Updates on the risk markers and outcomes of severe juvenile idiopathic arthritis-associated uveitis

Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis, which is the most common systemic cause of uveitis in children. Known risk factors for uveitis include antinuclear antibody seropositivity, young age of arthritis onset, specific juvenile idiopathic arthritis subtype and short duration of disease. Risk markers for severe ocular disease include gender, age and complications at initial visit. Due to the risk for vision-compromising sequelae such as cataracts, band keratopathy, glaucoma, vision loss and blindness, an understanding of the risk factors for uveitis development and severe ocular disease is crucial to help prevent serious visual disability and complications. This paper reviews the pathogenesis of uveitis, known risk factors for uveitis development and severe visual outcome, and addresses the need for additional biomarkers of uveitis risk, prognosis and remission.

KEYWORDS: juvenile arthritis ■ juvenile idiopathic arthritis-associated uveitis ■ ocular disease ■ pediatric rheumatology ■ risk ■ uveitis

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Epidemiology of juvenile idiopathic arthritis-associated uveitis

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease of childhood with a prevalence of 1:1000 [1]. It is an arthritis of unknown etiology of at least 3 months duration diagnosed in children ≤16 years of age. The most common extra-articular manifestation of JIA in North America is uveitis, most commonly anterior uveitis, which has also been variably termed iritis or iridocyclitis [2–8].

JIA-associated uveitis (JIA-U) is an anterior, nongranulomatous, chronic, inflammatory ocular disease that has been reported in up to 38% of children with JIA but typically occurs in 10–20% [8–14]. It is bilateral in approximately 80% of children [13,15,16]. Ocular complications such as cataracts, glaucoma, band keratopathy, synechiae, vision loss and even blindness can develop in as high as 37% of children [17,18]. Oftentimes, there is no correlation between arthritis and uveitis activity or severity, and this appears to be the typical course [13,18,19]. Unfortunately, uveitis can present insidiously and children are asymptomatic, hence routine slit lamp examinations for early detection should be performed. Likewise, an understanding of the risks for uveitis susceptibility and severity is essential due to potential sight-threatening complications.

Numerous risk factors are associated with different types of uveitis (idiopathic uveitis [I-U], sarcoid uveitis and so on), and we will specifically discuss those associated with juvenile arthritis. Various juvenile arthritis classification schemes consisting of different arthritis subtypes are used clinically and and have varied historically in the literature (Table 1). These include juvenile rheumatoid arthritis (JRA), JIA and juvenile chronic arthritis (JCA) [20]. Although the current International League of Associations of Rheumatology JIA classification is conventional, studies reviewed in this paper varied in their use of the different arthritis classification schemes, and we retained the original classification used by the authors.

This review will focus on: risk factors that increase a child's susceptibility to developing uveitis including JIA status, serology (i.e., antinuclear antibody [ANA] and *HLA-B27* positivity), and duration of disease; risk factors for ocular complications secondary to uveitis such as gender, duration between arthritis and uveitis onset, and initial ophthalmology examination; differences in risk in JIA-U compared with uveitis alone; and risk factors for cataracts, which is the most common complication of uveitis.

Immunopathogenesis of uveitis

Knowledge of the pathogenesis of juvenile and adult arthritides and other autoimmune diseases, including uveitis, has led to the introduction of new biologic agents targeted at T and B lymphocytes and cytokines for therapy. The components of these inflammatory pathways have also provided risk markers for the development of these diseases, of which human lymphocyte antigens are a

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Table 1. Classification of juvenile arthritis.

Juvenile rheumatoid arthritis	Juvenile chronic arthritis	Juvenile idiopathic arthritis
Pauciarticular	Pauciarticular	Oligoarticular • Persistent • Extended
Polyarticular	Polyarticular	Polyarticular • Rheumatoid factor negative • Rheumatoid factor positive
Systemic	Systemic Juvenile psoriatic	Systemic Psoriatic Enthesis-related arthritis Undifferentiated

prime example. It is likely that better uveitis risk stratification will come from the genomic and proteomic analysis of the immunologic mechanisms reviewed here.

Uveitis is considered to be an autoimmune disease resulting from the loss of immune tolerance to retinal antigens [21]. Much of the current knowledge of the pathogenesis of this process is derived from experimental autoimmune uveitis (EAU) in rodents. Antigen targets for this immune response include S-antigen (arrestin) [22,23], rhodopsin [24] and interphotoreceptor retinoid-binding protein (IRBP) [25]. Both innate and adaptive immune responses have been shown to participate in uveitis and in the latter, $CD4^+$ T cells play a major role. IRBP-specific Th1 cells when induced by IL-12 produce large amounts of IFN-γ, the primary signature of Th1 lineage, and are uveitogenic in naive mice [26]. However, neutralizing IFN-γ by antibodies or by genetic deletion did not confer resistance to uveitis but worsened the disease, suggesting a protective effect for this cytokine [27,28]. Th17 cells, another subclass of $CD4^+$ T cells, are also important effector cells in uveitis. They are induced by the combined effects of IL-6 and TGF-β, or IL-1-β and TGF-β and IL-23 [29]. Mice lacking the p40 subunit of IL-23 are protected from EAU [30]. In addition, IL-23 has been shown to be elevated in Behcet's disease and Vogt–Koyanagi–Harada disease [31,32]. Proinflammatory cytokines produced by lymphocytes, monocyte/macrophages, dendritic cells and ocular cells including IL-1, IL-6 and TNF-α have been shown to be important in uveitis. Knockout mice lacking type 1 IL-1 receptor, IL-6 or type 1 TNF receptor are resistant to EAU [33–35]. Other cells such as naturally occurring $CD4^+CD25^+$ $Foxp3^+$ T-regulatory cells play an important role in keeping retinal autoimmunity in check [36,37]. Retinal cells also constitutively express CD200 for which macrophages bear a receptor. When retinal macrophages are triggered by CD200 their activity is dampened [38]. Recently, Mattapillil *et al.* have shown that uveitis-associated S-antigen epitopes are pathogenic in transgenic mice expressing human *HLA-DR3*, demonstrating the relevance of these retinal antigens in human uveitis [39]. Although the EAU model may have a closer analogy to adult uveitis than to uveitis in children, these pathogenic mechanisms are relevant and warrant further study. New information on the expression of pro- and anti-inflammatory cytokines and genetic polymorphisms governing their expression pose potential new biomarkers for uveitis risk and individualized therapy [40–43].

Risk factors for uveitis development

Screening for uveitis is an important step in preventing the development of severe ocular disease and visual complications. The American Academy of Pediatrics (AAP) Sections on Rheumatology and Ophthalmology created guidelines on the frequency of ophthalmology screening visits depending on a child's risk factors for uveitis [44,45]. These guidelines are specific to the JRA classification scheme. A child is considered to be at a higher risk for uveitis if he/she is ANA seropositive, of oligoarticular or polyarticular JRA subtype, has early age of arthritis onset (≤6 years), and has <4 years duration of arthritis. It is recommended that these children are screened by slit lamp examination every 3 months irrespective of gender or ANA status. We will discuss the role of JIA subtype, ANA status, age, gender and genetic markers.

Juvenile arthritis subtype

Generally, uveitis is thought to be more common in the oligoarticular JIA or pauciarticular JRA subtypes, particularly in the extended oligoarticular JIA subtype [13,14,16,18,46–48]. BenEzra and colleagues noted that children with polyarticular or systemic JRA did not develop uveitis during the first 3 years after their initial arthritis diagnosis [13,14,16,18,47,48]. They examined 172 children with JIA, 51 (~30%) of whom developed uveitis. Of these, 39 children were diagnosed with pauciarticular JRA, and 32 of the 39 (82%) were noted to have uveitis at their initial ocular examination or as a presenting symptom. Hence, their group

suggests that frequent ophthalmic visits may not be necessary for all children and that arthritis subtype plays an important role.

While the AAP guidelines are important for the JRA subtypes, they do not take into account the subtypes that are included in the JIA classification scheme that are also at risk for uveitis development such as psoriatic JIA and enthesitis-related arthritis [46,47,49,50]. Heiligenhaus *et al.* have suggested modifications to the current guidelines for uveitis screening based on a child's JIA subtype and have developed the first recommendations for JIA [47]. They examined 3271 children with JIA of whom 406 (12%) had uveitis, and obtained ophthalmology records for 115 of the uveitis patients [47]. There was a greater risk of uveitis in children with extended oligoarticular JIA (Odds ratio [OR]: 33; 95% CI: 7.9–136.6; $p < 0.01$), persistent oligoarticular JIA (OR: 19; 95% CI: 4.7–78.1; $p \leq 0.01$), other arthritis (OR: 12; 95% CI: 2.9–52.4; $p = 0.001$), and psoriatic JIA (OR: 11; 95% CI: 2.7–48.3; $p = 0.001$). In accordance with the AAP guidelines, they also noted an association with younger age of arthritis onset, disease duration and ANA positivity. Hence, a child would be considered at greater risk for uveitis based on their JIA subtype (persistent oligoarthritis, extended oligoarthritis, psoriatic arthritis and other arthritis), ANA status (positive), age at JIA onset (≤6 years) and JIA duration (≤4 years). The authors proposed increased screening intervals to every 3 months for children with oligoarthritis, RF negative polyarthritis, psoriatic arthritis and other arthritis who are ≤6 years of age at JIA onset and have had JIA for ≤4 years.

A study by Saurenmann *et al.* examined the charts of 1081 patients with JIA, JRA, juvenile psoriatic arthritis and juvenile spondyloarthritis and found 142 children (13.1%) with uveitis [49]. Oligoarticular JIA was the most common JIA subtype with uveitis (n = 87, 20.9%), followed by polyarticular RF-negative JIA (n = 32, 14.1%) and psoriatic JIA (n = 12, 9.8%). Similar to the AAP guidelines, of the 142 children (13.1%) who developed arthritis, they determined that ANA positivity, age <6 years at arthritis diagnosis, and subtype of JIA were significant independent risk factors (relative risk [RR]: 1.44; $p = 0.02$), but female gender and RF negativity were not. Interestingly, they also studied potential risk factors for uveitis development based on JIA subtype. Children with: persistent oligoarticular JIA were at higher risk if they were ANA positive, female gender and had a young age of onset; RF- polyarticular JIA were at higher risk if they were ANA positive and were young at the age of onset; and enthesitis-related JIA were at higher risk if they had a positive ANA.

Similarly, Woreta *et al.* noted that 75 children with JIA-U were diagnosed primarily with persistent oligoarticular JIA (n = 61), polyarticular RF-negative JIA (n = 5) and polyarticular RF-positive JIA (n = 4) [51]. Five patients (psoriatic JIA, enthesitis-related arthritis and systemic JIA) only presented with episodic uveitis, which is different from the chronic uveitis noted in the other JIA subtypes.

Most studies demonstrated a significant association between uveitis risk, visual outcome and arthritis subtype, and only a few did not [15,52]. The JIA subtypes that appear to be at greatest risk for uveitis development include: RF negative polyarticular JIA, oligoarticular JIA, psoriatic JIA and enthesits-related JIA, and these require further investigation.

ANA

The ANA is traditionally considered a risk factor for uveitis development [14,18,47,49,53,54]. Ravelli *et al.* compared 256 children with oligoarticular persistent JIA, oligoarticular extended JIA and polyarticular RF negative JIA and categorized them by their ANA status: ANA negative (n = 66) and ANA positive (n = 190) [55]. They noted that 30% of the children that were ANA positive developed uveitis, whereas only 3% of the children who were ANA negative developed uveitis, regardless of JIA subtype. Likewise, on multivariate analysis, there was a strong correlation found between ANA positivity and development of uveitis (OR: 12.38; 95% CI: 1.56–98.11; $p = 0.0003$). The authors note that patients with similar characteristics are categorized into different JIA subtypes and conclude that grouping by ANA status may be more clinically relevant.

The significance of the titer of the ANA is unknown, although some studies note that patients with uveitis had higher median titers ≥320 [18,56]. One study demonstrated the relevance of ANA by indirect immunoflourescence using HEp-2 cells, whereas the ELISA method of ANA measurement did not [56]. Hence, the determination of a child's ANA status by immunoflourescence may be preferable. Manzotti showed that the ANA did not predict increased recurrences of uveitis [46,57,58].

Age

The AAP guidelines recommend more frequent uveitis screening for children who are ≤6 years of age since younger age of arthritis onset may be associated with uveitis development [14,45]. Hence these children undergo slit lamp examinations every 3 months if they have other risk factors.

It appears that approximately 75% of children will have developed uveitis by their 7th birthday [47], and the risk decreases after 7 years of disease [16,46,54]. According to Saurenmann and Woreta, 75% of children who developed uveitis did so within approximately 3 years of their JIA diagnosis [49,51], and 90% exhibited uveitis within the first 4 years of arthritis development [14,47]. Other reports have been similar [46,50], although some long-term follow-up studies demonstrate the rare appearance of uveitis complications such as cataracts and glaucoma after 7 years of disease or after 16 years of age [59,60]. No guidelines exist for adults with a history of JIA-U. Regular ophthalmology screening may be necessary well into adulthood, even if on an annual basis.

Gender

Females generally appear to have a higher risk for uveitis. In 2010, Saurenmann *et al.* examined the risk for uveitis based on age at onset of JIA, gender and ANA status in 1047 children with JIA, 122 (11.7%) of whom had uveitis [52]. Females had a higher rate of a positive ANA (66%) and a greater risk for uveitis development when they were younger. Overall, risk factors for uveitis development include female gender (likelihood ratio [LR]: 8; p = 0.004), females at a young age at time of diagnosis (LR: 6.7; p = 0.009), age at diagnosis (LR: 16.7; p < 0.0001) and ANA positive (LR: 13.1; p = 0.0003). Interestingly, JIA subtype was not a significant risk factor. There was a mild significant risk for uveitis in males related to their ANA status but not in any other factors. Hence, risk markers for uveitis may differ depending on gender wherein females who are ANA positive and young at time of diagnosis (≤6 years of age) are at higher risk for developing uveitis, regardless of their JIA subtype.

Role of genetic markers in uveitis development

Few studies have examined the association between genetic markers and uveitis. An association has been observed between HLA class I and II genes and JIA-U wherein *HLA-B27* and *HLA-DR11* increase disease susceptibility, and *HLA-DR1* is protective [16,58,61–68]. Children with *HLA-DR11* may have a significant risk (26%) for developing uveitis even 5 years after the onset of arthritis [62]. Other HLA alleles such as the *HLA-DRw5*, *HLA-DRB1*1104*, *HLA-DRB1*1301* have also been reported to be associated with an increased uveitis risk [63,64,67]. However, the association between HLA polymorphisms and uveitis severity and development of complications is largely unknown.

One study by Paroli *et al.* examined HLA-DR 11 in 63 patients with JRA and noted its presence in 36 of 43 tested (83.7%) [16]. In comparing the worst eye's final visual acuity (VA; of >20/100 vs ≤20/100) in the groups with *HLA-DR11*, there was no difference in the final VA since 16 of 25 patients had a VA of >20/100 and 13 of 17 patients had a final VA of ≤20/100. Hence, *HLA-DR 11* may be important in uveitis susceptibility but not severity.

Most genetic studies focus on children with oligoarticular or polyarticular JIA. Zulian *et al.* examined 316 Caucasian children with oligoarticular JIA followed for at least 2 years [61]. There was an association between uveitis onset and *HLA-A19* (OR: 2.87; 95% CI: 1.35–36.87; p < 0.001), *HLA-B22* (OR: 4.51; 95% CI: 1.36–22.97; p < 0.001) and *HLA-DR9* (OR: 2.33; 95% CI: 1.07–08.92; p < 0.001). As expected, *HLA-DR1* (OR: 0.13; 95% CI: 0.04–00.27; p < 0.001) appeared protective for uveitis development. The authors did not note a significant association between HLA allele and severity of uveitis. The association between uveitis, other JIA arthritis subtypes and HLA variants has not been investigated.

Of even greater interest, one study looked at the association between HLA and ANA status. The authors noted that patients with both *HLA-DR11* and positive ANA had a high incidence of uveitis [63]. ANA alone had a positive predictive value (PPV) of 44.6% and a negative predictive value (NPV) of 68.8%, whereas *HLA-DRB1*1104* had a PPV of 70.4% and a NPV of 59.2% [64]. Sensitivity and specificity were 85.3 and 23.4% for ANA, and 31.1 and 88.4% for *DRB1*1104*, respectively.

The *HLA-B27* is commonly associated with acute painful uveitis, redness and photosensitivity in older children which is different from the asymptomatic uveitis seen in younger children [69]. Most studies that examine HLA associations with uveitis have observed the association with *HLA-B27*, and it is rare not to find this association [14].

Risk factors for ocular complications & severe visual outcomes

Several risk factors have been associated with vision loss and ocular complications in JIA-U, such as severe disease and complications at initial ophthalmology examination, presence of uveitis before arthritis, short duration between arthritis and uveitis onset, young age, male gender and presence of anterior chamber flare [47,51,61,70–73]. The reported frequency of children who develop blindness is wide (6–41%) and there is inconsistency regarding the true incidence of complications [14,15,48,50,54,71,74–76]. In a study by Ozdal that examined 18 adults with a history of JIA-U, all patients had at least one ocular complication and 70% of eyes were visually handicapped (VA of 20/50 or worse) or blind at last follow-up [48]. Paroli reports a complication rate of 82.5% in their 63 patients with JRA-associated uveitis [16]. However, other studies report an improved outcome, which has been attributed to regular ophthalmology screening and better therapeutic options [14,16,50,76–78]. These inconsistencies may be secondary to differences in the arthritis classification scheme used (JIA, JRA and JCA), which include different arthritis subtypes that vary in their risk for uveitis, and length of follow-up.

Sabri *et al.* noted that in 10 of 142 (7%) children with uveitis who became blind, risk factors for a blind visual outcome included cataract formation, synechiae, early age at uveitis diagnosis, type of uveitis and history of ocular surgery [17]. Thorne *et al.* observed that the presence of ocular inflammation of ≥0.5+ cells on follow-up had an increased risk for visual impairment and blindness. We will discuss some of these factors individually.

Gender

Differences in uveitis characteristics between males and females have been reported [49]. Saurenmann found that males were more likely to have symptomatic uveitis, a shorter interval between arthritis and uveitis diagnosis and to be older at both JIA and uveitis diagnosis. Although females tend to have a higher risk for uveitis development, male gender appears to play a role in uveitis severity [61,72,73,76,79].

Edelsten *et al.* noted that males had a higher complication rate, especially in the first 4 years (RR: 4.3; 95% CI: 1.1–16.6; p = 0.032) [76]. This risk continued after 8 years wherein males had a complication rate of 38.4% and females had a rate of 9.7%.

In a study of 65 children (117 affected eyes) with JIA or ANA-positive uveitis, there were 18 males with uveitis who presented with ocular disease as the initial manifestation of JIA [80]. Although there were more females diagnosed with uveitis (47 out of 65), males had worse visual outcomes, more complications and a higher incidence of blindness. Anatomic complications included posterior synechiae, cataract surgery, band keratopathy, cystoid macular edema and papillitis. Amblyopia was a functional complication associated with uveitis [79,80].

In 409 patients who were diagnosed with JIA and arthritis subtypes needing prolonged ophthalmology screening (excluded systemic onset JIA, enthesitis-related JIA and RF positive polyarticular JIA), Chia *et al.* noted that the proportion of males with severe uveitis at diagnosis was higher (55% of 22, OR: 3.5; 95% CI: 1.4–8.3; p = 0.006), and male gender was one factor independently associated with severe disease at diagnosis (OR: 3.7; 95% CI: 1.3–10.7) [73].

Likewise, in a study by Holland *et al.* of 115 patients (220 eyes) with I-U (60%) or JIA-U (38%), male gender was associated with vision loss of VA 20/200 or less (OR: 3.65; 95% CI: 1.29–10.37; p = 0.15), but not with secondary complications [72]. Woreta *et al.* also suggested that male gender inferred a greater risk for a VA 20/200 or worse at presentation although results only approached statistical significance [51].

On the contrary, not all studies demonstrated that gender significantly influenced visual outcomes [14,16,46,47,81]. In 43 children with JRA-associated uveitis, females had a significantly longer duration of disease than males (p < 0.001), and male gender had a significant association with improvement in VA (OR: 19.4; p = 0.006) and a final VA of 20/40 or better (OR: 24.6; p = 0.03) [15].

Hence, although uveitis may occur less frequently in males, they may have a poor visual prognosis with severe visual outcomes, more complications and a higher incidence of blindness. Clearly, additional studies are needed to further investigate the role of gender in uveitis outcomes.

Young age at disease onset

Studies have shown that age at onset significantly influenced visual complications, and children who develop uveitis at a younger age tend to have a greater risk for severe complications [13,16,47]. Holland *et al.* demonstrated that

children <3 years of age had an increased risk for anterior synechiae (OR: 31.67; 95% CI: 3.79–264.3; p = 0.001). Likewise, Dana *et al.* noted that individuals who were older at uveitis onset tended to have improvement in their VA (OR: 1.16; p = 0.02) and a final VA of 20/40 or better (OR: 1.31; p = 0.02) [15]. However, Edelsten *et al.* noted that children who developed uveitis complications were older at arthritis onset, and age at onset of uveitis was not a factor [76].

ANA

Although ANA has been noted to be a risk factor for uveitis development, its role as a predictor of uveitis complications is unknown [15,16,47,48]. One study showed that ANA negative children with uveitis developed worse complications compared with children who were ANA positive [77]. However, Thorne *et al.* noted an increased risk for visual loss of VA 20/200 or worse with a positive ANA (RR: 4.60; 95% CI: 1.58–13.4; p = 0.005) with similar results noted for a VA of 20/50 or worse [71]. Hence, children with other risk markers for uveitis may require close follow-up despite their ANA status.

Duration between arthritis & uveitis diagnosis

Children with ocular complications appear to have a shorter time interval between diagnosis of arthritis and subsequent diagnosis of uveitis [17,18,61,82]. Likewise, Chia *et al.* found that a short interval between the onset of arthritis symptoms and uveitis diagnosis was associated with severe disease at diagnosis [73]. However, disease duration does not appear to predict development of visual complications [47].

Development of uveitis prior to arthritis

Approximately 10–14% of patients develop uveitis prior to arthritis [16,47]. These children may have a poorer visual prognosis with more complications [50,74,77,82]. However, it is plausible that children who are seemingly diagnosed with I-U never develop arthritis because of early aggressive treatment and may actually fall into the category of children who developed uveitis prior to arthritis, thus explaining the poor prognosis of I-U.

I-U is the most common form of childhood uveitis. However, 10% of children are at risk of developing arthritis. It is commonly thought that children with I-U have worse visual outcomes than children with JIA-U and may, therefore, need more aggressive therapy. Heinz *et al.* examined differences between 88 children with JIA-U and 49 with I-U and sought to identify factors that may differentiate between the two entities prior to the onset of arthritis. They found that children with JIA were more likely to be ANA positive (OR: 14.4; 95% CI: 5.8–35.6; p < 0.001), have complications at the initial diagnosis such as band keratopathy and cataract (OR: 2.5; 95% CI: 1.1–5.3; p = 0.027), insidious onset (OR: 3.4; 95% CI: 1.5–7.4; p = 0.003), duration over 3 months (OR: 4.6; 95% CI: 2.2–9.8; p < 0.001), VA ≤20/50 at first presentation (OR: 2.9; 95% CI: 1.5–5.6; p = 0.001) and age ≤3 years old at first manifestation of uveitis (OR: 6.8; 95% CI: 1.9–23.7; p ≤ 0.001). However, it is possible that children diagnosed with I-U may in fact be children with JIA-U whose uveitis appeared prior to arthritis but arthritis was never observed secondary to early aggressive treatment.

Complications at initial ophthalmology visit

In some children, ocular complications secondary to uveitis are detected at their initial visit. Thorne *et al.* observed that risk factors for vision loss (VA 20/50 or worse) at initial presentation were presence of posterior synechiae (RR: 2.73; 95% CI: 1.34–35.54; p = 0.005), anterior chamber flare ≥1+ (RR: 3.56; 95% CI: 2.16–15.88; p < 0.001) and abnormal intraocular pressure (<5 or >21 mmHG; RR: 3.08; 95% CI: 1.07–08.91; p = 0.04) [71]. Findings were similar for a VA of 20/200 or worse.

Similarly, in a study of 75 children with JIA-U, Woreta *et al.* noted that active intraocular inflammation at presentation was associated with at least one ocular complication at the initial visit (OR: 2.88; 95% CI: 1.40–45.92; p = 0.004) [51]. They further observed that other risk factors for ocular complications included shorter duration between the diagnosis of arthritis and uveitis (adjusted OR: 0.89; 95% CI: 0.82–80.96; p = 0.005), positive ANA (OR: 3.92; 95% CI: 1.19–12.87; p = 0.02), and the presence of anterior chamber flare ≥1+ (OR: 3.82; 95% CI: 1.39–10.49; p = 0.009) at initial visit.

Ocular complications at the initial ophthalmology visit was a predictor of later complications at the final visit (OR: 80.2; 95% CI: 16.7–383.9; p < 0.001) [47]. Holland *et al.* noted that elevated cells, elevated flare,

keratic precipitates, signs of intermediate uveitis and papillitis predicted future complications, with baseline cells ≥1 producing the greatest risk (RR: 16.06; 95% CI: 2.21–116.9; p = 0.006) [72]. Increased flare, presence of complications at baseline, signs of intermediate uveitis and papillitis predicted vision loss. The presence of any vision-threatening complication (i.e., band keratopathy, posterior synechiae, cataract or glaucoma/elevated intraocular pressure [IOP] was associated with vision loss of worse than VA 20/200 (RR: 17.24; 95% CI: 2.26–131.2; p = 0.006). Edelsten *et al.* confirmed that severe disease at onset (presence of synechiae) predicted ocular complications that were more likely to occur within the first 18 months [76].

Other factors

Other biologic predictors aside from the ANA have been evaluated. Nordal *et al.* discuss the utility of antihistone antibodies as predictors of uveitis with a level of IgM/IgG ≥8 U/ml being significant [56]. Zulian *et al.* examined the role of A2-globulin and found a significant association with severe uveitis course [61].

There is a paucity of studies on the impact of race on the risk for uveitis. Studies in JIA and JIA-U often describe children of European ancestry with only a few focused on children of African–American (AA) descent (n = 30–42) or other races [83–86]. Children of different races and ethnicities are predisposed to different JIA subtypes, which may confer varied uveitis risk. In three studies, the prevalence of JIA-U ranged from 4 to 8% in AA children, with varied ANA positivity. In a study of 89 children in India with JCA, only one child with ANA negative late-onset pauciarticular JCA developed uveitis [87]. Edelsten observed that Caucasian patients had a higher chance of remission [76]. Not all studies have shown an association with race [46]. Hence, the effects of race and ethnicity need further investigation.

Differences in uveitis in children with & without JIA

Risk factors for specific ocular complications

Sight-threatening complications such as cataracts, glaucoma and cystoid macular edema can lead to vision loss and even blindness. An understanding of the risk factors that lead to specific ocular sequelae is essential to improve monitoring for their occurrence. This section will focus on the most common JIA-U associated complication, cataracts [14–17,81,88].

Cataracts

Several retrospective studies describe risk factors for cataracts, which include: posterior synechiae on initial examination; systemic corticosteroid therapy; topical corticosteroid therapy >three drops/day; and active ongoing inflammation [74,81,89,90]. Unfortunately, up to 50% of children undergo cataract extraction and presence of posterior synechiae at diagnosis appears to be a risk factor. However, patients treated with methotrexate were less likely to need cataract extraction [13,15,16]. Differences were not noted in children who were diagnosed with uveitis prior to arthritis, gender and ANA status [91]. The use of topical corticosteroid of <three drops daily was associated with an 87% reduction in the risk of cataract development and 68% reduction in cataract surgery [90]. Hence, close monitoring for cataracts is needed in children requiring oral corticosteroids, frequent topical corticosteroid use, and those with synechiae on presentation and continued uveitis.

Outcomes & remission

Although studies describe risk markers for uveitis, little is known about the factors that influence disease remission, disease relapse, and optimal timing of medication discontinuation. Some factors associated with improved outcomes include overall duration of uveitis, shorter delay between diagnosis and presentation to a uveitis subspecialist, use of systemic NSAIDs and absence of glaucomatous neuropathy [15]. Edelsten *et al.* noted that predictors of remission include female gender, Caucasian race, a long duration between arthritis and uveitis onset, and mild onset of disease [76]. Clearly, we need better markers for uveitis risk, prognosis and remission.

There have been several studies designed to address bioinformatic evidence that supports uveitis remission. These include evaluation of changes in sIL-2R, ICAM-1, ANCA, T-cell subsets and plasmacytoid dendritic cells in IFN-α treated patients [92–96]. However, many of these approaches lack validation and are not sufficiently specific for broad application. A recent genome-wide association study (GWAS) in Behcet's disease not only confirmed the association with known *HLA-B*51*, but also identified associations within MHC class I, and at *IL-10* and *IL23R-IL12RB2* loci [97,98]. Although GWAS application to JIA has revealed other susceptibility loci that have been associated with other autoimmune diseases [99], there have

not been any such associations with uveitis. It is hoped that future genomic and proteomic analyses will lead to additional biomarkers for uveitis. Additional antigen targets in uveitis include recoverin, a calcium-binding protein [37], rhodopsin, phosducin, retinal pigment epithelium-derived RPE-65 and pigment epithelium-derived factor [42]. Examination of the immune response to these uveitogenic retinal ligands is a fertile area of research into the mechanisms of uveitis.

As the medical community continues to elucidate the risks for uveitis development and disease severity, improved methods of measuring visual outcome are crucial. A consensus effort by a multinational interdisciplinary working group that consisted of ophthalmologists and pediatric rheumatologists created potential outcome measures for clinical trials in childhood uveitis [100]. Proposed domains include grade of cells and flare in the anterior chamber, number of visits with active uveitis, VA, development of structural complications, quality of life, overall uveitis-related disability, social outcome, anti-inflammatory medications (corticosteroids), surgery and biomarkers. Standard measures of outcomes such as the Standardization of the Uveitis Nomenclature Working Group criteria for the ocular examination, and the above proposed measures for clinical trials are crucial [101].

Studies on the visual outcome of children with uveitis focus on the clinical ocular examination, but the significance of these findings on the patient's visual function and vision-related quality of life (QOL) are relatively unknown. There are few patient-based instruments that take into consideration the child and parent perspective on the impact of ophthalmologic disease on a child's life, with only one disease-specific measure for the uveitis population [102–105]. Our group has developed a parent and patient self-report instrument to assess the performance of activities that rely on vision common to children aged 8–18 years old with uveitis that is entitled, 'Effects of Youngsters' Eyesight on QOL' (EYE-Q) [106,107]. The EYE-Q could complement ophthalmologic examinations and global health measures and augment the assessment of the impact and utility of treatment, which could in turn improve overall outcomes of children with JIA-U.

Table 2. Common risk factors for uveitis and their association with uveitis development and visual complications.

Risk factors	Risk for uveitis development	Risk for visual complications	Ref.†‡
ANA	ANA seropositivity	N/A	[14,17,45,47,52,53]†
Disease duration	N/A	Short duration between arthritis diagnosis and uveitis diagnosis	[16,17,59,71,80]‡
Age at onset	Young age at arthritis onset	Young age at uveitis onset	[13,43,45,47,49]† [12,14,15,45]‡
Juvenile arthritis subtype	• Oligoarticular JIA • Pauciarticular JRA • Psoriatic JIA • Enthesitis-related JIA • Other arthritis	N/A	[12,17,44,45,47–49]†
Gender	Females	Males	[50]† [49,59,70,71,74,77,78]‡
HLA	• *HLA-B27* • *HLA-DR11*	N/A	[15,56,59–67]†
Relationship between uveitis and arthritis onset	N/A	Uveitis diagnosed prior to arthritis	[48,72,75,80]‡
Initial ophthalmology visit	N/A	Presence of complications at first examination	[45,70,74]‡

†Risk factors associated with uveitis development.
‡Risk factors associated with visual complications.
ANA: Antinuclear antibody; JIA: Juvenile idiopathic arthritis; JRA: Juvenile rheumatoid arthritis; N/A: Not available.

Conclusion

There are various risk factors associated with uveitis development, severe ocular outcomes and uveitis complications (Table 2). A thorough understanding of these factors can help to optimize management of children with uveitis, and improve direct screening and therapy. A larger number of children may be at greater risk for uveitis development and may need more frequent screening. Likewise, current screening guidelines focus on the JRA subtypes and neglect other arthritis subtypes found in the JIA classification scheme, which are also at risk for uveitis. Hence, modification of the guidelines to include the JIA subtypes should be carried out.

Notably, many children with uveitis carry many of these clinical risk markers for uveitis development and poor ocular outcomes. The identification of other factors such as biomarkers and genetic markers may be important in determining overall risk for ocular complications, vision loss and blindness. The risks of developing clinical complications of uveitis may not correlate directly with the risk of a poor functional outcome. Therefore, the inclusion of outcome parameters, measured by both clinical and subjective examination such as the Standardization of the Uveitis Nomenclature Working Group criteria, will enhance the quality and relevance of uveitis risk analyses. Hence, the determination of the impact of clinical factors, genetic markers and biomarkers warrants further study.

Future perspective

While numerous studies have focused on clinical risk factors for the development of uveitis, including JIA disease subtype, young age, female gender and ANA status, genetic markers including HLA-subtypes that confer a greater risk of development of uveitis remain largely unknown. Prior studies that have provided valuable information regarding risk for vision threatening, ocular complications of JIA-associated uveitis (i.e., cataract, glaucoma and posterior synechiae), have affirmed the importance of ANA status, shorter duration of time between arthritis and uveitis, and possibly the role of male gender. Although these clinical risk markers for the development of uveitis and ocular complications are extremely valuable for visual patient counseling purposes, the variability of patient presentations and response to therapy over time requires further study both in the clinic and in the laboratory. The identification of genetic risk markers predictive of the development of uveitis may prompt heightened surveillance of JIA patients, while the identification of biomarkers indicative of increased risk for ocular complications may aid the clinician in the timely escalation of immunosuppression.

Biologic response modifiers, including the TNF-α inhibitors in addition to traditionally used antimetabolites, have demonstrated efficacy for JIA-U; however, questions that will require additional study include the appropriate duration of disease remission prior to the tapering of immunosuppressive medication, the mechanisms underlying tachyphylaxis in some patients following long-term exposure to biologics and patient biomarkers predictive of clinical efficacy of a biologic response modifier prior to its initiation.

Beyond ophthalmic measures of success including VA and inflammatory eye disease control, future directions for research also include the establishing of an objective instrument that measures vision-related QOL in pediatric age patients, which is a key aspect of the development of the EYE-Q instrument. Correlating improvement of the clinical ophthalmologic status of patients with JIA-U with the EYE-Q will ultimately improve our research and patient care tools and improve the overall quality of care and QOL of these complex patients.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Epidemiology of juvenile idiopathic arthritis-associated uveitis

- Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease of childhood affecting one in 1000 children.
- Uveitis is the most common extra-articular manifestation of JIA and likely affects between 10 and 20% of JIA patients.

Immunopathogenesis of uveitis

- Animal models of uveitis including experimental autoimmune uveitis have been useful in elucidating the mechanisms underlying ocular inflammation.
- Uveitis is thought to arise primarily as a result of T-cell targeting of uveal antigens, and upregulation of local inflammatory cytokine production including IL-1, IL-6 and TNF-α in patients with genetic predisposition.

Risk for uveitis development

- The American Academy of Pediatrics has developed guidelines for the early detection of uveitis in patients who are considered at greater risk for uveitis development.
- Uveitis is considered more common in patients with the oligoarticular JIA or particular juvenile rheumatoid arthritis subtype although other risk factors may include positive antinuclear antibody (ANA) status, female gender, age ≤6 years at onset and JIA duration ≤4 years.

Role of genetic markers in uveitis development

- The role of genetic markers in uveitis development and uveitis severity remains incompletely studied although *HLA-B27*-positivity is more commonly associated with acute, painful uveitis in older children (cf. painless uveitis in younger patients with *HLA-B27*-negative JIA-associated uveitis).
- *HLA-DR11* and ANA positivity may confer increased risk of uveitis development in JIA patients.

Risk factors for ocular complications at initial visit

- Moderate visual loss of 20/50 or worse and severe visual loss of 20/200 or worse at initial presentation are associated with posterior synechiae, elevated intraocular pressure and anterior chamber flare, findings that may be associated with disease chronicity and inadequately treated inflammation.
- Other risk factors for ocular complications include shorter duration between the diagnoses of arthritis and uveitis, positive ANA and the presence of ≥1+ anterior chamber flare at initial evaluation.

Prognostic factors for severe outcomes

- Prognostic factors for poor visual acuity outcomes despite therapy include severe disease and complications at initial examination, the development of uveitis before arthritis, short duration between arthritis onset and uveitis, young age and male gender.
- Ocular complications that have previously been associated with visual loss to the legal blindness level include cataract, posterior synechiae, early age of uveitis diagnosis and history of ocular surgery.

Differences in uveitis in children with and without JIA

- While uveitis more commonly affects anterior segment structures (i.e., anterior uveitis in JIA), intermediate uveitis (I-U) is the most common form of childhood uveitis.
- JIA patients are more likely to be ANA positive, have ocular complications at their initial diagnosis and present at a younger age, with some patients presenting ≤3 years old with uveitis as the initial manifestation of JIA.

Risk factors for specific ophthalmic complications

- Risk factors for cataract include other secondary complications of chronic inflammation including posterior synechiae, use of systemic corticosteroid therapy, topical corticosteroids at greater than three-times daily dosing and the presence of active, ongoing inflammation.
- ANA status, diagnosis of uveitis prior to arthritis and female gender are factors that have not been found to be a risk factor for cataract development.

Outcomes & remission

- While a number of series have identified risk factors for uveitis and the secondary complications of uveitis, little is known about patient-related factors predictive of disease remission, ongoing risk for disease relapse and the optimal timing of medication discontinuation.
- Future research using the 'Effect of Youngsters' Eyesight on Quality of Life' instrument will allow us to further assess outcomes of therapeutic interventions on vision-related activities in patients aged 8–18 years old.

Conclusion

- While risk factors for the development of uveitis and clinical features of eye disease may be predictive of visual outcomes, additional research is needed into biomarkers that may be predictive of disease response to therapeutic interventions.
- Correlation of changes in ophthalmic inflammation with an objective patient and parent self-reporting instrument will allow us to globally evaluate the therapeutic response of JIA-U patients and with the goal of ultimately improving vision-related quality of life in JIA patients.

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