Ocular Immunology and Inflammation

ISSN: 0927-3948 (Print) 1744-5078 (Online) Journal homepage: https://www.tandfonline.com/loi/ioii20

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To cite this article: Emmett T. Cunningham Jr., Justine R. Smith, Ilknur Tugal-Tutkun, Aniki Rothova & Manfred Zierhut (2016) Uveitis in Children and Adolescents, Ocular Immunology and Inflammation, 24:4, 365-371, DOI: 10.1080/09273948.2016.1204777

To link to this article: https://doi.org/10.1080/09273948.2016.1204777

Published online: 29 Jul 2016.

Ocular Immunology & Inflammation, 2016; 24(4): 365–371
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ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.1080/09273948.2016.1204777

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EDITORIAL

Uveitis in Children and Adolescents

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A number of authors have reviewed the epidemiology, diagnosis, and treatment of uveitis in children and adolescents.[1–16] Data from both clinic- and population-based surveys have shown that children and adolescents develop ocular inflammation less frequently than adults.[17,18] Children and adolescents with uveitis are more likely to have severe, chronic inflammation however, and therefore tend to be at higher risk of developing ocular complications and permanent vision loss[19,20]—consequences that can impact vision-related quality of life and function for many future decades.[21] Moreover, while the etiology of the inflammation remains indeterminate, referred to as idiopathic by some or undifferentiated by others, in a sizable minority of patients, identified causes of uveitis clearly differ in young patients compared with adults. By definition, juvenile idiopathic arthritis (JIA)[22–28] presents in children, for example, and adolescents are much more likely to develop intermediate uveitis/pars planitis[29–31] or tubulointerstitial nephritis with uveitis (TINU)[32–34] than are either the middle-aged or elderly. Children also develop a disproportionate burden of infectious uveitis,[19,35] much of which is posterior, including toxoplasmic retinochoroiditis, necrotizing herpetic retinitis, toxocariasis, and both *Bartonella henselae* and nematode-associated neuroretinitis. In infants, congenital toxoplasmosis, rubella, cytomegalovirus, and Herpes simplex virus (TORCH)-related syndromes need to be considered.[36–38] Similarly, otherwise-uncommon uveitic masquerade syndromes also occur in children, such as retinoblastoma, juvenile xanthogranuloma,[39] and a recently reported genetically determined retinal dystrophy masquerading as severe intermediate uveitis.[40] Unique treatment issues, particularly the management of cataracts to minimize the risk of amblyopia[41,42] and judicious use of systemic corticosteroids to avoid growth retardation, are also encountered.[43,44] Three reviews,[34,45,46] seven original articles,[47–53] and two letters[54,55] in this issue of *Ocular Immunology & Inflammation* (*OII*) address important aspects of the causes, management, complications, and outcomes of uveitis in children and adolescents.

Aguilar et al.[34] described a 62-year-old woman from Bogotá, Colombia, who developed histopathologically confirmed TINU, an uncommon condition in the elderly, in the setting of relapsing polychoondritis—an association not reported previously. As with many patients with TINU, the patient had mild, bilateral, non-granulomatous, anterior uveitis, ultimately requiring the administration of a systemic immunosuppressive agent, mycophenolate mofetil, to achieve lasting control. As summarized by the authors[34] and others,[56–59] TINU constitutes 1–2% of patients seen at uveitis referral centers, and is particularly common in children and adolescents who develop bilateral anterior uveitis of sudden onset. Frequent systemic symptoms include fever, fatigue or malaise, and abdominal pain. Both systemic symptoms and the nephritis typically precede the uveitis, but in about 20% of cases, the uveitis occurs first and in 15%, they occur concurrently. While definitive diagnosis requires histopathologic confirmation of acute interstitial nephritis (AIN), renal biopsy is often difficult to justify in the absence of acute signs or symptoms suggestive of AIN, particularly in children. A presumptive diagnosis of AIN may be made in patients with: (1) abnormal renal function, defined as elevated creatinine or creatinine clearance; (2) abnormal findings on urinalysis consistent with AIN; and (3) a history of acute systemic illness lasting for at least 2 weeks and characterized by typical signs, symptoms, and laboratory findings.[57]

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In practice, many tend to order urinalysis with a specific request for a urinary β2-microglobulin level and a serum creatinine level when considering the diagnosis of TINU in patients with uveitis, since together these simple screening tests have been shown to be both sensitive and predictive.[60] Chronic or recurrent inflammation develops in ≥50% of cases, often requiring long-term immunosuppression. The prognosis tends to be good with prompt and adequate therapy. In addition to TINU, the main diagnoses to consider in children and adolescents with both uveitis and renal disease include systemic lupus erythematosus, sarcoidosis, granulomatosis with polyangiitis, and Sjögren syndrome.[60]

Petrushkin et al.[45] provided a systematic overview of the pathogenesis, clinical features, and treatment of familial Mediterranean fever (FMF), a recessively inherited, multisystem, autoinflammatory disease that affects children from the Mediterranean basin—most notably those with Turkish, Armenian, Arabic, and Sephardic Jewish ancestry. Genetic polymorphisms associated with FMF occur in the MEFV (Mediterranean fever) gene, located on chromosome 16 and now known to code for pyrin—a 781 amino acid protein with incompletely understood roles in the regulation of the cellular cytoskeleton, apoptosis, and activation of intracellular pathways involved in inflammatory cytokine signaling. Approximately 300 different polymorphisms have been described, many resulting in phenotypically diverse presentations. Roughly half of all FMF patients will experience a neuropsychiatric prodrome 1–2 days prior to an attack—typically anxiety or depression. A vast majority of patients will then develop high fever and generalized abdominal pain. Many also develop arthralgias and/or pleuritis, which is typically unilateral and may be mistaken for pneumonia. Children who develop episodes of joint pain and swelling may be misdiagnosed as having acute rheumatic fever or JIA. Pericarditis and erysipelas-like dermatitis have also been described, but are uncommon. Amyloidosis occurs in a minority of patients, but can be severe, resulting in frank renal failure. As discussed by Petrushkin et al.,[45] ophthalmic manifestations are generally quite rare, but isolated case reports have described episcleritis, scleritis, anterior, intermediate, posterior, and panuveitis—including one case with unilateral frosted branch angiitis. Subretinal drusenoid deposits have been described most frequently, but mostly in the older literature, prior to the advent of modern multimodal imaging. Abnormal or delayed corneal wound healing has been described in several patients. Oral colchicine constitutes the mainstay of therapy and is at least partially effective in the vast majority of patients. Inhibitors of both interleukin-1 (IL-1) and tumor necrosis factor (TNF) signaling have been used with good therapeutic results in patients who were either refractory or incompletely responsive to colchicine.

Alim et al.[47] used spectral domain-optical coherence tomography (SD-OCT) to measure the thickness of the peripapillary retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GCIPL) in the eyes of 39 patients with FMF without ocular complaints, and 36 age- and gender-matched healthy control subjects. All patients were Turkish with a mean age of approximately 10 years. The authors identified no statistically significant differences in mean RNFL, mean GCIPL, or mean macula thickness between FMF patients versus controls. Further analysis of the results requested in a letter by Uzun et al.[54] revealed no effect of either refractive error or the presence or absence of the M694V mutation.[55] These results were generally consistent with those reported by Erdurmuş et al.[61] and were perhaps not unsurprising, given how uncommon retinal findings are in patients with FMF.

Abu Samra et al.[46] reviewed the occurrence, cause, and management of ocular complications in patients with JIA. The authors reminded us of the often asymptomatic nature of the uveitis and thus the importance of scheduled ophthalmic screening examinations. Guidelines formulated in 2006 by the American Academy of Pediatrics are directed by JIA subgroup, ANA status, age at onset, and disease duration. Patients who have oligoarticular JIA, are ANA-positive, were relatively young at disease onset, and who have had JIA for a relatively short time are recommended for screening every 3 months.[62,63] They also outlined their "step-ladder" approach to therapy, which involves topical corticosteroids initially, then oral non-steroidal anti-inflammatory drugs (NSAIDs), followed by immunomodulatory therapy (IMT) – typically methotrexate. Children requiring a second agent are usually administered adalimumab at their center. The authors succinctly summarized the common ocular complications of JIA, including band keratopathy, cataract, macular edema, epiretinal membrane formation, and glaucomatous optic neuropathy. While the reported prevalence of such complications from referral centers has varied dramatically, depending most directly on disease duration, treatment patterns, and follow-up, the largest study of the ocular complications of JIA was performed by The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study research group, a five-center consortium that reported on 327 patients (596 affected eyes) with JIA-associated uveitis.[64] In this multicenter study, vision loss ≤20/50 and ≤20/200 occurred in 40.3% and 24.2% of eyes, respectively. The frequency per eye of any complication over the variable course of follow-up (0–24 years; median 2.62 years) was 60.2% (0.15 per eye-year, EY). Reported individual complications

included posterior synechiae (29.0%; 0.10 per EY), band keratopathy (34.1%; 0.14 per EY), macular edema (5.4%; 0.04 per EY), epiretinal membrane formation (4.9%; 0.03 per EY), hypotony <5 mmHg (4.5%; 0.05 per EY), and ocular hypertension ≥21 mmHg (14.8%; 0.10 per EY). The research group also showed that increased uveitis activity was associated with a significantly increased risk of vision loss, while use of IMT was associated with a significantly reduced risk of vision loss. From these findings, the authors concluded that control of inflammation and appropriate use of immunosuppression are important contributors to improved outcomes of patients with JIA-related uveitis. While the frequency of cataract was not provided, an earlier study of a subgroup of 75 (22.9%) of these patients (132 affected eyes; 22.1%) from the Wilmer Eye Institute reported a frequency of cataract of 22.5% (0.04 per EY).[65] Of these various complications, management of JIA-associated cataract is perhaps the most controversial – specifically the choice of anterior versus posterior, pars plana approach and whether an intraocular lens should be implanted. Abu Samra et al.[46] recommended an anterior approach with standard intraocular lens implant (IOL) placement in eyes with well-controlled, inactive uveitis, versus performing a pars plana lensectomy/vitrectomy without IOL placement in eyes with more difficult to control inflammation, particularly when clinically significant vitreous inflammation is present. Phatak et al.[41] provided a thoughtful recent review of this specific topic, and advised specifically against placement of an IOL in very young children, or in eyes with active uveitis, despite maximal medication, with hypotony, or with rubeosis. They also cautioned against IOL implantation in patients with uveitis of indeterminate cause, and when there is a history of IOL-related complications having occurred in the fellow eye. Sijssens et al.[66] showed that early treatment with an antimetabolite, such as methotrexate (MTX), was associated with a mean delay in the development of cataract requiring surgery of 3.5 years, which might positively influence the surgery outcomes.

Kolomeyer et al.[48] described the clinical findings and outcomes in a series of 82 patients (147 eyes) with JIA-associated uveitis. Patients were seen over 11 years at two referral centers: one in New Jersey, USA, and the second in Milan, Italy. All patients were followed at least 2 months. Overall, the frequencies of specific JIA-associated ocular complications were comparable with, although slightly higher than, those reported by the SITE research group. A multivariate analysis of outcomes using generalized estimating equations identified older age at onset, lack of posterior segment involvement, and use of TNF inhibitors (OR 6.24; 95% CI 2.93–13.26) all as being positively correlated with control of inflammation. Use of cyclosporine (CsA), in contrast, was negatively correlated with uveitis control (OR 0.26; 95% CI 0.079–0.86). These findings support an expert panel recommendation that TNF inhibitors should be considered second-line therapy in JIA.[67] They also appear to reflect a general trend among uveitis specialists away from the use of CsA.[68,69] Younger age at onset and posterior segment involvement were also positively correlated with the need for subsequent surgical intervention.

Liang et al.[49] described the occurrence and treatment of foveal serous retinal detachment (FSRD) in nine patients with bilateral JIA-associated uveitis. The cohort consisted of eight girls and one boy. All subjects had oligoarthritis and were ANA-positive. The FSRD was bilateral in six (66.7%) patients (15 of 18 eyes; 83.3%). While the sample size was small, eyes with FSRD tended to have persistent flare and appeared to have a particularly high rate of complications, including formation of posterior synechiae (87%), cataract (80%), and band keratopathy (60%). The authors reported that the FSRD resolved in 14 of the 15 affected eyes with intensive immunosuppressive therapy.

Couto et al.[50] performed a retrospective analysis of the visual prognosis and remission rate in 35 children (61 eyes) with chronic anterior uveitis seen in a referral clinic at the University of Buenos Aires. A total of 20 of the 35 subjects (57.2%) had JIA and the remainder were diagnosed with idiopathic or undifferentiated uveitis. Of the patients, 29 (82.9%) had one or more complication at presentation, including band keratopathy (29.5%), cataract (27.8%), and posterior synechiae (22.9%). Medical treatments included systemic corticosteroids in 82%, and systemic IMT in 91%, and topical corticosteroids in all patients. In total, 15 of the 61 eyes (24.6%) underwent one or more surgical procedures, most commonly anterior cataract removal with IOL placement (14.7%) or pars plana vitrectomy/lensectomy (4.9%). Either a TNF inhibitor or rituximab was used alone or in combination in 14 patients (40.0%). All 35 patients were followed and treated for at least 1 year, at which point best-corrected visual acuity (BCVA) was ≥20/40 in 72.1% and ≤20/200 in 6.6%. Uveitis remission, which was defined in accordance with the Standardization of Uveitis Nomenclature (SUN) criteria[70] as inactive disease for at least 3 months after discontinuing all forms of treatment, was achieved in 2.86% of 35 followed for at least 1 year and eight patients (22.9%) overall – although only 16 patients were followed for at least 5 years and only two for at least 15 years. The authors concluded that while prolonged therapy was usually required and complications were common in children with both JIA-associated and idiopathic chronic anterior uveitis, visual prognosis tended to be good with therapy.

Wiese et al.[51] from Germany evaluated the change in inflammatory activity in 32 eyes with JIA-

associated uveitis following two different types of glaucoma surgery: limbus-based trabeculectomy with mitomycin (TE; 21 eyes) or Ahmed glaucoma valve (AGV; 11 eyes) surgery. Among the 11 eyes that underwent AGV placement, six (54.5%) had prior TE surgery, and three (27.3%) had prior goniotomy. The average time from presentation to TE surgery was 13.8 ± 4.2 years, and for AGV placement 17.8 ± 6.1 years—an understandable difference given the authors' acknowledged preference for TE and their first incisional glaucoma surgery in such patients. Both procedures were generally successful at lowering intraocular pressure (IOP) at 2 years, with the TE group yielding a mean IOP of 12.8 ± 6.1 mmHg, and the AGV group 14.9 ± 6.6 mmHg. In contrast, whereas the TE group showed reduced anterior chamber flare, the AGV group had persistent flare. The authors suggested that JIA-associated uveitis is reduced after TE, but not following AGV surgery. To support this conclusion, they cite a study by Stavrou and Murray,[71] which showed a similar reduction in the severity of the inflammation, decreased number of relapses, and reduced treatment burden in a high proportion of eyes with uveitis following TE surgery. The mechanisms that might explain such improved control, and why they would be operative following TE, but not AGV surgery remain undefined.

Ganesh et al.[52] reviewed the causes, complications, medical and surgical management, and visual outcomes in a cohort of 190 children and adolescents with uveitis seen over approximately a 3-year period at a referral center in Chennai, India. Patients were included up to 18 years of age, with a median age of 11 years. Boys comprised 64.2% of the cohort. Approximately half (52.1%) had anterior uveitis, 30.3% of which was bilateral. Other anatomic patterns of uveitis included intermediate (25.8%; 59.2% bilateral), posterior (14.2%; 37.0% bilateral), and panuveitis (7.9%; 60.0% bilateral). The cause of uveitis remained indeterminant in 37.4% of cases. Trauma (14.2%) and JIA (11.6%) were the most commonly identifed causes of inflammation, followed by tuberculosis (7.4%), viral uveitis (6.3%), toxoplasmosis (4.2%), toxocariasis (4.2%), sarcoidosis (4.2%), and Vogt–Koyanagi–Harada (VKH) disease (3.2%). Of note, infections accounted collectively for nearly one-quarter (23.2%) of all cases. Topical, regional, or systemic corticosteroids were used in 94.7% of patients, with 5.3% not requiring treatment at presentation. Non-corticosteroid immunosuppressive agents were added in 24.2% of patients. Infections were typically treated with appropriate anti-infective therapy in conjunction with oral corticosteroids. Cysticercosis cysts were removed surgically in the two affected patients; one of whom also received systemic antihelminthic therapy to treat additional cysts. Children with ocular toxocariasis were treated with corticosteroids alone. A total of 77 patients (40.5%) were observed to have a total of 90 complications, 61 at presentation and 16 over the course of follow-up. Among the entire cohort, common complications included cataract (40; 21.1%), band keratopathy (13; 6.8%), elevated IOP (13; 6.8%), and retinal detachment (10; 5.3%). Surgical procedures were performed in 55 (28.9%) cases, with lensectomy far and away the most common, having been performed in 83.6%—half of which were done with a posterior, or pars plana approach. The proportion of these patients who received IOL placement was not reported. While a detailed analysis of visual acuity outcomes was not reported, the authors noted that with treatment, vision improved in about two-thirds and remained stable in about one-quarter of cases. They concluded that a poorer prognosis was assocated with younger age at onset, delayed referral, and longer duration of uveitis.

Finally, Lonngi et al.[53] reviewed the clinical features at presentation in a cohort of 310 children and adolescents (463 eyes) with uveitis seen over a 13-year period at two referral centers in Bogotá, Colombia. Patients were included up to 18 years of age, with a mean age of 10.1 ± 5.3 years. Girls comprised 51.9% of the combined cohort. Just over half (58.7%) had posterior uveitis, 37.9% of which was bilateral. Other anatomic patterns of uveitis included anterior (14.2%; 31.8% bilateral), intermediate (16.5%; 82.4% bilateral), and panuveitis (10.6%; 84.8% bilateral). The cause of uveitis remained indeterminant in 34.2% of cases. Toxoplasmosis (44.9%) and toxocariasis (10.3%) were the most commonly identifed causes of inflammation, followed by trauma (3.5%), JIA (1.9%), and VKH disease (1.0%). Together, infections accounted collectively for over half (58.4%) of all cases. Among the 435 eyes for which BCVA was available at presentation, Snellen acuity measured ≥20/50 in 41.5% and ≤20/200 in 42.5%. Common complications included chorioretinal scars (44.5%), posterior synechiae (13.5%), retinal detachment (9.4%), glaucoma (5.2%), cataract (4.8%), macular edema (3.5%), and band keratoapthy (3.5%). The authors emphasized the importance of posterior infections, particularly toxoplasmosis and toxocariasis, as well as the high prevalence of resulting monocular (32.6%) and binocular (6.1%) blindness, in children and adolescents with uveitis in Columbia.

Collectively, these studies highlight the often chronic and visually compromising course of uveitis in children and adolescents, especially in the setting of JIA. They also confirm the importance of identifying and treating common infections, particularly in eyes with posterior or panuveitis. In eyes with non-infectious chronic or frequently recurrent uveitis, a tailored, step-ladder approach to control the inflammation appears to provide the best chance for good long-term prognosis. This should involve initial short-term use of corticosteroids, an early switch to an

antimetabolite, such as MTX or mycophenolate mofetil as first-line IMT, and the use of a TNF inhibitor, such as adalimumab or infliximab as second-line IMT. Prolonged topical therapy in patients with ongoing inflammation should be avoided, as this can be associated with the late development of severe complications, such as hypotony and phthisis. Recently presented data from the SYCAMORE trial, a randomized controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with MTX for the treatment of JIA-associated uveitis, demonstrated a positive treatment effect in favor of adalimumab plus MTX versus MTX alone—supporting a common practice of combining a TNF inhibitor with an antimetabolite as second-line therapy.[72,73]

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

JRS has acted on behalf of Flinders University as a consultant for AbbVie. AR has acted as an adviser for AbbVie, the Netherlands.

FUNDING

This work was supported in part by The Pacific Vision Foundation (ETC), The San Francisco Retina Foundation (ETC), and the Australian Research Council (FT130101648 to JRS).

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