Risk Factors for the Development of Cataract in Children with Uveitis

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Short title: Risk factors of cataract development in pediatric uveitis

Introduction

Uveitis accounts for 10-15% of blindness in the developed world.[1] Although pediatric uveitis is relatively uncommon, accounting for only 5-10% of all uveitis cases,[2] it affects young patients, who in most cases are otherwise healthy. Vision loss results from ongoing inflammation that leads to ocular structural changes such as cataract, corneal opacities, optic neuropathy and retinal lesions. The most common causes of vision loss in children with uveitis are cataract, glaucoma and chronic cystoid macular edema (CME).[2,3] Furthermore, any chronic visual obstruction can result in the development of amblyopia in the younger children, with vision loss persisting after the inciting cause is treated.[4] Such changes, together with the need for long term treatment and continuous monitoring can have a profound impact on their development, independence and education.

The prevalence of cataract in eyes with uveitis ranges between 20-64%[4-7] and it is the most common complication of uveitis in children,[8] occurring in approximately 35% of children with juvenile idiopathic arthritis (JIA) associated uveitis[9] and increasing up to 80% in adults.[10,11] Cataract progression can be the result of persistent intraocular inflammation,[12,13] secondary to surgery for uveitis complications (eg trabeculectomies and repair of retinal detachments) or as a consequence of uveitis treatment, particularly use of local or systemic corticosteroids.[14-17] It results in reduced visual acuity and can have a detrimental effect on the development and academic achievements of these children.[18]

Studies have examined risk factors for the development of cataract among children with JIA-associated uveitis, identifying risk factors such as presence of posterior synechiae (PS) at presentation;[12,19] use of systemic corticosteroids[13] topical corticosteroid therapy exceeding 3 drops a day;[12] or persistent, uncontrolled active inflammation,[3] while early treatment with methotrexate delayed cataract progression.[19] However, JIA is a unique cause of uveitis, often localized to the anterior chamber, with frequent intra-ocular structural changes and early use of systemic immunosuppressive agents, and it may not represent the same risks as other causes of pediatric uveitis.

In this study we examined disease and treatment related risk factors for cataract development in children with uveitis of any etiology. We investigated clinical and ophthalmological characteristics, as well as treatment strategies in relation to the time interval between the first presentation with uveitis and cataract development.

Methods

This is a retrospective study conducted at Moorfields Eye Hospital, London, UK (ethical approval for data collection ROAD16039, visual loss in uveitis), and at the Schneider Children's Medical Center of Israel/Rabin Medical Center, Petah Tikva, Israel (ethical approval 0307-14-RMC) with data was collected between the years 2000-2014. The study adheres to the Declaration of Helsinki and all state laws. The pediatric uveitis clinics are tertiary referral centers with children referred by ophthalmologists, pediatric rheumatologists or patients may present directly to the accident and emergency department.

Patients were included if they were under the age of 18 at the time uveitis was diagnosed. Eyes were excluded if they had other conditions which could cause cataract (e.g. trauma, congenital cataract). For estimating the time and risk factors for cataract development we excluded any patients who had cataract extraction surgery prior to the diagnosis of uveitis, had documented cataract at presentation or were followed for less than six months. Information about the patients was gathered until the time they developed cataract, or if none developed, until their last follow-up visit.

Patients' clinical details and treatment information was gathered from their clinical notes, during the time interval from presentation to the diagnosis of cataract. The following information was gathered: gender, age at presentation, anatomical diagnosis, etiology when identified following relevant investigations, presence of posterior synechia (PS) at presentation, cystoid macular edema (CME) at any time, use of systemic corticosteroids, second line immunosuppressive therapy (IMT), use of local corticosteroids injections (orbital floor injections (OFI), intravitreal triamcinolone acetate injections (IVTA) and dexamethasone implants), the number of weeks that the patient was treated with topical corticosteroids of more than 3 drops per day and the number of uveitis flare-ups.

The type of uveitis was classified using the criteria of the Standardization of Uveitis Nomenclature working group.[20] Cataract was defined as any opacity of the lens related to a non-transient decrease in vision. Uveitis flare-ups were defined as any event of increased intraocular inflammation that required treatment. Active inflammation was defined as presence of any intra-ocular cells or flare. Flare-ups were treated using local or systemic immunosuppression treated to achieve rapid disease control.

The main outcome measures were the prevalence and incidence of cataract for the entire cohort, time to and risk factors for cataract development among those with no cataract at diagnosis.

Statistical Analysis

Analysis was performed on a per-eye basis. The time to cataract development was calculated using Kaplan–Meier survival analysis. A multivariate Cox regression analysis was conducted to assess the hazard ratio (HR) and 95% confidence intervals (CI) for risk factors to developing cataract for which we used all variables that were significant ($p<0.05$) in a univariate analysis. All Cox regression models used robust variance estimation to account for correlation between eyes in patients with bilateral uveitis. Analyses were performed using SPSS statistical software (version 21, IBM, Chicago, IL). Results are presented as averages ± standard error of mean. A p value of <0.05 was considered significant.

Results

Our study included 247 eyes of 140 pediatric patients (59% female) diagnosed with uveitis. The average age at presentation was 10.3±0.4 years. There were 107 (76.4%) patients with bilateral uveitis. The mean follow up time was 51.6±3.4 months (range 6-261 months)and the prevalence of cataract in the entire cohort was 44.2% of eyes and occurred in 12.9% of eyes with acute anterior uveitis (AAU), 48.3% of those with chronic anterior uveitis (CAU), 48.0% with intermediate uveitis (IU), 16.7% with posterior uveitis (PostU) and 77.1% with panuveitis (PanU). The most common etiologies related to cataract were idiopathic (48.6%), JIA (12.9%), antinuclear antibody (ANA) positive vasculitis with no evidence of joint involvement (8.6%), infections (such as acute retinal necrosis, tuberculosis, toxoplasmosis and human immunodeficiency virus infections- 7.8%), idiopathic posterior uveitis (multi focal choroiditis and acute multifocal placoid pigment epitheliopathy- 5.7%), HLA-B27 positive (5%) and Sarcoidosis (4.3%).

At presentation 164 eyes of 94 patients (62.8% female) were phakic with no cataract. We examined this cohort to determine risk factors for the development of cataract following the diagnosis of uveitis. The mean age at presentation was 11.2±0.4 years (range 3 to 18 years) and 70 children (74.5%) had bilateral uveitis. During follow-up, 61 eyes developed cataract (37.2%).

The median time to develop cataract was 96 months (95% CI: 56.9-135.1, Figure 1), with an overall incidence of 0.1 cases per eye-year (95% CI: 0.07- 0.1) and we estimated that up to 69% of eyes would ultimately develop cataract by 129.5 months (95% CI: 104.1-154.9). The distribution of newly diagnosed cataract by uveitis type was 28 eyes (17.1%) AAU, 52 eyes (31.7%) CAU, 23 eyes (14%) PanU, 50 eyes (30.5%) IU and 11 eyes (6.7%) PostU. Forty eight eyes (29.3%) had PS at presentation and 43 eyes (26.2%) developed CME during follow up. Forty eight patients (87 eyes, 53%) were treated with systemic corticosteroids for a period of at least six months, 37 patients (67 eyes, 40.9%) received IMT, 24 eyes (14.6%) received OFI of corticosteroids, 15 eyes (9.1%) received IVTA and 7 eyes (4.3%) were given dexamethasone implants. Injections lasted on average 6 weeks for OFI, 12 weeks for IVTA and 9 months for dexamethasone implants. Local treatment was repeated as clinically required, when inflammation was active.

We examined factors related with cataract development in these patients (Table 1). Among types of uveitis PanU was found to be a statistically significant risk factor for cataract development (p=0.02), while CAU was related to an increased risk of cataract development, but did not reach statistical significance (p=0.07). We examined separately clinical properties that might be related to cataract development and found that in the univariate analysis all clinical factors, apart from gender, laterality and treatment with IMT, were found to be significantly related to an increased risk of developing cataract. However once all factors were adjusted for, only the number of flare-ups per year (HR 3.06, 95% CI 2.15-4.35, p<0.001), PS (HR 2.85, 95% CI 1.53-5.30, p=0.001), local corticosteroid injections (HR 2.37, 95% CI 1.18-4.75, p=0.02) and development of a CME remained significant (HR 2.87, 95% CI 1.41-5.82, p=0.004, Table 1). Use of systemic corticosteroids and the length of time of more than three drops of topical corticosteroids per day lost significance.

Discussion

In this study we evaluated risk factors for the development of cataract in children with uveitis. Complications of uveitis are considered more prevalent in children than in adults due to delayed diagnosis as well as difficulty in clinical examination and treatment, with the most common complication being cataract.[5,21]

The prevalence of cataract based on the published literature ranges between 20-64% of eyes.[5,6,8] Studies focusing on JIA-related uveitis found a lower prevalence than studies examining children with diverse causes of uveitis. Our results correspond with the higher values of this range (44.2%), with the majority developing cataract within several years of the diagnosis of uveitis, suggesting that cataract development remains an important complication in all patients. In our cohort, more than one third of the eyes that did not have cataract at presentation developed cataract during the average 4 year follow-up.

Studies examining the rate of cataract development among JIA patients noted an incidence of approximately 0.04/eye-year,[12] which was lower than that found in our cohort (0.09/eye-year). This may be related to the impact of JIA screening programs, in which uveitis may be detected early and rapidly controlled. These results suggest that children with all types of uveitis, not exclusively JIA-related, require tight monitoring to detect and prevent visually impairing lens opacities. Our definition of cataract, pertaining to a lens opacity that corresponds to consistent visual deterioration, may be stricter than that of other studies, some using surgical extraction as a diagnostic criterion[9,19] and may be the source of our higher incidence.

The type of uveitis influences treatment strategies as well as the development of ocular complications and final visual outcome. The distribution of anatomical diagnosis in our cohort was similar to that of other studies,[5,22] in which AU was the most frequent diagnosis, followed by IU, PanU and PostU. One of the reasons for the development of cataract in uveitis may be a consequence of ongoing inflammation and the anatomical location of this inflammation is an important factor. Amongst our cohort, cataract developed most commonly in eyes with PanU, CAU and IU respectively, whereas it was far less common in those with PostU, despite extensive use of systemic corticosteroids and local corticosteroids injections,[5] suggesting inflammation is a far more significant risk factor. Indeed, once extent of inflammation was accounted for, treatment lost significance as a risk factor to cataract development. Inflammatory mediators are known to result in structural changes in the eye (i.e. PS, peripheral anterior synechiae, cataract, CME and formation of vitreous opacities) and the development of these is related to the location of the inflammation, as well as its extent and duration. The prolonged exposure to local inflammatory mediators is known to be related to the development of anterior chamber complications,[23] among which cataract formation has the greatest visual impact.

In this study we investigated clinical and treatment strategies that may be related to the development of cataract. Previous reports have examined risk factors in JIA uveitis but we included children with uveitis from any etiology. We found high correlation between cataract development and manifestations as frequent disease relapses and presence of complications such as CME and PS, which overshadowed the impact of topical and systemic treatment strategies. Chronic, refractory disease mandates the use of more potent treatment options for extensive periods of time, and cataract formation may be the result of either the long standing active

inflammation, or as a consequence of corticosteroids. Through our multivariate analysis we found that the number of flare-ups predominated as a risk factor and that once adjusted for both systemic and extensive topical corticosteroid treatment were no longer a significant risk factors, while local corticosteroid treatment had become less significant. This result contrasts with previous studies that found extensive topical treatment to be a risk factor of cataract development.[12,13,19] However, as these studies focused primarily on JIA-related uveitis the effect of treatment may be different in other conditions. We propose that recurrent inflammation may be closely related to the development of ocular complications and should be considered when evaluating such risks. It must be stressed that treatment related complications are well established and one should always aim to control disease using the minimal dose of medication possible.

The retrospective design of this study has limitations, particularly a selection bias as these tertiary centers may represent the more severe cases, some of which had already received partial treatment prior to presentation. Nevertheless, the large number of patients, long follow-up and extensive clinical and treatment information allow us to examine the impact of many factors and highlight the need for early diagnosis, prompt treatment and close monitoring to prevent cataract development in children with uveitis.

To conclude, in this study we found that formation of cataract is common among pediatric eyes treated for uveitis and may develop over several years. Risk factors for cataract formation include presence of PS, CME, local injections of corticosteroids and recurrences of active inflammation (flare-ups). These appear to be more important than other potential factors, including extent and intensiveness of systemic and topical corticosteroid treatments. Therefore disease control should be our primary goal, aiming to avoid disease relapses.

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Figure Legend

Figure 1: Cumulative incidence analysis for cataract development among phakic eyes with no cataract at presentation. Median time to cataract development was 96 months (95% CI: 57.0-135.0), with an overall incidence of newly diagnosed cataract of 0.09/eye-year (95% CI: 0.07–0.11).