CLINICAL SCIENCE

An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood

Clive Edelsten, Vickie Lee, Christopher R Bentley, Jack J Kanski, Elizabeth M Graham

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See end of article for authors' affiliations

Correspondence to: Mr Clive Edelsten, Ophthalmology Department, Ipswich Hospital, Heath Road, Ipswich IP4 5PD, UK; edelsten@easynet.co.uk

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Background/aims: The clinical course for childhood chronic anterior uveitis can vary from mild, self limiting disease to bilateral blindness. The purpose of this study was to identify those risk factors at onset that predict disease severity.

Methods: A retrospective case note review of all patients with painless anterior uveitis diagnosed from 1982 to 1998. Patients were divided into two cohorts based on route of referral, diagnosis, and compliance with treatment. The standard cohort consisted of only those diagnosed from routine screening of juvenile idiopathic arthritis.

Results: Complications—cataract surgery, ocular hypertension treatment, and visual acuity <6/24. Remission: inactive uveitis on no topical treatment for >6 months. Results—163 patients were included. 34 patients (21%) developed at least one complication. The most significant predictor of complications was severe disease at onset (p = 0.001). Other factors included uveitis at the first examination (p = 0.034), membership of the non-standard cohort (p = 0.0001), non-oligoarticular disease (p = 0.02), and late onset arthritis (p = 0.024). Male sex was associated with increased complications in the standard cohort (p = 0.001). Factors predisposing to remission included membership of the standard cohort (p = 0.003), onset after 1990 (p = 0.016), white race (p = 0.015), mild disease onset (p = 0.003), and a long gap between arthritis and uveitis onset (p = 0.015).

Conclusions: It is possible to characterise the severity of those with childhood chronic anterior uveitis at the onset of disease. The majority of patients remit without visually disabling complications. It may be possible to reduce the complication rate by targeting aggressive immunosuppression on high risk patients before complications develop.

Uveitis associated with juvenile idiopathic arthritis (JIA) has an insidious onset and is usually asymptomatic before the development of sight threatening complications. Screening for uveitis has been instituted for many years and may have contributed to the decrease in prevalence of patients with severe visual loss.[1] Screening guidelines vary in the United States,[2] the United Kingdom,[3] and other parts of the world,[4] and are mainly based on the perceived risk of developing uveitis: risk factors include the pattern of initial joint disease, the patients' sex, ANA status, and age at onset. Chronic anterior uveitis may also occur associated with other systemic diseases, such as inflammatory bowel disease and sarcoidosis, and as an isolated phenomenon. Screening programmes for other childhood inflammatory diseases are not well established and only universal screening will reduce the delays of presentation found in idiopathic uveitis.

The screening guidelines do not take into account the risk of visual loss: reducing blindness should be the prime purpose of the screening programme; also the optimal screening intervals to minimise visual loss have not been established. The purpose of this study was to identify those at most risk of long term complications.

The severity of JIA associated uveitis varies from a trivial self limiting disease to one causing bilateral blindness. It is not clear how much contemporary visual loss is due to delays in presentation and how much is due to failure of contemporary treatment. Both screening programmes and levels of systemic immunosuppression have changed considerably over the past 20 years and are likely to still vary considerably between centres. We have therefore examined the influence of referral patterns and mode of presentation on the result of this study. The paediatric rheumatology department at Great Ormond Street Hospital provides a tertiary referral service for the south of England and the majority of patients are seen soon after the onset of symptoms of arthritis. The rheumatology department and the medical ophthalmology service also see patients from all over the UK for diagnosis and treatment. These patients may have had their initial management elsewhere or be referred long after complications have developed and will have a correspondingly poorer outcome. In this study we have analysed separately these two groups in order that comparison can be made with previous studies from departments with widely different referral practices. Some children develop chronic anterior uveitis without any evidence of JIA and some have other systemic inflammatory diseases. It is not clear whether the poor outcome of idiopathic chronic anterior uveitis is solely due to their inevitably delayed presentation or intrinsic severity. It is also not known whether the systemic diagnosis alters the prognosis of patients with clinically similar intraocular inflammation. These patients were therefore included in the study group.

The severity of signs at the initial examination and persistent inflammation are associated with visual loss and delays in referral to a specialist centre have been suggested as an additional contributing factor.[5–7] Treatment should aim to prevent sight threatening complications from developing with an acceptable level of side effects. There is some evidence that methotrexate, which is most effective in the subtype of JIA most closely associated with uveitis,[8] is also effective in controlling uveitis and in recent years has been given for those with active uveitis but no active arthritis.[9] Effective immunosuppression is best given before irreversible complications develop, rather than waiting for their onset, but may be unnecessary in those with the mildest disease. There are no

Table 1 Demographics and complications in standard and non-standard cohorts, in patients with and without complications

Variable	Total (% of total) (n=163)	Standard (n=123)	Non-standard (n=40)	With complications (n=34)	Without complications (n=129)
Male	40 (25%)	29	11	12	28
Non-white	20 (12%)	10	10	7	13
Seen after 1990	129 (79%)	100	29	15	76
Complications	34 (21%)	15	19		
On methotrexate	30 (18%)	22	8	7	23
ANA positive (n=155)	124 (80%)	99	25	24	100
Uveitis preceding arthritis	8 (5%)	0	8	6	2
Uveitis at first visit (n=161)	76 (47%)	51	25	21	55
Unilateral	51 (31%)	43	8	7	44
Mild disease at onset	122 (75%)	103	19	12	110
Severe disease at onset	26 (16%)	7	19	17	9
Unknown disease severity at onset	15 (9%)	13	2	5	10
Visual acuity reduced to <6/24	26 (16%)	10	16	26	
Cataract surgery	34 (21%)	14	20	34	
Requiring glaucoma treatment	23 (14%)	11	12	23	
Median (range) age of joint onset (months)	28 (2–140)	24 (6–121)	46 (2–140)	46 (6–108)	25 (2–140)
Median (range) age of uveitis onset (months)	50 (4–149)	48 (4–121)	61 (18–149)	52 (4–145)	49 (19–149)
Median gap (range) between joint and uveitis (months)	13 (0–128)	13 (1–100)	14 (0–127)	11 (0–127)	14 (1–100)
Oligoarticular at onset	140 (86%)	116	24	25	115
Polyarticular at onset	23 (16%)	7	16	9	14
Contemporaneous oligoarticular	98 (60%)	81	18	21	78
Contemporaneous polyarticular	41 (25%)	35	6	4	37
Contemporaneous extended oligoarticular	23 (14%)	7	16	9	14

If data are not available for all patients, the number of patients in the category is denoted separately.

methods yet available to predict which patients with uveitis will develop cataracts or glaucoma from the nature of the preceding intraocular inflammation. This is especially true for those with chronic anterior uveitis where the severity of inflammation is not accompanied by episodic visual loss from posterior segment inflammation or episodes of pain (both of which may be an indicator of disease severity) in other forms of uveitis, before the development of cataract, glaucoma, or irreversible visual loss. It is therefore important to be able to predict at an early stage those patients for whom the dangers of potentially toxic systemic immunosuppression are not warranted. We therefore also examined the baseline characteristics of patients who underwent early remission and who are at no risk of complications and in whom the present regimen of topical steroids alone may be sufficient and safe.

MATERIALS AND METHODS

Study design

The patients all attended the screening programmes of the clinical research centre rheumatology department, Northwick Park Hospital (now transferred to Great Ormond Street Hospital, London) and Wexham Park Hospital, Slough. All patients had chronic painless anterior uveitis. Screening for uveitis in those with suspected JIA was performed according to a standard protocol.[3] Some patients with chronic painless anterior uveitis first presented with painful red eyes when severe inflammation was untreated. No patient developed pain or redness with each relapse or episode of increased disease activity.

We included patients who first attended after January 1982 and who had ophthalmic records from the onset of uveitis. Patient factors recorded included sex, race, year seen (pre/post 1990), age at joint disease and uveitis onset, the gap to the first slit lamp examination, antinuclear antibody (ANA) status, past ocular and medical history, length of follow up, regularity of attendance, and any ophthalmic treatment outside our unit. Disease factors recorded included laterality, uveitis severity at onset, the total duration of the uveitis, best corrected visual acuities at onset and at the last visit, and any ocular co-morbidities. JIA type at onset and current disease were reviewed by a rheumatologist to ensure a consistent and contemporary joint diagnosis. Therapeutic measures noted included the duration and the type of treatment, the use of systemic immunosuppression, ocular hypertensive medication, the timing and type of ocular surgery. The JIA diagnosis subtypes were established according to the ILAR Task Force classification.[10] Severe uveitis at onset was defined as the presence of synechiae. The year of presentation was noted as an indicator of consistency of clinical practice and referral patterns over the period of the study. 1990 was the median year of presentation in this group of patients. There were two comprehensive searches of the outpatient database in 1990 and 1998. Patients developing uveitis before 1990 were more likely to have been lost to this method of case retrieval. The British paediatric rheumatology database started in 1986 and cases before this date are likely to be biased towards more severe and prolonged disease.

Patients with chronic anterior uveitis may develop many complications over many years. Some complications such as amblyopia and retinal detachment only occur in association with and subsequent to other complications. Some complications such as posterior synechiae or band keratopathy are not necessarily visually disabling. We chose end points that were both frequent and primary—both cataracts and ocular hypertension are usually the first complications in those that subsequently develop visual loss. The first end points were an intraocular pressure above 21 mm Hg given treatment, the development of visually significant cataract requiring surgery, and any visual loss reducing best corrected Snellen visual acuity to 6/24 or less, or any combination of the three. The second end point was disease remission defined as a period of inactive uveitis, lasting a minimum of 6 months, off all topical and systemic treatment. We present the rates of complications and remission overall. The subgroup of patients treated from the onset of disease in our institute, and who were compliant with treatment, were designated the *standard cohort*. The majority of patients were originally referred for assessment of their arthritis and automatically undergo ophthalmological screening. A minority of patients are referred for ophthalmological assessment alone or for severe arthritis or other systemic inflammatory disease. In order to assess the effect of patient

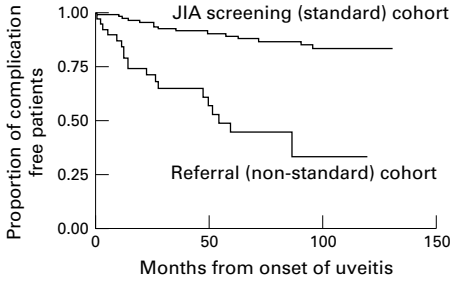

Figure 1 Complication rate by referral source. Kaplan-Meier estimate of cumulative complication free survival of patients in the standard (JIA screening cohort) and the non-standard (referral) cohort.

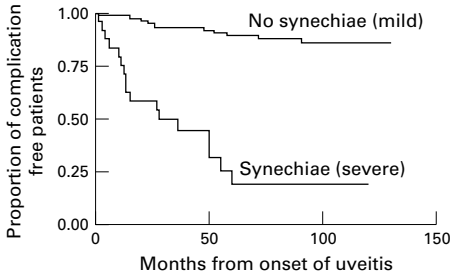

Figure 2 Complication rate by severity of uveitis at onset. Kaplan-Meier estimate of cumulative complication free survival of patients with severe (with synechiae) and mild (no synechiae) disease at onset.

recruitment resulting from these variations in referral source and initial presentation, the following were excluded from the standard cohort: those undergoing uveitis treatment outside our unit for at least 6 months at the onset of disease; those known to have poor compliance with treatment; those with systemic disease other than JIA; JIA patients who first presented with uveitis rather than arthritis. These were designated the *non-standard cohort*.

Patient treatment and follow up

The treatment of all patients was with topical dexamethasone 0.1%, doses ranging from twice a week to hourly. Patients received cyclopentolate 1% at night when the disease was sufficiently active that they were at risk of synechiae. The dose of steroid was titrated against the number of anterior chamber cells as determined by slit lamp examination and the patients were reviewed at 4–8 weekly intervals during periods of active disease. Occasionally, subconjunctival injections of triamcinolone were given under general anaesthesia if topical steroids fail to provide adequate disease control. Systemic treatment was rarely given for eye disease alone during the greater part of the period examined, but the majority of patients required such treatment for their arthritis. This consisted mainly of non-steroidal anti-inflammatory drugs, with methotrexate as a second line immunosuppressant. The majority of patients were given weekly low dose oral methotrexate according to standard protocols of trials and were in the range of 10–20 mg/m^2. In patients with poorly controlled uveitis or arthritis, doses of up to 40 mg/m^2 were given. Some patients were given other immunosuppressants in the earlier part of the study period.

Statistical analysis

All time variables are given as median and range. Significant differences between patient groups were initially tested by χ^2 (for the non-continuous variables) or Kruskal-Wallis tests. Significant factors were entered into a multivariate Cox proportional hazard model.

Table 2 Factors associated with complications and remission (univariate analysis, all patients)

Risk factors	With complications	Odds ratio	p Value
Cohort			
Referral cohort	19/40	6.5 (2.9–14.7)	0.001
Standard cohort	15/123		
Onset severity		17.3 (6.4–46.7)	0.001
Severe	17/26		
Mild	12/122		
Disease at first visit		2.3 (1.1–5.1)	0.034
Present	21/76		
Absent	12/85		
Mean age of onset of arthritis			0.024
With complications	48.3 months		
Without complications	35.5 months		
Cohort	*With remission*	*Odds ratio*	*p Value*
Standard cohort	56/120	3.5 (1.5–8.1)	0.0029
Referral cohort	8/40		
Onset severity		4.8 (1.6–14.1)	0.0032
Mild	57/122		
Severe	4/26		
Onset before 1990	35/69	2.2 (1.2–4.2)	0.0159
Onset after 1990	29/91		
White	61/140	4.4 (1.3–14.6)	0.0147
Non-white	3/20		
Extended JIA *v* others		2.8 (1.3–5.8)	0.0054

RESULTS

Demographic variables

There were 163 (275 eyes) patients in the study with 123 and 40 patients in the standard and non-standard cohorts respectively. Some patients had multiple reasons for inclusion in the non-standard cohort. There were 21 initially treated elsewhere and two who were non-compliant with treatment for extended periods. Ten patients developed uveitis before arthritis or had idiopathic uveitis, seven patients had systemic disease other than JIA including three with psoriatic arthritis, one with sarcoidosis, one with Reiter's disease, and one with ulcerative colitis.

The median follow up was 4 years. Twenty five per cent (40) were male and 12% (20) were non-white; 129 (79%) patients were seen after 1990 and 124 (124/155, 80%) were ANA positive. Fifty one patients (31%) had unilateral disease and 76 (76/161, 47%) had uveitis at their first slit lamp examination. Thirty patients (18%) received methotrexate during the course of their disease and 26 (16%) had severe uveitis at presentation. Twelve patients had other immunosuppressants including 10 with oral prednisolone, three with gold injections, three with penicillamine, and three with hydroxychloroquine. The median age of arthritis onset was 28 (2–140) months and the median age of uveitis at 50 (4–149) months and a median gap of 13 (0–128) months. In 15 patients (five with and 10 without complications) the records of the original visit were lost and the severity of disease presentation was unknown. The demography for the standard/non-standard cohorts and patients with and without complications are given in Table 1.

Factors associated with complications

Thirty four (21%) patients developed complications. Complications were significantly more common in the non-standard cohort (47% *v* 12%) (Fig 1), those with uveitis found at their

Table 3 Factors associated with complications and remissions

	t	p Value	Hazard ratio
(A) Multivariate analysis, all patients			
Patients with complications			
Severe onset	3.8	0.001	6.60 (2.51–17.4)
Non-standard cohort	−1.8	0.068	0.40 (0.15–1.07)
			Log likelihood 114, p=0.001
Patients with remission			
Severe onset	−2.62	0.009	0.22 (0.07–0.73)
Non-white race	−2.5	0.043	0.16 (0.04–0.67)
			Log likelihood 235, p=0.0001
(B) Multivariate analysis, standard cohort			
Patients with complications			
Severe onset	4.13	0.001	16.2 (4.3–61.0)
Male	2.14	0.032	4.3 (1.1–16.6)
			Log likelihood 36, p=0.001
Patients with remission			
Severe onset	−2.62	0.0026	no HR
Females		0.039	2.6 (1.04–6.4)

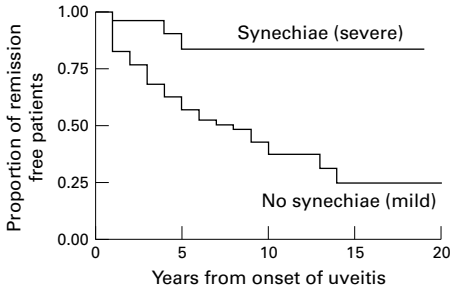

Figure 3 Remission rate by severity of uveitis at onset. Kaplan-Meier estimate of cumulative remission free survival of patients with severe (with synechiae) and mild (no synechiae) disease at onset.

initial visit (28% *v* 14%), and those with severe disease at presentation (65% *v* 10%) (Fig 2). Complications were less common in those with oligoarticular JIA (18%) compared with other diagnoses (39%). Those with complications were older at the onset of arthritis (49 months *v* 36 months, p = 0.024) but there was no significant difference in the age at onset of their uveitis. There was no significant association with race, sex, date of onset, use of systemic immunosuppression, ANA status, or whether disease involved one or both eyes (Table 2).

The only significant variables on multivariate analysis were severity of disease onset—relative risk (RR 6.60 (2.51–17.4), p = 0.001), and membership of the standard cohort (RR 0.40 (0.15–1.07), p = 0.068) (Table 3). The majority of complications in those presenting with severe disease developed within the first 18 months. Complications in those with mild onset disease developed at a constant rate over the first 9 years (Fig 2). The actual complication rate in the standard cohort was 12% (13/110) and 47% (18/38) in the non-standard cohort (Fig 1). The individual end points of poor vision, cataract extraction, and glaucoma were all associated with severe uveitis at onset and membership of the non-standard cohort (all p<0.001).

Subgroup analysis of the standard cohort confirmed that uveitis severity at onset was the most significant independent risk factor for the development of complications (RR 16.2 (4.3–61.0), p = 0.001). Male sex was also found to be independently associated with a higher complication rate (RR 4.3 (1.1–16.6), p = 0.032), and the rate appeared to be higher

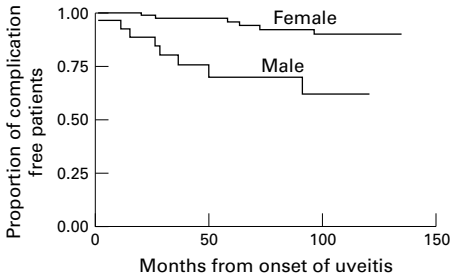

Figure 4 Sex differences in JIA uveitis complications (standard cohort only). Kaplan-Meier estimate of cumulative complication free survival of patients of male and female sex.

Table 4 Frequency of complications and remission by subgroup, severity of onset, and sex

	Subgroup	Complications	Remissions
Non-standard cohort	Severe onset	12/19 (63%)	4/19 (21%)
	Mild onset	6/19 (32%)	4/19 (21%)
Standard cohort	Severe onset	5/7 (71%)	0/7
	Mild onset	6/103 (6%)	53/103 (51%)
	Males	7/25 (28%)	7/25 (28%)
	Females	4/85 (5%)	46/85 (54%)

in the first 4 years when compared with females (Fig 3). After 8 years the complication rate was 38.4% for males and 9.7% for females. There was no association of complications with sex in the non-standard cohort.

Associations with disease remission

Factors significantly associated with disease remission on univariate analysis were similar to those associated with lack of complications (Table 2). Multivariate analysis (Table 3) found that mild onset, a long interval between the onset of arthritis and uveitis, and white race were independent predictors of remission. In the standard cohort mild onset and female sex were independent predictors of remission (Fig 4).

Frequency of complications and remission in the standard cohort

The group with the highest rate of complications and lowest rate of remission were those with severe onset in the standard cohort (71% and 0%). Females in the standard cohort had the most benign disease with 5% complication rate and 54% remission rate (Table 4).

Rates of blindness

The overall rate of severe visual loss (<6/60) was 6% (17/275 eyes), and in the standard cohort 8/203 (4%) suffered severe visual loss. The overall rate of moderate or severe visual loss was 30/275 (11%) and 13/203 (6%) in the standard cohort.

DISCUSSION

JIA associated uveitis is the most common cause of chronic anterior uveitis in childhood and is associated with significant ocular morbidity (Tables 5 and 6). Screening in JIA uveitis appears to be successful in decreasing prevalence and the rate of blindness in one population based study.[1] However, a subset of patients still progress onto severe disease and complications. Their identification is necessary in order to plan effective methods of reducing visual loss. There is a wide range of visual loss reported even in the last decade (Table 6) from 0[11] to 25%[7] and this reflects the importance of accounting for varying follow up and referral patterns when assessing temporal changes in disease severity. In Table 6 blindness rates do show

Table 5 Rates of cataract, glaucoma, and band keratopathy in JIA uveitis in the literature

Author	Cataract (%)	Glaucoma (%)	Band keratopathy (%)
Smiley 1974[21]	41	20	45
Chylack 1977[22]	19	11	11
Kanski 1977[19]	42	19	41
Cassidy 1977[23]	32	N/A	21
Wolf 1987[5]	35	38	6
Foster 1992[15]	18	N/A	N/A
Tugal-Tutkun 1996[16]	71	30	66
This study	21	14	N/A

Table 6 Rates of blindness reported in JIA uveitis

Year	Author	Blind/total (eyes)	Blindness rate (%)
1941	Blegvad[24]	4/12	33
1950	Vesterdal[25]	23/62	37
1958	Edstrom[26]	7/24	29
1966	Laaksonen[27]	13/54	24
1969	Schaller[28]	6/16	38
1970	Calabro[29]	1/13	8
1974	Smiley[21]	34/83	41
1975	Key[30]	32/85	38
1977	Chylack[17]	14/52	27
1977	Cassidy[23]	10/96	10
1977	Kanski[19]	55/223	25
1987	Wolf[5]	20/89	22
1989	Sherry[1]	0/13	0
1995	Gori[11]	0/34	0
1997	Dana[7]	19/76	25
2001	This study	17/275	6

a decline but the exact reasons for this are not clear as screening, surgical technique, and referral patterns have changed over this period.

Kanski[12] estimated 25% of the JCA uveitis population to have severe disease and found those presenting with uveitis to have a particularly poor outcome. These patients range from 7%[6] to 31%[13] of the published cohorts. Both authors found a poor visual outcome with the latter noting 66% rate of visual loss in this subgroup. Wolf *et al*[5] found that the degree of final visual loss correlated well with the degree of visual loss at onset and the risk of ocular complications correlated well with the severity of inflammation observed at the initial examination. Chalom *et al*[14] found, as we did, that there was an increased complication rate in uveitis associated with a short gap between the joint and eye disease onset and that uveitis developing after a long gap from the onset of arthritis had a more benign outcome.

In this study we have confirmed that severe disease at presentation is a major factor in determining the outcome of uveitis. We have also examined the influence of referral patterns and modes of presentation and demonstrated the large effect that patient selection and length of follow up has on the reported outcomes of this condition. A study from Boston, USA[15] reports an unusually elderly cohort whose uveitis started at the age of 11 and who were seen 5 years after disease onset and the complication rates compare with our non-standard cohort. Similarly, another referral cohort reported from the same unit had an exceptionally high complication rate.[16] In contrast, others[1 11] have noted much smaller complication rates which are similar to those found in our standard cohort after a similar follow up period. Our non-standard cohort was necessarily heterogeneous and numbers of each group are too small to determine whether systemic diagnosis or late referral truly affect outcome. It is encouraging that complication rates of our standard cohort for cataract and glaucoma are lower than in other series (Table 5) but the rate is unlikely to be reduced significantly until the percentage of late presentations can be reduced

Kanski[3] found that most uveitis was inactive by 7 years. Chylack *et al*[17] found that 41% required treatment for more than 6 months. We found that just over half of those in low risk groups went into remission. We could not determine in this study the incidence of very long term complication and remission rates of those who have very persistent disease but who escape the initial complications found in the first 9 years. Unfortunately, these patients are a difficult to group to follow as they have usually been discharged from the care of specialist rheumatologists by their teens. In this study we have used the initial complications as the end point. Late complications in the aphakic eye are likely to continue for decades and the risk factors for late visual loss may be very different from those found in this study, but are likely to be confined to those who have already incurred at least one complication in the duration of this study.

The proportion of females developing uveitis have ranged from 62%[18] to 83%.[17] Kanksi[19] found that girls were at higher risk of severe disease, and the female sex has been found to be a risk factor for severe arthritis in JIA.[20] We unexpectedly found in the standard JIA cohort that boys were at much higher risk of developing complications. The reasons for this are unclear. There were no significant differences in the delay in diagnosis and no sex difference in the demographic or HLA associations (unpublished data). These findings may suggest a lower threshold for the admininstration of systemic immunosuppression in males with JIA uveitis.

In this study it was not possible to demonstrate any effect of systemic immunosuppression on the ocular complication rate. The major impact of disease severity at onset and the variable indications and timing of systemic treatment during the period of this study may have hidden any significant effect. It is important to account for these factors in the design of future studies on the effect of treatment.

The significance of signs noted at the diagnosis of uveitis are twofold. Firstly, they may represent a prolonged period of untreated disease and, secondly, they may represent the rapid onset of signs of aggressive disease. New posterior synechiae rarely occur once the patient is on treatment and our experience of poorly compliant patients suggests that it takes at least 1–2 months for synechiae to develop in untreated patients. The high rate of complications in those with posterior synechiae suggests that short periods of untreated disease at onset may cause irreversible anterior segment changes increasing the chance of cataract and glaucoma for several years despite apparently adequate control of subsequent anterior uveitis. Phakic patients with persistent flare in the absence of cellular activity rarely achieve full remission and anecdotal reports claim the flare itself places the eye at increased risk of glaucoma. It is therefore logical to treat this group very aggressively as soon as they are diagnosed in order to reduce further risks of complications accumulating. Initiating aggressive immunosuppression once complications have started to develop may be too late to reduce the risks of long term visual loss from post-cataract surgery, macular oedema, and phithsis.

Twelve of the 29 patients developing complications were known to have mild disease at onset. The only way to reduce severe disease at presentation is by earlier diagnosis of JIA, earlier referral for slit lamp examination and, ultimately, by universal screening of vision in childhood. These strategies alone will not eliminate the complication rate as nearly half our patients with complications initially had mild disease and their outcome can only be improved by initiating more effective immunosuppression. The low rates of severe disease in the majority of patients cannot justify the universal use of toxic

systemic treatment and we require further studies to characterise more accurately those who start with mild disease but then go on to develop persistent disease and a high risk of complications. Only with a dual strategy of improving early screening and developing more effective treatment can the complication rate be significantly reduced.

Authors' affiliations
C Edelsten, V Lee, C R Bentley, J J Kanski, E M Graham, Medical Ophthalmology Department, Great Ormond Street Hospital and Prince Charles Eye Unit, King Edward VII Hospital, Windsor, UK

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