Title: Long Term Outcomes of Pediatric Idiopathic Intermediate Uveitis

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Short Title: Outcomes of Pediatric Intermediate Uveitis
Supplemental Material available at AJO.com (Tables 1-4)

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Abstract:

Purpose: To describe the course of childhood-onset intermediate uveitis without associated systemic disease, and investigate determinants of outcomes.

Design: A retrospective cohort study

Setting: Institutional.

Patients: 125 children (221 eyes) (aged 16 years and under).

Main Outcomes and Measures: Outcomes of interest were visual acuity, severity of inflammation, and the occurrence of sight-threatening complications. Variables examined included age and clinical findings at presentation, treatment, and duration of follow-up. Multivariable analysis was undertaken to investigate potential predictors of outcomes.

Results: Median follow-up duration was 57 months. At presentation, best-corrected visual acuity worse than 20/160 was recorded in 11 (4.4%) eyes, and significant vitreous haze (≥2+SUN) in 35 (14%) eyes. Corticosteroid-sparing agents were used in 41 children (33%), with methotrexate most commonly used (27 children, 21.6%). The most frequent complications were raised intraocular pressure n=65 (29.4%), cataract n=41 (18.5%), and cystoid macular edema n=29 (13.1%). At the last visit, 116 (92.8%) patients achieved best-corrected vision of 20/40 or better with quiescent uveitis. The absence of the use of a steroid-sparing immunomodulatory agent was the strongest predictive factor for the development of new macular edema (OR 6.3, 95% CI 2.3 – 16.9, $p<0.001$) or glaucoma (OR, 6.6, 95% CI 2.5 – 17.9, $p<0.001$) over the period of observation.

Conclusions: The visual outcomes of childhood-onset idiopathic intermediate uveitis are favorable. The frequency of sight-threatening sequelae of inflammation, which

confer a life-long risk of further visual loss, is high. The use of immunomodulatory therapy is associated with a lower risk of developing macular edema and ocular hypertension.

Introduction:

Uveitis in children is an uncommon ocular inflammatory condition, comprising a collection of heterogeneous disorders which often pose diagnostic and therapeutic challenges.[1-3] Intermediate uveitis (IU), the subset of disease with vitreous inflammation as the major sign, often accompanied by peripheral vascular sheathing and macular edema,[4] comprises between 1.8% and 41.7% of childhood uveitis cases.[5] This is a higher proportion of uveitis cases than that seen in adult disease, and childhood IU is also associated with a higher frequency of sight-threatening complications than seen in adult IU.[1,6–10]

Childhood IU can occur in association with systemic conditions such as sarcoidosis, tuberculosis, and multiple sclerosis; however, the majority of cases are idiopathic.[5] There is a reported association between the human leukocyte antigen (HLA)-class II allotypes (HLA-DR2 and HLA-DR15) however, HLA typing does not comprise part of routine clinical testing and is of unclear clinical significance.[11] Children may also develop pars planitis; a form of IU characterized by vitreous condensations, "snowballs", or pars plana exudates, "snowbanks". The majority of pediatric IU cases are bilateral, with a slight male predominance.[12–15] The natural course of pediatric IIU is a prolonged course of vitreous inflammation with remissions and exacerbations that can lead to substantial ocular complications and visual loss.[16,17] The most common complication associated with IU is cystoid macular edema (CME).[8–20] Other complications include cataract, ocular hypertension, optic disc edema, retinoschisis, vitreous hemorrhage, epiretinal membrane, and retinal detachment.[17,21,22]

This retrospective clinical study aimed to describe the clinical findings, complications, treatment, and long term visual outcomes for a large series of children

with idiopathic intermediate uveitis (IIU), and investigate the factors associated with clinical outcome.

Methods:

Participants:

Included children were all those aged under 16 years of age diagnosed with IIU, comprising those with non-infectious IU in the absence of systemic disease, who presented to the uveitis service at a tertiary care center (Moorfields Eye Hospital, NHS Foundation Trust) between 1992 and 2020. Cases were identified using an electronic patient record (OpenEyes v1.18, code at https://github.com/AppertaFoundation/openeyes, deposited by the Apperta Foundation https://apperta.org). The research followed the tenets of the Declaration of Helsinki and was approved by relevant regulatory boards at Moorfields Eye Hospital NHS foundation trust, London, UK.

The SUN definition of IIU was used as a case definition: intraocular inflammation predominantly involving the vitreous, where specific causative or etiologic diagnoses have been excluded (juvenile idiopathic arthritis-related uveitis, which can sometimes present with intermediate uveitis was not included in this series). The causative diagnoses were excluded based on a detailed clinical history including comprehensive review of systems (gastrointestinal, genito-urinary, respiratory, musculoskeletal, and neurological) uveitis workup as indicated by ocular features and systems review. Children with suspected systemic or infectious etiology were referred to the general pediatrician within the Uveitis service, with subsequent referral to pediatric specialist care (for example, rheumatologist or infectious disease) if indicated.

Data collection

A study-specific data proforma was developed for the collection of data. Demographic data included age (as a continuous variable and also as categorized using school milestones as a proxy for developmental stage, i.e. age 0-5yrs, 6-10yrs, and over 11yrs) and gender. Clinical data included presenting symptoms, laterality, best-corrected visual acuities (BCVA) categorized using thresholds of 20/40 (mild visual impairment, VI), 20/60 (moderate VI) and 20/200 (severe VI),[23] intraocular pressure, results of slit-lamp examination including the severity of anterior chamber and vitreous inflammation based on SUN classification.[4] Data on complications included CME, cataract, band-shaped keratopathy, ocular hypertension (IOP >21), glaucoma (defined as ocular hypertension plus optic nerve head thinning, corneal change, myopic shift or visual field defect), hypotony (define it as an intraocular pressure of less than 5 mmHg), neovascularization, papillitis, epiretinal membrane, and retinal detachment were also collected. A detailed description of treatment modalities including topical, intravitreal, and systemic modalities were recorded. Within this care center, during the study period, management of pediatric IIU was semi-standardized, and depended on factors such as degree of inflammation and the course of the disease. Anterior chamber inflammation associated with IIU was treated with frequent dexamethasone 0.1% drops. Initial presentation with, or new-onset or recurrence of significant bilateral disease (vitreous haze >2+ SUN) or severe vision-threatening IIU is treated with systemic corticosteroids (oral prednisolone 0.5-1mg/kg) which is tapered according to clinical response. Any relapsing disease or uveitis or refractory to the cessation of oral steroids is typically an indication for second-line agents, either methotrexate (MTX) or mycophenolate mofetil (MMF), with the use of a biologic such as adalimumab in refractory cases. Immunomodulatory

therapy is typically weaned after two years of inactivity after the discontinuation of all corticosteroids.

Statistical Analyses

Descriptive analysis was undertaken, with categorical and ordinal variables presented as frequencies and percentages and continuous variables in the form of mean (for normally distributed data), median, range, and interquartile range (IQR). Investigation of potential predictors of the risk of developing a new occurrence of an adverse outcome (severely impaired vision in one eye, severely impaired vision in both eyes, blindness, or sight-threatening complication) was undertaken using multivariable analysis. As we are reporting outcomes following systemic treatment, the patient is the sampling unit and the child was the unit of analysis. Visual impairment at child level was defined using vision in best-corrected vision in the better-seeing eye. The co-variables considered in analyses were decided a priori based on previous work, and comprised: poorer vision at presentation, age, duration of follow up (which reflects time since presentation as children are typically discharged to local care at age 16), severity of inflammation at outset, use of oral steroids, and use of steroid-sparing immunomodulatory agents. Associations between variables were examined using non-parametric tests. Multivariable models were constructed using conventional forward and backward stepwise regression, considering variables significant at a 10% level in initial univariable analysis, and retaining variables with known associations to outcome (such as duration of follow-up). A *p*-value of less than 0.05 was interpreted as an indicator of statistical significance. Analyses were undertaken using Stata (version 12.1, StataCorp, College Station, Texas).

Results:

Patient demographics

The initial search identified 146 individuals, however, 21 had another cause identified (e.g. sarcoidosis or tuberculosis) and were excluded. The subjects of this study that met the inclusion criteria were 125 children (221 eyes) with IIU managed at Moorfields between 1995 and 2020 (Figure 1), comprising five children aged five years or younger (4%), 52 (41.6%) children aged 6 – 10, and 68 aged between 11 and 16 years (54.4%). There were 71 (56.8%) boys and 54 (43.2%) girls. For the whole study group, the mean follow-up duration was 72.44 ±57.8 months (IQR 22-200; range: 3-222, and 10 children had follow-up duration of less than 1 year).

Clinical findings at presentation

At presentation, uveitis was unilateral in 29 (23.2%) children and bilateral in 96 (76.8%) children. The most common presenting symptom was decreased vision (96, 76.8%) children. Other symptoms included floaters, conjunctival hyperemia, pain and headache (Table 1). Eighteen (14.4%) children were asymptomatic (14%, 95% CI 9.3 -21.6%): 1/5 (20%) from the youngest group, 8/52 (15%) from the middle group and 9/68 (13%) from the oldest group. These differences did not reach statistical significance. All eyes had vitreous involvement at presentation, with 35 (13.6%) eyes having vitreous haze ≥2+, and 115 (52.0%) eyes also having anterior chamber inflammation. A diagnosis of pars planitis was made in 14 (11.2%) of the 125 children.

Uveitis workup

Of the 125 patients, uveitis workup was available for 98 (78.4%) children. This included the QuantiFERON-TB Gold test in 79 (63.2%) children and syphilis serology in 73 (58%) children (all negative). *HLA-B*27* typing was requested for 69 (55.2%) children, with five (4%) possessing the allele. Eighty-one (64.8%) children had serum angiotensin converting enzyme (ACE) checked (range 5-100 U/L, Median

48, IQR 34-71). Other workup included C reactive protein (CRP), which was performed in 57 (45.6%) children (range 1-50, median 1, IQR 1-3) and erythrocyte sedimentation rate (ESR), which was performed in 62 (49.9%) children (range 1-57, Median 5, IQR 2-9). Univariable analysis showed that poor vision at presentation was not associated with a higher level of level ACE (regression co-efficient -6.6, p=0.2, 95% CI -16.7 to 3.5), CRP (1.2, p=0.5, 95% CI -2.1 to 4.5) or ESR (-1.4, p=0.6, 95% CI -6.7 to 3.9).

Treatment of uveitis

Conservative management was used in 10 (8%) children who did not receive any treatment. All ten had a vitreous haze of ≤1+ and maintained excellent vision during follow-up. Topical dexamethasone 0.1% was used in 107 (85.6%) of children at presentation (eTable 1). Treatment with oral prednisolone was used in 62 (49.6%) children at 0.5-1mg/kg. Of these, more than half (41/62, 66.1%) children had only one course, 10 (16.1%) children had two courses, two (3.2%) children had three courses, three (4.8%) children had four courses, and six (9.7%) children had five courses over the period of observation. Intravitreal steroid injections used included triamcinolone acetonide 4 mg in 10 (8%) children and dexamethasone 700 µg (Ozurdex; Allergan) implant in 15 (12%) children. The outcomes of intravitreal steroids injections were previously published from this group of children.[24] Orbital floor steroids were not used.

Second-line immunomodulatory therapy (IMT) was used in 41 (32.8%) children. All children were initially started on IMT monotherapy (in addition to topical or systemic corticosteroids). The median time to start IMT was 7.4 months from presentation (IQR 3.9 – 37.5m, range 0 – 175). Common first-line IMT agents were MTX, which was used in 27 of the whole cohort (27/125, 21.6%), MMF (12/125, 9.6%).

Azathioprine and cyclosporine were used in one child (<1%) each. Median duration of IMT use was 31 months IQR 9-93, range 1-191 (for those children with at least 1 year follow up, median 48, 17 – 113, 1 – 191). Of the 41 children started on IMT, 26 remained on treatment at final follow-up (median follow-up duration for the children who were started on IMT was 55 months, range 4 – 200 months). Of the 41 children started on IMT, avoidance of further topical steroid use during the study period was achieved in 31 (75.6%, 95% CI 59-88%), and avoidance of further oral steroid use was achieved in 36 (87.8%, 95% CI 73 – 96%). This was in comparison to the 84 children who remained naïve to IMT, of whom 13 children avoided topical steroid use (15.4%, 95% CI 9-25%), and 68 avoided oral steroid use (81%, 95% CI 71-89%). Out of 13 children who had fundus fluorescein angiography (FFA) at presentation, 7 children were initiated on IMT due to the presence of significant inflammation and vascular leakage on FFA.

At presentation, children with poor vision in both eyes or those with poor vision in at least one eye were more likely to start on IMT (Pearson χ^2 = *8.8824, p= 0.03* and Pearson χ^2 = 18.5843, p= 0.001), respectively. In eight of the 27 children who started on MTX, there was a 'switch' to another agent during follow-up (Table 2). The main reasons for switching were lack of efficacy in four children and intolerance in three children. MMF was given to 12 (26.3%) children at initial presentation and in five children, it was switched to another agent mainly due to the lack of efficacy. Adalimumab was used in five children after being switched from another failed IMT agent (3 MTX, 1 MMF and 1 azathioprine). Table 2 summarizes the indications and intervals of switching between different IMT agents.

Uveitis complications

Raised intraocular pressure (>21 mmHg) was the most common complication, occurring in 65 (52%) children, with 63 (50.4%) children requiring anti-glaucoma medications. Other common complications were cataract in 41 (32.8%) children, CME in 29 (13.1%) children, glaucoma in 15 (6.8%) children, and papillitis in 14 (6.3%) children. Less frequent complications included epiretinal membrane, retinal detachment, band-shaped keratopathy and retina/disc neovascularization (Table 3). The eight children with retinal detachment all had moderate to severe disease at initial presentation (>2+ SUN vitreous haze and/or vitreous hemorrhage and/or persistent snow banking). Of the eight, two children presented with a retinal tear and or detachment, and the other six developed the detachment during the period of observation. No child with pars planitis developed retinal detachment. Adverse structural complications were more common in children with pars planitis, although there was no statistically significant difference in the occurrence of cataract (29% in pars planitis versus 16% in other IIU, χ^2 p=0.3), glaucoma (43% versus 30%, χ^2 p=0.3) or macular edema, (43% versus 26%, χ^2 p=0.2).

During follow-up, cataract extraction was performed in 34 (15.4%) eyes. The cataract extraction was combined with vitrectomy in 11 (5%) eyes and the intra-ocular lens implanted into 20 (9%) eyes. The interval between presentation and having cataract extraction ranged between 1 and 133 months, with a median of 21.5 months. Seventeen (7.7%) eyes required glaucoma surgery during follow-up. These included trabeculectomy in eight (3.6%) eyes and tube surgery in eight (3.6%) eyes. The interval between presentation and having glaucoma treatment ranged between 1 and 101 months, with a median of 12 months.

Status of uveitis during follow-up

Table 4 shows the status of the vitreous inflammation during follow-up. At the final follow-up, none of the patients had vitreous haze ≥2+, and 116 (92.8%) patients had quiet eyes.

Visual outcomes

At the final review, 50 (40%) children had mildly impaired vision or worse in at least one eye, and 16 (12.8%) children had mildly impaired vision or worse in the best-seeing eye (eTable 2). The leading causes of poor vision were attributed to the recurrent CME in 10 (8%) children, retinal detachment in 5 (4%) children, and cataract in one (0.8%) child. The proportion of eyes with BCVA with significantly reduced vision (20/200 or worse) decreased from 11 (4.4%) eyes at presentation to 6 (2.4%) eyes at the last follow-up. Out of 125 children included, 17 (13.6%) children were identified to have amblyopia during the follow-up. Children in the amblyogenic age range with an unexplained drop in vision (a drop not explained by media opacity, macular edema or optic disc changes), were treated and managed in conjunction with orthoptists.

Predictors of Outcome

As children who received IMT were typically prescribed the agent to reduce dependence on steroids, which in turn had been prescribed for deteriorating vision or the onset of a new complication, multivariable analysis of the predictors of outcome excluded any child who had presented with a structural complication or developed a complication prior to commencement of IMT (excluding a total of 27 children). Following adjustment for age at onset, duration of follow-up, and worse vision at presentation (eTables 3-6 in the Supplement), naivety to IMTs was associated with higher odds of developing new-onset macular edema (OR 6.3, 95% CI 2.3 – 16.9, $p<0.001$). Following adjustment for age at presentation, use of steroids and duration

of follow-up (OR 1.01 for each month, 95% CI 1.0 – 1.01, p=0.02), naivety to IMTs was associated with higher odds of developing new glaucoma (OR 6.6, 95% CI 2.4 – 17.9, p<0.001). Follow-up duration was also an independent predictor of the occurrence of secondary cataract (OR 1.01 for each month, 95% CI 1.0 – 1.02, p=0.002, following adjustment for age at onset and worse vision at presentation).

Discussion

From this large case series of childhood-onset IIU, we report good long-term visual outcomes, but a tendency towards worsening vision over time and a high frequency of inflammation-related complications, particularly ocular hypertension. The complications which led to visual loss during childhood were retinal detachment and macular edema. Most children were symptomatic at presentation. Non-specific systemic biomarkers of inflammation were often noted, but these did not predict disease severity. Topical and/or systemic steroids were widely used, and subsequent therapeutic intervention involved a range of therapeutic agents. The use of steroid-sparing IMT was associated with protection against the further development of macular edema and ocular hypertension. Follow-up duration was associated with ocular hypertension and cataract. This study represents the largest and most 'mature' series of IIU in children, with a total of 754 follow-up years.[7,10,16,20–22,25-28]

Management of uveitis in the pediatric age group represents a specific challenge regarding compliance and the presence of potential side effects.[16,29,30] Corticosteroids in different forms (topical and systemic) are usually considered the first-line treatment of IIU. The associated side-effects limit their long-term use in the pediatric age group. In contrast, corticosteroid-sparing agents are much safer and effective for the long-term control of uveitis.[29,30] Drugs such as MTX and MMF carry the risk of adverse

drug effects such as nausea, fatigue, neutropenia and transaminitis. Our findings may justify their use in moderate disease where the goal is to protect the child's visual function. MTX has been shown to be safe and effective in controlling inflammation in children; hence, it is commonly used as a corticosteroid-sparing agent, although there is still no evidence of superiority over other agents such as MMF for childhood or adult-onset disease.[13,16,17,21,31–35] Anti-tumor necrosis factor-alpha agents such as adalimumab can be combined with these first-line agents to synergistic effect,[36–39] and were used successfully in a number of children in this cohort.

The majority of children in this cohort were symptomatic at disease onset, demonstrating the importance of educating families about eye health, the importance of seeking medical attention for children who describe visual symptoms, and the importance of ensuring that appropriate eye care health provision remains accessible. However, some children were asymptomatic. Intermediate uveitis in children can be discovered incidentally during a routine eye examination, again highlighting the importance of ongoing eye health surveillance in childhood.[17] Early recognition and prompt treatment are essential to control the inflammation and prevent visual loss. Retinal detachment, CME and cataract are frequently reported complications and were, in our study, common causes for poor visual outcomes.[7,10,17,20–22,26,27] Raised intra-ocular pressure, however emerged as the key sight-threatening complication for our study cohort. The incidence of secondary glaucoma in childhood-onset IIU can be expected to rise as the child ages. Ocular hypertension could be related to the uveitis itself or due to concomitant corticosteroid use, and our data suggest that IMT, by controlling inflammation and limiting use of corticosteroids, can confer protection against this complication and its potentially far-reaching consequences.

Poor visual outcome in pediatric IIU is attributed to several factors that include younger age at presentation.[7,25] Although this study had few children aged under five years, there was a large group of younger children (aged under 11 years). These children were more likely to have longer-term outcome data within our cohort, and their final visual outcome in our study was comparable with a previous study in which BCVA of 20/40 or better was achieved in 92.8 % of the eyes.[10,21,22,27,28]

There are several limitations related to the retrospective nature of the current study. One limitation of our study is the heterogeneity of this study group, with regards to the age at presentation and disease severity. This is consistent with previous studies, which have shown wide variability in the severity of inflammation at initial presentation in childhood IIU.[16,27,28] We also report significant heterogeneity in therapeutic choices, specifically with regard to the choice of IMT. This may limit the generalizability of our findings, as there may have been particular drug-related drivers of the associations seen. However, we did not find evidence of differential protective effects from different IMT agents, perhaps due to the relatively common use of multiple agents. Another clear limitation is the retrospective nature of the dataset. The 'attrition' (loss to follow-up due to discharge, transfer to adult care or transfer to local care centers) may not have occurred at random, as there may have been a differential loss of those children with mild disease who did well despite continued naivety to IMT. Nevertheless, this 'attrition' is likely to be reflected in other specialist clinics, and the strong protective effect with IMT is a powerful ballast to the use of these therapies within these centers. Some children will have only mild disease which can be managed conservatively. Others will have a significant visual loss due to vitritis, or sight-threatening complications, which trigger prompt commencement of corticosteroids and IMT to protect remaining vision. However, the largest group are

those with moderate levels of inflammation, who are yet to develop sight-threatening complications.

This study is limited in its retrospective design as some investigations were unavailable to us as they were carried out in other centers. Finally, as the study analyses patients who presented as far back as 1992, we must acknowledge the improvements that have been made in patient care. These include the accessibility of subcutaneous biologic anti-TNF agents (ie adalimumab) for childhood non-anterior uveitis (approved for use in the UK in 2017) and the adoption of OCT imaging. As only 5 children in this cohort received adalimumab, this is unlikely to have had a significant effect on the associations we describe. It is possible that many patients with CME would have been missed prior to the advent of OCT. Equally, prior to high definition OCT, much of the inner retinal and nerve fiber layer thickening that is visible today would have been missed. These incremental improvements in our diagnostic abilities have undoubtedly impacted our threshold for treatment. In conclusion, the course of IIU during childhood in our series was favorable, with children retaining good vision. However, there was a trend towards worsening vision overall, which is important considering the ongoing risk of adverse outcomes in adulthood for this cohort. The use of IMT can be supported in those with ongoing activity in the absence of the development of a sight-threatening complication, as steroid-sparing agents are likely to have a long-term protective effect. Future research will need to focus on identification of potential subtypes of IIU and any differential response to the range of IMT used in these children, and on the longer-term outcomes (i.e. in mid to late adulthood) of apparently mild disease.

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