigen (DFS70) antibodies in JIA-U (N = 19) and idiopathic uveitis (N = 7), found in 10.5% and 14.3% of children respectively, and 11.5% (3/26) when combined [22*]. Although not statistically significant when compared with 145 healthy children (2.1%), the frequency was increased in comparison to 183 JIA children without uveitis (1.6%).

Discovery of biomarkers that aid in the screening, monitoring of disease activity, and targeted treatment of uveitis could improve final visual outcomes.

B. Risk factors for severe uveitis

Sight-threatening complications occur in pediatric non-infectious uveitis. Risk factors include a short duration between arthritis and uveitis diagnoses, young age at uveitis onset, male gender, uveitis diagnosed prior to arthritis, and the presence of vision loss or complications at first ophthalmology exam.

Racial associations—Differences in the epidemiology of uveitis based on geographic location are described [23, 24]. For example, in a 10 year study of 107 children with JIA in Oman there was no development of uveitis [25]. Variations in prevalence may be related to race, especially since race and ethnicity affect development of autoimmune diseases.

Few studies on uveitis focus on African American (AA) children despite distinctions in the prevalence of JIA categories based on race. Approximately 8% of AA children with JIA develop uveitis, with few descriptions of their visual outcomes [26–29]. The association of race with visual outcomes was examined by Angeles-Han in 287 JIA children. Fifty-two

(18%) developed uveitis, of whom 8 (15%) were AA [1*]. Eight children were legally blind, and of these, 5 were AA (62%). In addition, AA children averaged 3 times more eye complications compared to NHW ($p<0.01$). In a larger cohort of 94 children with varied forms of non-infectious uveitis, 28 (30%) were AA [30*]. Of the 22 NHW and AA children with a history of blindness, 18 (82%) were AA; all 8 with bilateral blindness were AA. At last follow up, 50% of the AA children were still blind compared to 25% of NHW. AA race increased the risk for blindness by 30-fold (OR 31.64 [95% CI 5.94–168.49], $p<0.001$), and when analysis was restricted to AU only, there was still a 10-fold increased risk of blindness (OR 10.58 [95% CI 1.76–63.75], $p<0.001$.) AA children also had an increased risk of complications (OR 2.21 [95% CI 1.40–3.49], $p<0.001$).

Further investigation into the etiology of poor visual outcomes in AA, such as variance in health care access, medication adherence or biologic differences, need more study.

Risk for elevated intraocular pressure (IOP)—Kothari showed that risk factors for increased IOP include IOP in the contralateral eye, and the need for topical (>1 drop prednisolone acetate 1% or equivalent) or intraocular corticosteroids [31*].

C. Treatment

There are panel recommendations on treatment of non-infectious uveitis based on expert opinion, but no large randomized controlled trials [32, 33]. Initially, topical corticosteroids are used, but in refractory cases, methotrexate and/or biologic therapies, typically tumor necrosis alpha inhibitor (TNFi) drugs such as infliximab or adalimumab, are recommended. A comprehensive set of stepwise treatment algorithms for children with JIA-related uveitis was recently proposed based on an interdisciplinary panel consensus which provides recommendations for use of methotrexate, anti-TNF- α agents, abatacept and tocilizumab [34*].

Dexamethasone intravitreal implants are used in intermediate and posterior uveitis with low rates of development of cataracts and increased IOP [35]. Henderson examined data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, a registry of patients with pediatric rheumatic disease in North America, to examine practice patterns of pediatric rheumatologists [36*]. In 646 children with JIA-associated uveitis and 92 with idiopathic uveitis, 80% of children in both groups were treated with a disease-modifying anti-rheumatic drugs (DMARD), and approximately 50% with a biologic agent. However, since indication for treatment in children with JIA-associated uveitis was not specified (arthritis or uveitis), medication analysis was restricted to the 92 with idiopathic uveitis. Methotrexate was the most common steroid sparing agent (76%) with equal use of oral and SQ routes, and 53% required a TNFi (infliximab 36, adalimumab 18, golimumab 1). Furthermore, 6 children needed multiple biologic agents, and two were treated with a biologic without a preceding DMARD [36]. Thus, many children with uveitis need immunosuppressive therapy with greater than half requiring biologics.

Treatment of TNFi refractory uveitis—In cases requiring escalation of therapy beyond TNFi agents, there are no large studies to help guide use, rather, small case series exist. Abatacept has been shown to be effective in small case reports and series of children

with JIA-associated uveitis. However, Tappeiner retrospectively described an unsustained response to monthly abatacept (10 mg/kg, max 750 mg) in 21 children with severe, chronic and refractory JIA-U treated with steroids, DMARDs (all treated with methotrexate), and at least 1 TNFi [37*]. Ten did not respond and had persistently active uveitis. Of the 11 with response, 8 relapsed. Additionally, there were 3 patients with new onset ocular complications, and 5 with progression of a preexisting cataract. There was no significant improvement in BCVA. Thus, abatacept did not prove effective in chronic refractory severe uveitis, although only 12 completed 12 months follow up. Alternatively, Marrani reported on the successful use of abatacept in 3 children with idiopathic uveitis followed for a range of 18–42 months [38*]. All discontinued systemic steroids but 2 needed ongoing methotrexate.

Miserocchi examined 5 patients with severe and longstanding oligoarticular JIA-U treated with corticosteroids, DMARDs (methotrexate and/or cyclosporine), and at least one TNFi and/or abatacept in whom they administered rituximab, an anti-CD20 B cell monoclonal antibody. [39**]. Rituximab was dosed as 1000 mg on days 1 and 14 and after 6 months if needed for active arthritis and/or uveitis. Patients were older (ages 16–34 years) with AU (n = 5) or anterior and posterior pole complications (N = 3) and a mean uveitis duration of 17.7 ± 5.6 years. At last follow up (mean follow up time 44.75 ± 4.9 months), all patients were in remission, with improvement seen 4 months from first infusion. Systemic corticosteroids were discontinued in 6 patients, and other immunosuppressants were tapered wherein only 2 patients used weekly methotrexate. Thus, rituximab may be an alternative treatment option in long-standing severe refractory uveitis.

Uveitis occurrence during treatment—Accurate estimates of the incidence and prevalence of uveitis are challenging since treatment for JIA and uveitis are similar. Underlying systemic therapy for JIA may influence the development of uveitis.

Foeldvari examined the protective effect of methotrexate using the adverse event-reporting system of the German Biologics in Pediatric Rheumatology (BIKER) Registry [40*]. They analyzed the number of uveitis events during treatment of JIA. In patients treated with methotrexate and a biologic agent there were less uveitis occurrences versus biologic agent alone. Although there was a decreased rate of uveitis in patients on etanercept alone vs. adalimumab, there are several confounding factors, including a significant selection bias for treatment.

Tappeiner utilized a German national database to describe the impact of methotrexate on the occurrence of uveitis in a cohort of 3,512 JIA patients in whom 431 developed uveitis [41**]. Children treated with methotrexate early in the JIA diagnosis had a reduced risk for uveitis development (HR 0.29, [95% CI 0.19–0.45], $p < 0.001$) with the greatest effect seen with the combined use of TNFi and methotrexate (HR 0.10 [95% CI 0.05–0.23], $p < 0.001$).

Risk of Reactivation or Relapse—Optimal duration of therapy for uveitis is largely unknown. Treatment with methotrexate is recommended for at least 3 years with delayed withdrawal in younger children since uveitis relapse is high [42, 43].

Lerman examined 19 children with non-infectious uveitis who discontinued TNFi treatment and factors associated with uveitis relapse [44**]. Of these, 68.4% were treated for more than 1 year and 36.8% were treated for 2 years after achieving quiescence with a median time of 1.73 years (IQR: 0.25–2.15) from inactive disease to drug discontinuation. There was an increased risk for failure on adalimumab vs. infliximab (hazard ratio (HR) 13.4, [95% CI: 2.2–82.5], p = 0.01) and in children older at uveitis diagnosis (HR 1.32, 95% CI 1.03–1.69], p = 0.03). Incidence of failure was not associated with additional immunomodulatory therapy, duration of suppression, gender, race, diagnosis, time from diagnosis to drug initiation, or uveitis severity at drug initiation. The probability of a uveitis reactivation after discontinuation of TNFi was estimated at 18% by 3 months, 38% by 6 months, and 55% by 9 months with the median time to failure of 3.9 months. Thus younger children at diagnosis and treated with infliximab may have an increased chance of remission. However, others have shown that adalimumab is superior to infliximab [45]. In addition, half will relapse before 1 year after discontinuation of drug.

D. Measurement of uveitis outcomes

Accurate measurement of the impact of disease and treatment on a child's daily life is crucial. We rely on the clinical ocular exam, specifically VA, as a proxy for visual function; the number of anterior chamber cells from the Standardization of Uveitis Nomenclature (SUN) criteria as a measure of disease activity; and the presence of complications as a measure of tissue damage [46]. Uveitis studies often overlook the child's perspective on disease and treatment burden, as well as the holistic effects of visual disability. There is a general consensus that incorporating patient reported outcome (PRO) measures improves our understanding of the interaction between disease and quality of life (QOL). Of 94 studies on medication efficacy in adults with uveitis, none included PROs but focused on uveitis activity (74%), visual acuity (52%) and tissue damage (4%) [47]. For children, there is a paucity of vision-specific pediatric QOL instruments [48].

The first uveitis-specific instrument, the Effects of Youngsters' Eyesight on QOL (EYE-Q), was developed and validated in children with normal vision, various ocular disorders, JIA, and uveitis [49*–51]. Fifty-seven children (8 JIA, 24 JIA-uveitis, 25 uveitis alone) were administered the EYE-Q; 102 ocular examinations were performed within 1 month of completing the EYE-Q and the Pediatric Quality of Life Inventory (PedsQL), a general QOL assessment [49*]. Children with vision loss in their better eye (VA ≤ 20/50) had worse vision-related function and overall QOL as measured by the EYE-Q (p = 0.002) and PedsQL (p = 0.028). However, correlations between these measures and VA, a proxy of visual function, showed that the EYE-Q moderately correlated with logMAR VA ($r_s = -0.43$), whereas the PedsQL did not. Hence, the EYE-Q appears to be a valid and reliable measure of vision-related function in association with VA. The PedsQL failed to show variation in QOL based on VA, underlining the importance of a uveitis-specific measure.

Conclusion

Early identification of children at greatest risk for uveitis and targeted treatment may improve visual outcomes. This review provides information on risk factors for uveitis

development and a severe course that considers clinical and genetic risk factors and novel biomarkers. We describe treatment of refractory disease, and provide data on the epidemiology of disease related to medication use. In addition, we discuss the importance of PROs, and describe a uveitis-specific tool.

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Key Points

1. Novel biomarkers and genetic factors may aid in the screening and monitoring of uveitis and lead to targeted treatment.
2. Race may be associated with visual outcomes wherein African American children have increased vision loss and ocular complications.
3. Refractory uveitis may need escalated therapy beyond TNFi, but there is little data to guide therapy of severe refractory disease.
4. Reactivation of uveitis after medication discontinuation is high, and elucidation of factors that predict remission are needed.
5. In order to appropriately measure visual outcomes in children with uveitis, we need to consider other factors aside from the clinical ocular exam.