Juvenile Idiopathic Arthritis associated uveitis
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JIA-associated uveitis

Definition
Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood. It represents up to 70% of arthritic disease in children. [1] JIA encompasses several distinct clinical entities, and is divided into three subtypes based upon the initial presentation of the disease.

Table 1. Classification of subtypes of JIA

Subtype of JIA	*Features*	*Association with uveitis*
Systemic	High grade fever, multiple extra-articular manifestations	Uveitis is rare.
Polyarticular	Five or more joints involved within 3 months of onset of disease	Uveitis is uncommon.
Pauciarticular	Less than five joints involved within 3 months of onset of disease	Highest association with uveitis.

Systemic JIA represents 20% of all JIA cases. It is characterized by the onset of high-grade fever associated with multiple extra-articular manifestations. [2] These include maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, pericarditis, and pleuritis. Joint involvement is initially mild or absent, but becomes the more prominent feature of the disease as the patient ages. Severe joint involvement constitutes the major morbidity in these patients. Uveitis is rare in this subtype.
Polyarticular JIA is defined by the involvement of 5 or more joints in the first three months following initial presentation of the disease, and represents 20%-37% of all JIA cases. [2] Progression is typically asymmetrical, with 15% of patients experiencing severe joint destruction. Uveitis is uncommon in this subtype, but more common than seen with systemic JIA.
Pauciarticular JIA, the most common subtype, comprises 37%-60% of all JIA cases. It is defined as the involvement of less than 5 joints during the first three months of disease. [2] Systemic symptoms, like fever or rash, are mild if present. The knees are the most common joints involved, but the small bones of the hands or feet may also be affected. Patients with the pauciarticular subtype are those at highest risk of developing uveitis.

Epidemiology
JIA is the most common cause of arthritis in children, followed by idiopathic, viral arthritis, and rheumatic fever. The prevalence rate for JIA is about 1.1 per 1000 children. [3]
JIA represents the most commonly identified etiology of childhood uveitis in most published series. [4] The exact proportion of childhood uveitis attributed to JIA depends on the region of the world and the nature of the uveitis referral practice. Toxoplasmosis and pars planitis are among the other commonly associated etiologies of uveitis in children. [5] In a review of our patients on the Ocular Immunology & Uveitis Service at the Massachusetts Eye & Ear Infirmary, JIA represented 41.5% of patients in whom uveitis developed before the age of 17. [4]
JIA associated uveitis most commonly affects young girls seropositive for ANA with pauciarticular-onset arthritis. [6,7] JIA patient with uveitis that fit into this category ranges from 84% to 100% in published series.[6,8] The prevalence of uveitis in ANA+ children with JIA is estimated around 20%. [8] The prevalence of uveitis in JIA overall is reported around 8%-9.3%. [8,9] This includes patients in whom uveitis develops first, suggesting that children with uveitis and ANA+ without a diagnosis of JIA should be screened closely for the onset of arthritis. [10]

Clinical Presentation
The classic presentation is an asymptomatic, bilateral, non-granulomatous iridocyclitis in a white eye. [8,11] The arthritis typically precedes the onset of uveitis [11] Arthritis onset tends to be at a young age, with one series reporting 72% of children with iridocyclitis in whom arthritis began before the age of four. [12] The latency between onset of arthritis and detection of uveitis is around two years, but can range from a few weeks to as much as 34 years. [11] However, the wide range of reported delay of onset of ocular inflammation may be due to the difficulty of determining the onset of an asymptomatic disease, as well as the occurrence of uveitis in a patient who is preverbal. [13] Less commonly, uveitis can precede joint involvement. [7]

Table 2. Typical features of JIA-associated uveitis

Classic features of JIA-associated uveitis
Anterior uveitis or iridocyclitis
Asymptomatic
Bilateral
Non-granulomatous
Otherwise white eye
Preceding history of arthritis

Posterior synechiae, cataract, and band keratopathy are some of the more common findings. [7,12] These findings are not specific for JIA, and may be present in children with uveitis due to other etiologies. Glaucoma is also commonly seen in this form of uveitis. [12] Acute or chronic angle-closure glaucoma can occur from progressive posterior synechiae or peripheral anterior synechiae respectively. Open angle glaucoma may result from presumed trabeculitis or secondary to topical or systemic steroids therapy. Cyclitic membranes may develop on the posterior surface of the iris and ciliary body, and may be associated with hypotony. If left unchecked, the membrane may extend onto the peripheral retina and cause a tractional retinal detachment. Macular edema and disk edema represent the most common posterior segment findings.

Pathophysiology
The pathogenesis of JIA and its associated uveitis is unknown. It is presumed to be autoimmune in nature. [14,15] This is supported by the presence of auto-antibodies in serum of patients with JIA, as well as the positive response to immunosuppressive therapy.
Anti-nuclear antibodies (ANA) are the autoantibodies most commonly associated with JIA. [16] The ANA titers in JIA are not as high as those found in SLE. Both IgM and IgG subtypes are represented among the antinuclear antibodies. [17] Studies of the ANA find that they appear to be directed against a variety of antigens, particularly histone H1. Anti-histone antibodies are found in patients with SLE and with RA who have vasculitis. [18] Antibodies against H3, another histone, have been shown to be present in children with uveitis. [19,20] C3 fixing ANA are found in JIA patients with iridocyclitis, and not present in the systemic subtype of JIA. This suggests that immune complex deposition may be more important in the pathogenesis of uveitis than arthritis in this patient population. [17]
The presence of auto-antibodies other than ANA further supports the autoimmune nature of JIA. Serum from patients with pauciarticular and polyarticular JIA contain antibodies that react with ocular tissues, notably iris epithelium, ciliary body epithelium, and retinal pigment epithelium. These antibodies are present in the sera of these particular types of JIA in both patients with and without uveitis. [21] Antibodies have also been found against a low molecular weight fraction of bovine iris. [22] Serum levels of antibodies against retinal S-antigen and antibodies against are not elevated in children with JIA associated uveitis. [19,20] Antibodies against collagens I – IV,

although elevated in children with JIA, are not associated with eye disease. [20]

Diagnosis

Diagnosis is not difficult in most cases of JIA associated uveitis. Arthritis precedes the onset of uveitis in 85%-90% of patients, so the ophthalmologist will usually see the child after the diagnosis has been established by the pediatrician or rheumatologist. This also means that in 10%-15% of the cases, it is the ocular disease that presents initially. It is in this circumstance that the diagnosis of the etiology of uveitis may be a dilemma.

The differential diagnosis of uveitis in children is displayed in table 3. Notably, sarcoidosis presents more like an arthritic disease than what is commonly seen in adults (i.e. lung disease). Additionally, Lyme disease may present with arthritis and uveitis, quite clinically similar to of uveitis associated with auto-immune arthritic disease.

Table 3. Differential diagnosis of uveitis in children

Diagnosis	
JIA	HLA-B27-related
Pars planitis	Tubular interstitial nephritis & uveitis
Toxoplasmosis	Lyme disease
Toxocariasis	ARN
Sarcoidosis	Others (SLE, Behcet, Fuch's, VKH)
Reiter's	Idiopathic

Initial testing should include serum ANA. ANA positivity is more common in girls with JIA associated uveitis, and particularly higher in the pauciarticular subtype. [8] Series have shown that ANA+ children with uveitis have a significant risk for developing arthritic disease. This mandates frequent screening by the pediatrician for the onset of arthritis in a child with uveitis and a positive serum ANA. Other tests are aimed at the other entities on the differential, and will depend on the clinical presentation, clinical history, and review of systems.

Finally, there exists in the older literature a term called "chronic iridocyclitis in young girls". The term leaves much to be desired, since it is by definition a diagnosis of exclusion, and even then, does not add to our understanding of the pathogenesis or management of the disorder. It may indeed represent a subgroup of patients who have a clinical picture identical to JIA associated uveitis, but who never manifest the arthritic disease.

TREATMENT

Topical steroids with topical mydriatic/cycloplegic drops are the mainstay treatment. Inflammation is difficult to control. [15] Despite this, some authors advocate using only mydriatic or cycloplegic drops if cellular activity is limited to 1+ cell or less, and will only add topical corticosteroid therapy if cellular activity is greater than this. [8] Though we recognize that this strategy attempts to address the well-known fact that topical steroids contributes to cataract formation and glaucoma, we have had good experience with systemic steroid-sparing immunosuppressives in achieving less than 1+ cellular reaction for the long term. Furthermore, one series reported that only one-third of JIA uveitis patients were controllable with short courses of topical steroids, leaving two-thirds requiring systemic treatment. Chronic systemic steroids is particularly undesirable in this patient population, in whom stunting of growth becomes a major concern in addition to the usual steroid-associated adverse reactions.

In the group of patients who will not respond to topical steroids, or will require long-term treatment, it is necessary proceed to non-steroidal immunosuppressives. Among the immunosuppressives studied, NSAIDs, chlorambucil, azathioprine, and methotrexate have all been reported to be effective in selected series of JIA patients. [23-30] In review of JIA patients treated here at the Massachusetts Eye & Ear Infirmary, 44% required use of steroid-sparing immunosuppressive therapy. [4]

Cataract formation is commonly seen in these patients. The development of cataracts in patients with JIA is reported around 50%. [31] In our series, cataracts developed in 71% of JIA patients, and nearly half of these were visually significant enough to warrant cataract surgery. [4]
Intraocular lens implantation in patients is contraindicated in patients with active JIA. One series found that intraocular implantation in adults with a history of JIA uveitis was well tolerated, and suggests that patients in whom uveitis is quiescent, or "burned out" may be able to tolerate IOLs. However, the children in the same series did not fair as well, and underscores the fact that placing an IOL in children with active JIA probably constitutes malpractice. [32]
We have achieved good results with cataract extraction combined with pars plana vitrectomy. [23,24] Other authors report similar successes with pars plana vitrectomy and cataract removal via the pars plana approach. [33,34] Flynn and Culbertson at Bascolm Palmer were able to achieve 20/40 or better vision in 8 of 10 cases with their pars plana approach. Their complications included hypotony (4 eyes) and glaucoma (2 eyes). [34] Complications, which include posterior synechiae, persistent or recurrent inflammation, and cyclitic membrane formation with subsequent hypotony, occur at a high rate in this disease. [32]

Complications
Visual complications include synechiae, band keratopathy, cataract, and glaucoma. [9] Cataract, glaucoma, and macular edema account for most permanent visual loss among these patients. In review of our JIA patients, cataracts were found in 71%, band keratopathy in 66%, and glaucoma in 30%. Cystoid macular edema developed in 37%, and one third of these had not undergone any surgery.[4] Some series report amblyopia as a significant cause of visual morbidity.
Complications from immunosuppressive therapy depend on the specific drug. All of them are associated with bone marrow suppression, chlorambucil in particular. Cyclosporine is associated with nephrotoxicity and hypertension, while methotrexate is associated with liver toxicity. It reminds ophthalmologists that this level of treatment requires careful monitoring by clinicians familiar with the use of these powerful drugs.
One concern among ophthalmologists unfamiliar with these medications is the association of immunosuppressives with malignancy. Although anecdotal reports have linked chlorambucil with lymphoma that responds to treatment withdrawal [35], evidence implicating the non-alkylating agents as potential direct causes of malignancy is scarce. To the author’s knowledge, there exists only one case report describing the onset of malignancy in a child with JIA while on low dose methotrexate. [35] Given that the prevalence in JIA in the United States is estimated at 30,000 children [3,24], that methotrexate is in common use in treatment of these patients [35], and that strong objective evidence linking low-dose methotrexate treatment in children and malignancy is non-existent, we feel that the excessive concern about malignancy associated with low-dose methotrexate treatment is unwarranted. On the other hand, there is plenty of evidence to support that it is both safe and effective in the treatment of joint disease in children with JIA, and initial evidence that it can control ocular inflammation in the uveitic subgroup. [26]

Prognosis
Risk factors for visual complications included early age of onset of the uveitis and ANA negative patients. [9] Wolf and co-authors found that uveitis onset at an early age was associated with a poor prognosis, but ANA was not. Severity of inflammation on initial exam was also predictive ocular problems in their series. [36] Cabral and colleagues found that being symptomatic at presentation also was associated with poor visual outcome. [37] In patients with JIA associated uveitis undergoing cataract surgery, poor prognosticators include postoperative glaucoma or hypotony, preexisting macular edema, or formation of epiretinal membrane. [38]

Conclusions
JIA associated uveitis is one of the most difficult of the uveitic entities to manage. Inflammation often resists topical steroid therapy. Inadequate control of inflammation or injudicious use of chronic systemic steroids both lead to glaucoma or cataract formation, posing further therapeutic dilemma for the treating ophthalmologist. Achieving adequate control of inflammation while attempting to avoid the complications of systemic steroids often requires the use of steroid-sparing immunosuppressive therapy. When surgery becomes necessary, adequate preoperative

control of inflammation is necessary to avoid serious postoperative sequelae. When cataract surgery is required, extraction with pars plana vitrectomy has been successful; intraocular implantation is contraindicated in children, and probably relatively contraindicated in adults, with the possible exception of "burned-out" JIA uveitis in adults. Although autoimmune disease is suggested, the true pathophysiology behind JIA associated uveitis is yet unknown, and requires further investigation.

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