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Improving quick and accurate diagnosis of childhood JIA-uveitis from a pediatric rheumatology perspective

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Abstract

Introduction: Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease associated with uveitis. JIA-associated uveitis (JIA-U) is typically asymptomatic, chronic, and can lead to sight-threatening complications. This review will provide approaches to improve the diagnosis and outcomes of children with JIA-U.

Areas covered: We will provide updates on risk factors for uveitis onset and ocular complications, improvements in the ophthalmic screening schedule for uveitis detection, and potential strategies to advance the diagnosis and monitoring of JIA-U using advanced ophthalmic imaging and diagnostic equipment and laboratory biomarkers.

Expert opinion: There is a lack of high-quality research in JIA-U and few randomized controlled trials, underscoring the urgent need for further studies in this population. Early uveitis diagnosis combined with timely and appropriate treatment can improve visual outcomes. Improved knowledge of uveitis pathogenesis, risk factors for uveitis onset, measurement of uveitis outcomes, and optimal treatment are crucial.

Keywords

biomarkers; childhood uveitis; juvenile idiopathic arthritis; uveitis; non-infectious uveitis; pediatric uveitis; risk factors; tears

1. Introduction

Uveitis is inflammation of the uvea that encompasses the iris, ciliary body, and choroid. Uveitis is classified by its anatomical location as anterior, intermediate, posterior, or panuveitis. The etiology is broad and comprised of infections, malignancies, and non-infectious origins. Pediatric rheumatic conditions associated with uveitis include juvenile

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idiopathic arthritis (JIA, previously juvenile rheumatoid arthritis), sarcoidosis, Behçet's disease, systemic lupus erythematosus, Blau Syndrome, and Tubulointerstitial nephritis and uveitis (TINU). Uveitis that is associated with JIA is one of the most common types of childhood uveitis with a significant risk for sight-threatening complications [1,2]. This review will focus on recent studies on the following topics in JIA-associated uveitis (JIA-U): 1) clinical presentation of JIA and JIA-U, 2) risk factors for uveitis onset, 3) importance of ophthalmic screening for diagnosis, 4) strategies to improve and accurately diagnose and monitor JIA-U, and 5) risk factors associated with ocular complications.

2. Juvenile Idiopathic Arthritis and Uveitis

JIA has an incidence and prevalence rate of 2–23 and 4–400/100,000 respectively and varies widely by geographic region [1,3–5]. It is the most common systemic disease associated with uveitis in childhood. The etiology of JIA is unknown. It is an arthritis that is diagnosed before 16 years of age, persists for more than 6 weeks, and excludes other known etiologies. Based on the International League of Associations for Rheumatology (ILAR) classification scheme, JIA encompasses 7 subtypes. They are differentiated by the number of joints involved and presence of extraarticular manifestations [6]. Oligoarthritis (4 joints) can be subdivided into an extended or persistent course, depending on arthritis involvement after 6 months. Polyarthritis (5 joints) is further subdivided by the presence of rheumatoid factor (RF) wherein polyarticular RF positive JIA resembles adult rheumatoid arthritis. Systemic JIA is characterized by arthritis and systemic features such as quotidian fever (once or twice-daily basis), evanescent rash, serositis, hepatosplenomegaly, and lymphadenopathy. Psoriatic arthritis includes a history of skin or nail involvement with or without a history of psoriasis in a first degree relative. Enthesitis-related arthritis (ERA) involves inflammation of tendons or ligament insertions, sacroiliac, and/or lumbosacral joints. JIA is classified as an undifferentiated arthritis when there is an overlap of categories or arthritis does not fit a specific category [6]. Of the JIA subtypes, oligoarticular JIA is relatively more common (~27–50%), followed by RF negative polyarticular JIA (15–20%), ERA (3–15%), psoriatic arthritis (2–10%), RF positive polyarticular JIA (2–7%), systemic JIA (~5%), and undifferentiated arthritis (5–20%) [5,7].

Uveitis is the most common extra articular manifestation of JIA. The frequency of uveitis varies by geographic regions with the highest frequency in Europe and North America (8–25%), and lowest in Asia (3–6%) [5,8–12]. The variation may be secondary to the distribution of JIA categories in different geographic regions. Oligoarticular JIA is the most common category in Europe and North America. Most children with JIA-U have the oligoarticular category (45–75%), followed by RF negative polyarticular (15–20%), psoriatic (~7–10%), undifferentiated arthritis (~10%), ERA (7%), and RF positive polyarticular and systemic JIA (<2%) [5,13–16].

3. Clinical presentation of JIA-associated uveitis

JIA-U is often anterior, bilateral, chronic, and clinically silent. However, the course of uveitis, onset, and frequency of symptoms varies among JIA categories. Uveitis associated with oligoarticular and RF negative polyarticular JIA is often insidious and chronic.

Although typically asymptomatic, one study reported that ~30% of 37 patients with oligoarticular JIA-U and 27% of 11 with polyarticular RF negative JIA-U had ocular symptoms at initial presentation [17]. Onset is typically around 3–5 years of age. In contrast, uveitis associated with *HLA-B27* positivity, especially in ERA and sometimes in psoriatic arthritis, is typically acute and symptomatic. Onset is most common during adolescence and associated with eye pain, photophobia, blurred vision, and/or redness [7,17,18].

A prior history of ocular symptoms does not indicate that symptoms will be present with a recurrence of uveitis. One-third of JIA patients who had symptoms at onset of uveitis experienced at least one recurrence without symptoms [17]. Additionally, the relationship between arthritis and uveitis activity and damage is not parallel. If arthritis is well controlled, a patient can still have active uveitis [19]. Thus, vigilant scheduled ophthalmic screening is important regardless of arthritis activity.

Uveitis occurs in about 80–90% JIA patients in the first 4 years of JIA and approximately half present during the first year of arthritis [5,7,8,14,20,21]. Yet, uveitis can occur more than 4 years after arthritis onset in about 10% of children [10,16,22]. Uveitis can also precede onset of arthritis in 3–10% of JIA patients [7,23]. Recent studies report that at initial uveitis diagnosis, 35–40% of JIA patients were on systemic immunosuppressants for arthritis such as oral methotrexate [9,14,24].

4. Issues and consequences of not diagnosing in a timely manner

Over the last 20 years, the prevalence of legal blindness (25%) and ocular complications (70–90%) appears to have decreased [24–26]. However, sight-threatening ocular complications remain a significant problem as reported in studies published in the last 3 years from several countries comparing clinical characteristics, complications, and treatment at initial JIA-U diagnosis and last follow up visit (5 years later). They reported that up to 7% of JIA-U patients have visual acuity equal to or worse than 20/200, and 14–37% of patients have ocular structural complications at initial uveitis diagnosis. Most common ocular complications are posterior synechia (14–20%), band keratopathy (0–13%), ocular hypertension (0–11%), glaucoma (0–7%), cataracts (0–10%), and macula edema (0–2.5%) [7,9,14,24].

These studies report that by the last follow up visit (5–10 years later), the prevalence of ocular complications increased to 45–58%, consisting of posterior synechia (10–37%), band keratopathy (17–19%), ocular hypertension (28%), glaucoma (9–12%), cataracts (19–29%), and macular edema (6–7%) [7,9,14,24]. Visual acuity equal to or worse than 20/200 remained unchanged (0–6%) [9,13,14]. By the last visit, 45–70% of these patients were on tumor necrosis factor (TNF)- α inhibitors such as adalimumab or infliximab, with or without methotrexate. However, it is unclear when biologics were initiated during the uveitis course [9,13,14,24]. Thus, a new diagnosis of uveitis and new-onset or worsening ocular complications can still occur despite current treatment.

The decline in ocular and visual complications could be attributed to increased awareness of the association between JIA and uveitis, adherence to ophthalmic screening, and utilization

of systemic treatment [27]. These complications continue to be a significant problem, reminding us that more studies are needed in the prevention of uveitis and improving outcomes.

5. Improving uveitis assessment

5.1 Risk factors associated with uveitis onset

The chronic course and clinically silent nature of JIA-U underscores the importance of vigilant ophthalmic screening to ensure prompt detection of ocular inflammation. Recognizing the risk factors for uveitis and ocular complications, and increased awareness and adherence to screening schedules is essential for primary and secondary prevention. Antinuclear antibody (ANA) positivity, young age of arthritis onset (< 6 years), and oligoarticular followed by polyarticular RF negative JIA have been reinforced as major risk factors for uveitis across geographical areas [9,14,15,20,28]. RF and anti-citrullinated cyclic peptide (CCP) appear to be protective [9,28]. The association with sex and uveitis remains unclear. Often, univariate analysis shows that female sex is significantly associated with uveitis onset, but when multiple-variable analysis is performed, no significant relationship has been found [9,20,28]. This discrepancy may be due to a female predominance in oligoarticular JIA especially in young children, and a higher prevalence of ANA positivity in females.

Other potential risk factors were reported in the prospective Inception Cohort of Newly Diagnosed JIA patients (ICON-JIA). Higher levels of ESR > 20mm/hour at baseline (HR 2.36 [95% CI 1.38–4.02], $P=0.002$) and follow up visits (HR 2.44 [95% CI 1.37–4.36], $P=0.003$), and baseline S100A12 levels > 250 ng/ml (HR 2.10 [95% CI 1.15–3.85], $P=0.016$) were identified as predictors of uveitis onset after adjusting for arthritis onset, JIA subtype, ANA positivity, and arthritis treatment [20]. Clinically moderate or high arthritis activity at follow up visits (not baseline) was a significant predictor of subsequent uveitis onset (HR 4.3 [95% CI 2.51–7.37], $P<0.001$) [20]. The association between elevated ESR level and uveitis development was also observed in a retrospective study [21].

Clinical risk factors and ANA positivity remain important determinants of the ophthalmic screening schedule. The roles of ESR, S100A12, and arthritis activity as risk factors of uveitis onset remain unclear. ESR and S100A12 are non-specific markers of inflammation in arthritis, infections, other autoimmune diseases, and malignancy [29,30]. Studies on risk factors that better predict uveitis risk to aid in early disease detection are critical.

5.2 Update on JIA screening recommendations

The high burden of ocular and visual complications associated with JIA-U led to the development of international uveitis screening guidelines. The American Academy of Pediatrics (AAP) published recommendations for children with arthritis in 2006. Those recommendations were based on older arthritis nomenclature, juvenile rheumatoid arthritis (JRA), and did not include screening recommendations for all ILAR JIA categories [6,31]. In 2007, the German Uveitis in Childhood Study Group proposed ophthalmic screening schedules using the JIA classification [32]. Angeles-Han et al. with the endorsement of the

American College of Rheumatology (ACR) and the Arthritis Foundation developed new guidelines for JIA-U in 2019 [18]. Unlike the two prior guidelines, this new guideline provides recommendations for the ophthalmic screening for uveitis onset as well as monitoring and treatment of children with an established diagnosis of uveitis. They recommend that patients with oligoarticular, RF negative polyarticular, psoriatic or undifferentiated arthritis with a positive ANA, JIA onset <7 years of age, and duration of arthritis ≥ 4 years need to undergo ophthalmic screening every 3 months since they are at high risk for uveitis. Patients with other JIA categories, negative ANA, JIA onset ≥ 7 years, or disease duration of ≥ 4 years can undergo ophthalmic screening every 6–12 months based on their combination of risk factors. Patients with JIA-ERA with positive *HLA-B27* should be educated on the warning signs of acute active uveitis.

5.3 Improve uveitis measurement

The development and utilization of objective, quantitative, and reproducible measurements for the monitoring of uveitis is an area of great interest. The slit lamp is typically the standard method to assess and grade anterior chamber (AC) cells, flare, and vitreous haze using the Standardization of Uveitis Nomenclature (SUN) classification [33,34]. This approach has helped standardize uveitis evaluation to guide treatment over the past two decades. However, the SUN criteria have not yet been validated in children, there is the potential for inter-observer variations since the examination is semiquantitative and subjective, and young children can be challenging to examine due to cooperation [33,35–37].

The presence of flare suggests a disruption of blood ocular barrier due to ocular inflammation. Unlike AC cells, flare is not routinely utilized as marker of active inflammation and treatment response because it is difficult to judge changes in flare using slit lamp [38]. Given the inter-observer variations and the challenge of measuring changes in flare with clinical examination, there is a need for objective, sensitive, quantitative tools for uveitis detection and monitoring [37].

5.3.1 Quantitative advanced ophthalmic imaging and diagnostic equipment

—The introduction of laser flare photometry, a non-invasive and objective measurement of AC flare, has led to re-evaluation of flare as a potential marker of uveitis activity and treatment response. Several studies have shown that high flare measured by laser flare photometry can be a predictor of ocular complications [38–40]. Additionally, laser flare photometry was used to document early improvement of treatment that would not be detected by slit lamp in the Effect of Adalimumab for the Treatment of Uveitis in JIA (ADJUVITE) trial that assessed the efficacy and safety of adalimumab in early onset JIA-U [41]. Current challenges of laser flare photometry that may prevent wide utilization is the lack of training, particularly in young children, time constraints, and cost [42].

Recent studies using Anterior Segment Optical Coherence Tomography (AS-OCT) have demonstrated promise in anterior chamber cell grading in uveitis which correlates with clinical slit lamp grade [35,43,44]. Automated analysis algorithms and correlation of swept-source anterior segment OCT with clinical grading has shown high correlation in recent

observational case series [43]. Generally there is a higher number of inflammatory cells counted by OCT compared to AC cells counted on clinical exam with same SUN grading [35,44]. It also appears OCT to be superior than clinical exam in detecting subclinical inflammation because when uveitic eyes with 0 cells assessed by clinical grading were evaluated with OCT images counts were 4–12 cells/mm² [43]. The use of OCT in measuring disease activity has potential for monitoring treatment response and in clinical studies especially when small changes cannot be appreciated by clinical exam.

Another potential application of OCT in anterior uveitis is in the monitoring of iris edema, macular edema, and choroidal thickness as a response to treatment [36]. A limitation of OCT of the posterior segment its inability to directly detect uveitis flare although macular edema secondary to uveitis may be monitored. This is particularly relevant in intermediate uveitis, pars planitis subtype, which may feature macular edema as a complication that can lead to vision decline. Indirect ways of measuring flare using OCT have been attempted, such as the aqueous to air relative intensity (ARI) which has a strong significant correlation to laser flare photometer in active uveitis. However, OCT has a low correlation when tested in patients with inactive uveitis and healthy controls, thus limiting OCT application in the evaluation of anterior chamber flare [44]. Additionally, OCT varies in technical aspects (e.g. Single line OCT, 3D cube OCT, Swept source OCT) that results in variations in the quantification of the number of cells using one technique over the other and the question whether hyperreflective spots on OCT are truly representative of individual cells [44]. Although OCT seems to be superior in the anterior chamber cell quantification relative to slit lamp, it still requires significant validation for use in JIA-U. Many of the uveitis studies using OCT include patients with various uveitis etiologies (infectious, idiopathic, and autoimmune associated conditions) and primarily involved adult patients.

5.3.2 Laboratory biomarkers—Measurement of inflammatory biomarkers is objective and quantifiable, thus can potentially be used as indicators of ocular inflammation. Proinflammatory cytokines and chemokines (e.g IL-6, IL-8, IL-18, sICAM), S100 proteins, and B cell markers of activity have been detected in aqueous humor and serum of children with JIA-U [45–47]. In JIA-U and idiopathic anterior uveitis (IAU) patients, S100A8/A9 proteins in aqueous humor and serum were significantly higher relative to controls. These elevated inflammatory markers likely reflect ocular inflammation because they were also elevated in IAU patients without arthritis [45]. In the same study, S100A8/A9 levels in the aqueous humor of clinically inactive uveitis patients were significantly higher than controls, suggesting there may be subclinical ocular inflammation undetected by the slit lamp.

Transthyretin (TTR) was significantly elevated in the aqueous humor of JIA-U and IAU patients compared to patients with other forms of inflammatory uveitis (systemic autoimmune diseases or infections) and noninflammatory controls (congenital cataracts, traumatic cataracts and congenital glaucoma). Expression was also higher in active compared to inactive uveitis. Interestingly, TTR was not detected in the serum of JIA-U and IAU suggesting that TTR could be a potential biomarker for uveitis because it has an intraocular origin and is specific for JIA-U and IAU [48].

B cell specific gene and protein profiles from iris biopsies and aqueous humor have been investigated because of the strong association between ANA associated autoantibodies with JIA-U [47]. JIA-U patients have significant upregulation of gene and proteins of immunoglobulin components, B cell related genes (CD19, CD20), and B cell activating and survival factors such as BAFF, APRIL, and IL-6, suggesting that B cells likely play a role in the immunopathology of JIA-U. Not surprisingly, Tocilizumab (IL-6 inhibitor) and rituximab (anti-CD20) are therapeutically beneficial for refractory JIA-U [49,50].

Measuring biomarkers in the aqueous humor is not practical because collection is invasive. Thus, it is not feasible to collect in children without eye disease or those not undergoing ocular surgery. Other biomarker studies have analyzed tear fluid in patients with ocular and non-ocular diseases such as dry eye syndrome, Sjögren's syndrome, thyroid orbitopathy, and Alzheimer's disease [51–56]. Thus, tears from uveitis patients have the potential to serve as a surrogate of ocular inflammation because the same inflammatory markers in the aqueous humor have been detected in tears [57–59]. Carreño et al. in 2017 reported that IL-1RA, IL-8, IP-10/ CXCL10, MCP-1, TGF- β 2 and VEGF were detected in > 75% of adult patients with different types of uveitis including JIA-U. Tear samples from patients with noninfectious uveitis compared to controls had significantly higher levels of IL-1RA, IL-8, IP-10/CXCL10, VEGF and TGF- β 2 [57]. A pilot proteomic study of 7 pediatric patients identified 29 unique proteins including S100 proteins and TTR in tears that significantly differed in JIA-U and IAU patients [58]. However, a limitation of these studies was the lack of comparison of biomarkers in serum, tears, and aqueous humors as studies on the correlation between intra- and extraocular mediators are important. Nevertheless, the potential use of tears is exciting because collection is noninvasive, feasible in children, and can be applied in the clinical setting.

Large longitudinal controlled studies are necessary to determine if proinflammatory cytokines, S100 proteins, and TTR are useful in the diagnosis and monitoring of JIA-U. Elevation of these inflammatory mediators can also be seen in general inflammatory processes such as autoimmune disease, infections and malignancies [45,52,57,60]. In JIA-U, other factors may also influence biomarker levels such as the presence and severity of arthritis, and use of immunosuppressive medications [45,60]. Therefore, serial assessments of these inflammatory mediators in the ocular and blood compartments may clarify clinical utility.

6. Improving uveitis outcomes

6.1 Risk factors associated with uveitis inactivity, recurrence, and complications

Protective factors for achieving uveitis inactivity (< 6 months) and recurrence of uveitis within 2 years of first uveitis documentation were investigated in the ICON-JIA cohort [61]. JIA and uveitis onset after 4 and 5 years of age, respectively, were positively associated with achieving uveitis inactivity (< 6 months) and protective for subsequent uveitis recurrence. Moderate or high arthritis activity, increased AC cell count, and the use of topical corticosteroids were associated with increased risk of uveitis recurrence, but not with uveitis inactivity [61]. Unlike uveitis onset, both ESR and S100A12 were not associated with

uveitis inactivity and recurrence, thus suggesting these inflammatory markers may be more useful prognostic biomarkers rather than monitoring uveitis activity [20,61].

Risk factors associated with vision loss and ocular complications include short duration between uveitis and arthritis, uveitis preceding arthritis diagnosis, young age at uveitis onset, high AC cell score ≥ 1 , and visual acuity of 20/200 [15,61,62]. In the ICON-JIA cohort, those with uveitis related complications at first uveitis diagnosis were more likely to have complications at 2 year follow up relative to patients without complications at first uveitis documentation (74% vs 13.5%, $P < 0.0001$). Sex, JIA subtype, ANA positivity, age of onset of arthritis, ESR, S100A12, and moderate or high arthritis activity were not associated with uveitis related complications [61].

Several studies in JIA-U patients suggest that high flare values determined by laser flare photometry are associated with ocular complications and low visual acuity [38–40]. Regardless of the AC cell scores, patients with low flare ($< 20\text{pu/msec}$) at baseline had a decreased risk for ocular complications and visual acuity loss compared to patients with high flare values at baseline ($> 20\text{pu/msec}$) [38]. The association between baseline flare and complications at follow up varies. Holland et al. and Tappeiner et al. found that high flare ($> 20\text{pu/msec}$) was an independent predictive factor for ocular complications and decreased visual acuity during follow up visits. These results were also independent of the presence and grading of AC cell scores [38,40]. However, a later study by Holland et al. showed that baseline high flare as a continuous variable did not correlate with ocular complication at follow up visits. The authors suggested that this discrepancy could be related to a threshold effect because cross sectional analyses indicated different thresholds between flare and specific complications. For example, those with glaucoma have a low threshold (2% of patients with flare $< 10\text{pu/msec}$ vs 17% with flare $\geq 10\text{pu/msec}$) and those with the presence of any complication have a higher threshold (39% for eyes with flare $< 50\text{pu/msec}$ vs 95% for eyes with flare $\geq 50\text{pu/msec}$) [38,63].

6.2 Impact of systemic treatment on uveitis onset, activity, and complications

Early treatment with biologic and non-biologic DMARDS has been associated with a lower risk of uveitis onset and ocular complications [20,30,64,65]. Children with JIA who were treated with DMARDS for their arthritis the year before uveitis onset had a significant decrease in uveitis development on methotrexate alone (hazard ratio (HR) 0.63, 95% CI 0.42–0.94, $P = 0.022$), TNF inhibitors alone (HR 0.56, 95% CI 0.38–0.81, $P = 0.001$), or combination of methotrexate and TNF inhibitors (HR 0.10, 95% CI 0.05–0.23, $P = 0.001$) relative to JIA patients who did not receive DMARDS [30]. These results were also more marked when methotrexate or combination methotrexate and TNF inhibitors were started within the first year of JIA diagnosis [30]. Another study also found that the frequency of uveitis onset was lower in children treated with methotrexate compared to those who were untreated (10.5% vs 20.2%, respectively, $P = 0.049$) [64].

Poor control of uveitis inflammation and treatment with topical steroids in a dose dependent manner independently increases rate of cataract and glaucoma development [27,66,67]. Systemic immunosuppression decreases ocular inflammation and are steroid sparing agents. Recently, Cheung et al. 2019 reported the impact of systemic immunosuppression on the

number of intraocular surgeries in JIA-U patients such as cataract extraction and glaucoma related procedures [27]. Patients who initiated methotrexate after 6 months of uveitis onset had a higher likelihood of needing ophthalmic surgery (OR=6.2, 95% CI 1.2 to 33.4; $p=0.033$) compared to those starting methotrexate within 6 months. This suggests that earlier uveitis control with systemic therapy reduces the need for surgery related to cataract and glaucoma [27].

Contrary to findings of the previous studies, Nordal et al. in 2017 reported no significant reduction in the risk of uveitis onset in JIA patients that started DMARDs for arthritis [8]. This discrepancy could be related to the temporal relationship of uveitis onset and initiation of treatment for arthritis, as well as the dose and route of administration of systemic treatment particularly for methotrexate (oral vs subcutaneous). For example, the efficacy of methotrexate is greater at a high dose (15mg/m²/ week) and when administered subcutaneously compared to oral and lower doses [68].

Treatment also impacts uveitis inactivity and recurrence. In 2019, Heiligenhaus et al. reported that in the ICON-JIA cohort, adalimumab was significantly associated with achieving inactive uveitis for at least 6 months. However, no systemic immunosuppressant (methotrexate and/or TNF inhibitor) was associated with a decreased risk in uveitis recurrence and complications. Topical corticosteroid use was associated with a significantly higher risk of uveitis recurrence and its complications such as cataracts [27,61]. In 2017, Simonini et al. also found that in 94 children (67 with JIA-U, 27 with idiopathic chronic uveitis) on methotrexate, adalimumab, and infliximab, there was an increased probability of maintaining remission after treatment discontinuation if remission was obtained within 6 months after starting therapy [69].

Overall it appears that early systemic treatment may impact the course of uveitis especially before complications are noted. The incidence of uveitis in children with JIA and the occurrence of ocular complications may be decreased. Early treatment and control of uveitis may lead to sustained disease remission.

7. Suggested workup before rheumatologist referral

Before referring a child with uveitis to a rheumatologist for work up of rheumatic conditions associated with uveitis, etiologies such as infection, malignancy, and masquerade syndromes should be excluded. Further workup would then be determined by concomitant clinical characteristics guided by history and physical examination.

JIA is the most common rheumatic condition associated with uveitis. Baseline labs should include a CBC with differential, ESR, CRP and CMP to include BUN, creatinine, AST, and ALT to assess for general inflammation, involvement of other organ systems, and also in preparation for potential systemic treatment. An ANA should be considered if there is concern for arthritis such as a history of joint swelling, increased warmth, and/or joint stiffness. The ANA status will help guide the ophthalmic screening schedule, but it is not specific for rheumatic diseases. The utility of the RF is questionable because a positive RF is less likely in children with polyarticular JIA and uveitis. *HLA-B27* should be considered in

a child with acute anterior uveitis or concerns for JIA-ERA or psoriatic arthritis. If there is a plan to start a biologic, a baseline QuantiFERON or tuberculin skin test (Mantoux test) is required to screen for tuberculosis. To summarize, if a child is referred to rheumatology for evaluation of JIA, other etiologies should be considered, and labs for CBC with differential, CMP, ESR, CRP, ANA and *HLA-B27* can be drawn.

Although this review article focuses on JIA-U, we briefly address workup of other rheumatic conditions associated with uveitis. If uveitis findings are concerning for one of these conditions, the general laboratory testing described above is appropriate. Depending on the patient's clinical characteristics, one can consider angiotensin converting enzyme (ACE), lysozyme, and chest x ray for sarcoidosis, urine β_2 microglobulin level for TINU, ANA with dsDNA and smith for SLE, *HLA-B51* for Behçet's, ANCA with reflex to proteinase 3 (PR3) and myeloperoxidase (MPO) for vasculitides such as granulomatosis polyangiitis, and NOD2 gene for Blau. However, specific testing can be completed at referral.

8. Expert opinion

Overall, there remains a lack of high quality research in pediatric uveitis. Studies to better determine uveitis risk, optimize treatment initiation and discontinuation, and measure outcomes in a standard manner are needed. The incidence of uveitis and associated ocular complications appears to have decreased in children with JIA-U. Several factors have likely contributed to improved visual outcomes. These include increased availability of effective systemic therapy such as biologic agents (TNF-alpha inhibitors, abatacept, tocilizumab), improved ophthalmic screening guidelines, better awareness of the association between JIA and uveitis, and increased collaboration and communication amongst rheumatologists, ophthalmologists, optometrists, pediatricians, and patients and families. However, there is still tremendous opportunity to improve vision outcomes as at least one-third of JIA-U patients still have ocular complications at initial diagnosis, with new or worsening complications after diagnosis [9,14,24].

Persistent uncontrolled uveitis and/or prolonged use of glucocorticoids leads to poor outcomes. Timely diagnosis and early treatment of ocular inflammation will prevent sight-threatening ocular complications. Although efforts have been made by several rheumatology and ophthalmology groups to optimize the ophthalmic screening and monitoring schedules, there are still difficulties with adherence. Of great importance is maintaining good communication amongst rheumatologists, ophthalmologists, patients and families, and encouraging adherence to visits since the rheumatologist often manages systemic therapy whereas the ophthalmologist performs the ophthalmic examination and manages topical therapy.

After uveitis is established, timely initiation of systemic treatment to minimize topical glucocorticoid exposure is critical. Significant steroid adverse effects due to prolonged glucocorticoid use are well-recognized (e.g. cataracts, glaucoma). Studies have also shown that use influences the uveitis course. Topical glucocorticoids, methotrexate, and TNF- α inhibitors are usual treatment of JIA-U. There are only two randomized control trials (RCTs) in JIA-U, thus highlighting the great need for therapeutic trials [41,70]. Adherence to

therapy to control uveitis and attending regular appointments is critical for better outcomes [71,72].

Several observational studies suggest that systemic immunosuppression for arthritis is protective for uveitis onset [20,30,64,65]. Thus, the early addition of biologic and/or non-biologic DMARDS may be beneficial to a JIA patient with a high risk of uveitis to prevent onset of uveitis. However, we must first determine accurate risk factors to better quantify risk through studies that identify genetic and biologic risk factors. For example, once risk factors are better elucidated, starting weekly methotrexate subcutaneous early to minimize risk of uveitis onset in a high risk patient to control arthritis may influence the disease course. Subcutaneous methotrexate is preferred over oral administration because it is more efficacious for both arthritis and uveitis.

Validation of standard outcome measures of uveitis is needed to compare clinical outcomes. The SUN criteria is a validated measure of uveitis activity in adults. However, the optimal combination of measures to quantify ocular inflammation in the pediatric population is unclear. The use of advanced ophthalmic imaging and diagnostic equipment such as AS-OCT and laser flare photometry as a window into diagnosing and measuring uveitis activity is promising. Additionally, tear biomarkers may provide an objective and clinically applicable measure of uveitis activity. The role of standardized, sensitive, quantifiable, and reproducible measures that can be easily applied in the clinical setting needs further investigation.

Most studies that assess the impact of uveitis in children focus on measuring physical disability secondary to arthritis and overall quality of life. A comprehensive assessment that includes vision-specific measures will better assess the effect of uveitis on a child's visual functioning and quality of life. Our group developed and validated the only pediatric uveitis questionnaire, the Effects of Youngsters' Eyesight on Quality of Life (EYE-Q), and has shown the importance of vision specific measures in this population [73–75].

To accomplish the above, collaboration amongst rheumatologists, ophthalmologists, optometrists, and patients and families is critical. Overall, improved understanding of risk factors of uveitis onset and disease course, of the impact of uveitis on a child, and of early and optimal treatment of both JIA and uveitis will prevent vision-threatening ocular complications and improve a child's outcomes.

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Article highlights

- Despite the decreased prevalence of JIA-U and associated complications, up to one-third of patients still present with ocular complications at initial uveitis diagnosis and up to 7% are legally blind.
- To improve the diagnosis of JIA-U, knowledge of the risk factors related to uveitis onset, ophthalmic screening recommendations, and the importance of parental and patient adherence to screening and medications is essential. Close collaboration and communication amongst pediatric rheumatologists and ophthalmologists and/or optometrists is also important.
- Early systemic treatment for arthritis and/or uveitis improves visual outcomes. JIA patients who are on systemic immunosuppressants for arthritis have a significantly lower rate of uveitis onset. Early introduction of systemic therapy at uveitis onset is associated with fewer ophthalmic surgeries.
- Objective, sensitive, reliable, and noninvasive quantitative measurements such as advanced ophthalmic imaging and diagnostic equipment and laboratory biomarkers could potentially augment early uveitis diagnosis and monitoring.