REVIEW ARTICLE

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Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature

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Abstract *Background:* Juvenile rheumatoid arthritis (JRA) is the most common systemic cause of pediatric uveitis in Europe and North America. Uveitis is commonly perceived as a frequent sequela of JRA and JRA-associated uveitis is commonly considered to have a complicated course with frequent adverse visual outcomes. *Methods:* We performed a systematic literature search for series of consecutive patients with JRA (as defined by the American College of Rheumatology criteria) reporting on the frequency of uveitis and/or complications of uveitis, published between January 1980 and December 2004. The main outcome measures were: the cumulative incidence of uveitis in JRA, the cumulative incidence of adverse visual outcome and that of complications in JRA-associated uveitis. Additionally, the influence of gender, presence of antinuclear antibody (ANA) and disease onset subtype to the likelihood of developing uveitis were examined. *Results:* Analysis of pooled data from the 26 eligible series suggested a cumulative incidence of uveitis in JRA of 8.3% [95% confidence intervals (CI), 7.5–9.1%]. The cumulative incidence of uveitis varied according to geographic location, being highest in Scandinavia, then the US, then Asia and lowest in India. JRA-associated uveitis was more common in pauciarticular than polyarticular onset patients [odds ratio (OR)=3.2, 95% CI, 2.33–4.36] and in ANA-positive than ANA-negative patients (OR=3.18, 95% CI, 2.22–4.54). Female gender was only a weak risk factor for the development of uveitis in JRA patients (OR=1.69, 95% CI 1.09–2.62) and was not statistically significant after considering disease onset subtypes. In JRA-associated uveitis the cumulative incidence of cumulative incidence of adverse outcome (visual acuity <20/40 OU) was 9.2% (95% CI: 4.7–15.8) of cataracts 20.5% (95% CI: 15.5–26.3), of glaucoma 18.9% (95% CI: 14.4–24.2) and of band keratopathy 15.7% (95% CI: 10.9–21.7). *Conclusion:* The cumulative incidence of uveitis in JRA varies according to geographic location, presence of ANA, type of JRA onset and gender. Uveitis, adverse visual outcome, and complications in JRA are less frequent than commonly accepted.

Keywords Juvenile rheumatoid arthritis · Uveitis · Meta-analysis · Ocular complications

Introduction

Juvenile rheumatoid arthritis (JRA)-associated uveitis is the most common systemic cause of uveitis of childhood in Europe and North America. [42, 58] Attempts to delineate the epidemiology and natural history of the ocular manifestations of JRA have been confounded by referral and publication bias, variability in study methodology including follow-up times, and by the multiplicity of classification schemes for juvenile arthritis (resulting in the overlapping, yet distinct, [6, 21, 38] entities of JRA, [7, 12], juvenile chronic arthritis (JCA) [18] and the twice revised juvenile idiopathic arthritis (JIA) [10, 45, 46]). Additionally, the introduction of routine screening for uveitis in JRA and advances in the management of JRA and JRA-associated uveitis (for example, the use of methotrexate) may have reduced the incidence of complications and may have improved visual outcome in recent years.

The range of cumulative incidence of JRA-associated uveitis has been reported to be between 1.4 and 25.0% [34, 55]. Complications of JRA-associated uveitis include secondary glaucoma (11–30% of patients) [23, 35], cataract (10–84% of patients) [16, 41], band keratopathy (0–70% of patients) and hypotony (0–17%) [11, 13, 35, 60]. An increased prevalence of myopia [20], keratoconjunctivitis sicca [29] and associations with spontaneous hyphema [22] and acquired Brown's syndrome have also been reported [59]. The cumulative incidence of patients with JRA-associated uveitis and a final visual acuity of less than 20/200 ranges from 0 to 38% [13, 31, 32, 41]. Consequently, whereas some studies suggest a complicated course in a substantial proportion of patients resulting in poor visual outcomes, yet other studies report fewer complications with better outcomes. The most common perception of the disease is more in line with the former reports [45, 31]. This is at odds with our own experience [11].

We have pooled available data published in the literature in order to appraise the frequency of JRA-associated uveitis in JRA patients, as well as the frequency of complications (cataract, glaucoma, band keratopathy) and adverse visual outcome.

Materials and methods

We conducted a meta-analysis, i.e. a formal and systematic review and quantitative analysis of the literature on JRA-associated uveitis and its complications [47]. We included series published between January 1980 and December 2004 reporting the incidence of uveitis (and/or the complications of JRA-associated uveitis) in consecutive patients diagnosed with JRA according to the American College of Rheumatology (ACR) criteria [7, 12]: persistent arthritis (swelling of a joint or limitation of motion with heat, pain or tenderness) of one or more joints for at least 6 weeks after exclusion of infectious, metabolic, traumatic and neoplastic causes as well as other autoimmune diseases (including psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, systemic lupus erythematosus). We chose to use the ACR criteria, as these have been used for more than 30 years, they are familiar to most ophthalmologists in North America and are practical to use. In contrast, the more recent criteria for JIA have undergone two revisions in the last 7 years [10, 44, 46] and their validity has been questioned by some [6, 21, 50], as has the exclusion of patients with a family history of psoriasis in a second degree relative from the category of oligoarthritis [5, 50, 57]. Series of patients with juvenile arthritis diagnosed and classified by the European League against Rheumatism (EULAR) [18], World Health Organization/ International League Against Rheumatism (WHO/ILAR) [10, 44, 46], the Answell and Bywaters criteria [3] or in which the diagnostic criteria used were not specified were excluded. We did not include case reports. Our search strategy is summarized in Table 1.

All eligible studies were retrieved in hard copy and abstracted by one of the authors (P.E.C.). The total number of patients with JRA, the number of patients with each

Table 1 Search strategy

Databases searched:	Keywords used:
MEDLINE (1966-)	Juvenile Arthritis OR JRA OR
International Dissertation Abstracts database	Juvenile Rheumatoid Arthritis
Cochrane Database of Systematic Reviews	OR Juvenile Chronic Arthritis
ACP Journal Club database	OR JCA OR Juvenile Idiopathic
Database of Abstracts of Reviews of Effectiveness	Arthritis OR JIA Arthritis
Cochrane controlled trials register	AND*
Restricted to articles in English	Eye OR Ocular OR Eye Diseases
Article references were scrutinized	OR Ophthalmic OR Ophthalmological
	OR Iritis OR Iridocyclitis OR Uveitis
	OR Cataract OR Glaucoma

*The combination was used for the MEDLINE and International Dissertation Abstract database. For the Cochrane databases/ ACP Journal Club only the upper set of keywords were used

subtype of JRA, the sex and age distribution, the incidence of uveitis among all patients and in each subgroup of patients, length of follow-up, the visual outcomes and the incidence of complications of JRA-associated uveitis were extracted.

Adverse visual outcome was defined as visual acuity of less than 20/40 OU. Cumulative incidence of JRA-associated uveitis was calculated as the ratio of patients with uveitis to patients with JRA in the subgroup considered. Similarly the cumulative incidence of a given complication was calculated as the ratio of patients with the complication to patients with JRA in the subgroup considered. Subgroup analysis was carried out according to disease onset pattern (pauciarticular, polyarticular or systemic), gender, presence of antinuclear

Table 2 Cumulative incidence of JRA-associated uveitis *n/s* not stated

Study	Country	Year	Patient cohort	Follow-up in years, mean (range)	JRA patients		Pauciarticular JRA patients		Polyarticular JRA patients	
					n	Cases of uveitis (%)	*n*	Cases of uveitis (%)	*n*	Cases of uveitis (%)
[11]	USA (MN)	2004	Population based	12.5 (1–36)	88	3 (3.4)	66	3 (4.5)	16	0 (0.0)
[35]	Finland	1999	series	n/s	114	18 (15.8)	86	13 (15.1)	21	5 (23.8)
[37]	Finland	1986		2–3 years	29	6 (20.6)	22	6 (27.3)	6	0 (0.0)
[39]	New Zealand	1987		9.3	55	1 (1.8)	38	1 (2.6)	8	0 (0.0)
[25]	Japan	1996	Series from	n/s	570	23 (4.3)	120	13 (10.8)	140	1 (0.7)
[41]	USA (NY)	2001	multiple centers	4.6 (0.5–23)	76	10 (13.1)	38	6 (15.7)	17	1 (5.9)
[9]	USA	2003		5	703	60 (8.5)	376	48 (12.7)	232	12 (5.2)
[13]	USA (PA)	1997		n/s	760	71 (9.3)	381	58 (15.2)	245	13 (5.3)
[1]	USA (MO)	1997	Tertiary referral	n/s	73	5 (6.8)	41	4 (9.7)	30	2 (6.7)
[8]	USA (MO)	1998	series	3.8 (1.4–6.6)	52	5 (9.6)	33	5 (15.1)	12	0 (0.0)
[12]	USA (OH)	1986		n/s	250	21 (8.4)	121	17 (14.0)	78	4 (5.1)
[14]	India	1996		n/s	331	10 (3.0)	116	5 (4.3)	171	5 (2.9)
[19]	Norway	2003		14.9[a] (11.77–25.1)	268	50 (18.7)	–	–	–	–
[34]	USA (NY)	2002		4 (0–13.8)	156	39 (25.0)	105	34 (32.4)	21	4 (19.0)
[40]	Korea	1996		7.0	140	7 (5.0)	87	7 (8.0)	38	0 (0.0)
[48]	India	1990		n/s	100	2 (2.0)	–	–	–	–
[52]	USA (MI)	1997		3.2	170	23 (13.5)	–	–	–	–
[53]	India	1996		n/s	361	12 (3.3)	108	5 (4.6)	166	5 (3.0)
[54]	USA (WA)	1991		5.9	–	–	134	13 (9.7)	–	–
[55]	India	1999		n/s	74	1 (1.4)	–	–	–	–
[61]	ROC	2001		n/s	228	13 (5.7)	127	9 (7.0)	82	3 (3.6)
All series					4598	8.3% (95% CI: 7.5–9.1)	1999	12.4% (95% CI: 10.9–13.9)	1283	4.3% (95% CI: 3.3–5.5)
All population-based series and series from multiple centers					2395	6.8% (95% CI: 5.8–7.9)	1127	13.1% (95% CI: 11.2–15.2)	685	4.7% (95% CI: 3.2–6.5)
All series with mean f/u greater than 4 years					1486	11.4% (95% CI: 9.9–13.2)	844	13.3% (95% CI: 11.0–15.8)	332	5.1% (95% CI: 3.0–8.0)

[a] Had been published electronically in 2004, therefore eligible for inclusion
[b] Median

Table 3 Geographic variation in the cumulative Incidence of JRA-associated uveitis

Geographic area	JRA patients		Pauciarticular JRA patients		Polyarticular JRA patients		Systemic JRA patients	
	n	Incidence of uveitis % (95% CI)	n	Incidence of uveitis % (95% CI)	n	Incidence of uveitis % (95% CI)	n	Incidence of uveitis % (95% CI)
USA[a]	2328	10.2 (9.0–11.5)	1295	14.5 (12.6–16.6)	651	5.5 (3.9–7.6)	308	0.0 (0.0–1.2)
East Asia[b]	938	4.6 (3.3–6.1)	334	8.7 (5.9–12.2)	260	1.5 (0.4–3.9)	344	2.9 (1.4–5.3)
South Asia[c]	866	2.9 (1.9–4.2)	224	4.5 (2.2–8.1)	337	3.0 (1.4–5.4)	131	1.5 (0.2–5.4)
Scandinavia[d]	411	18.0 (14.4–22.1)	108	17.6 (10.9–26.1)	27	18.5 (6.3–38.8)	8	0.0 (0.0–3.7)

[a] References: [1, 8, 9, 11–13, 34, 41, 52, 54]. Note that there were 17 patients without specified JRA onset pattern reported by Oren et al. [41], which are included in the category "JRA patients," but not in the other categories;
[b] References: [25, 40, 61];
[c] References for JRA patients: [14, 48, 53, 55]; for other subgroups: [14, 53];
[d] References for JRA patients: [19, 35, 37]; for other subgroups: [35, 37]

antibody (ANA) and according to geographic location (US, Scandinavian, Asian, Indian). Additionally, in order to see what the role of referral bias might be, we have presented separately the pooled results after excluding studies from single tertiary referral centers. Not all studies could be used for subgroup analysis or calculation of cumulative incidence rates of specific complications; on each occasion, all the available data were used. Since some series provided data for some subgroup analysis and not others, meaningful multivariate analysis for risk factors such as gender, ANA status and type of disease onset was not possible. 95% confidence intervals (CI) calculated using the exact binomial method are reported throughout our study. Comparisons were tested for statistical significance using the Fisher exact test or Spearman's R correlation coefficient and odds risk ratios were calculated.

Results

Thirty-six studies were identified as potentially relevant [1, 4, 8, 9, 11–16, 19, 23–25, 27, 30, 33–37, 39–41, 43, 47, 48, 51–56, 58, 60, 61]. Twenty-one series of JRA patients were included [1, 8, 9, 11–14, 19, 34, 35, 37, 39–41, 48, 52–55, 61], as well as five series of patients with JRA-associated uveitis [23, 24, 42, 51, 60]. Ten studies were excluded either because of overlap with series published at a later date (three studies) [36, 56, 58], because they used a duration criterion other than the ACR criterion of 6 weeks for the diagnosis of JRA (three studies) [16, 30, 33] or because they included patients that did not have JRA (four studies) [4, 15, 27, 47].

Methodological quality of included studies

The methodological quality of the studies meeting the inclusion criteria was variable. The length of follow-up was not specified in 12 of 25 series; the mean follow-up ranged from 2 to 12.7 years in the remaining 13 series (Tables 2 and 6). With the exception of a single prospective study [37], the remainder were retrospective studies. Only four of the studies were population based [11, 35, 37, 39], while four were multicenter studies [9, 13, 25, 41] including a single nationwide survey [25]. The majority of series came from the USA [1, 8, 9, 11–13, 23, 24, 34, 41, 52, 60], with four series from India [14, 48, 53, 55], three from East Asia [26, 40, 61], three from Scandinavia [19, 35, 37], and one each from Canada, Italy and New Zealand [39, 42, 51]. Sixteen studies provided data on the cumulative incidence of complications in patients with JRA-associated uveitis, while 13 studies provided data on the visual outcome of patients with JRA-associated uveitis (Table 6). With the exception of the series by Foster et al. [23, 24], none of the remaining series specified the diagnostic criteria for diagnosis of complications. Information on sex distribu-

Table 4 Gender differences in the cumulative incidence of uveitis

	All JRA patients[a]		Pauciarticular JRA patients[b]		Polyarticular JRA patients[c]	
	n	Cumulative incidence of uveitis % (95% CI)	n	Cumulative incidence of uveitis % (95% CI)	n	Cumulative incidence of uveitis % (95% CI)
Females	913	10.2 (8.3–12.3)	219	10.5 (6.8–15.3)	61	6.6 (2.0–16.0)
Males	445	6.3 (4.2–9.0)	178	7.9 (4.4–12.8)	22	4.6 (0.1–22.8)
P-value	–	0.019	–	0.39	–	0.73
Odds ratio	–	1.69 (1.09–2.62)	–	1.37 (0.69–2.76)	–	1.47 (0.16–13.9)

[a]References: [1, 8, 11, 13, 35, 39–41]
[b]References: [11, 25, 35, 39, 40]
[c]References: [11, 35, 39]

tion, ANA positivity, age at onset of uveitis and interval to uveitis from diagnosis of JRA was lacking in the majority of the studies. The number of patients in each series ranged from 52 to 760.

Cumulative incidence of JRA-associated uveitis

As seen in Table 3, the cumulative incidence of JRA associated uveitis was 8.3% (95%CI, 7.5–9.1%). The cumulative incidence of uveitis in patients with pauciarticular onset JRA is 12.4% (95%CI, 10.9–13.9%), in patients with polyarticular onset JRA 4.3% (95% CI, 3.3–5.5%) and in patients with systemic onset JRA 1.8% (95% CI, 1.0–3.0%). Excluding series from single tertiary referral centers did not significantly alter the results. Since most cases of uveitis occur within the first 4 years after onset of arthritis [2, 45], we performed an analysis of pooled data after excluding series which specified a mean follow-up time of less than 4 years: the cumulative incidence of JRA-associated uveitis was 11.4% (95% CI, 9.9–13.2), 13.3% (95% CI, 11.0–15.8) for pauciarticular onset JRA patients and 5.1% (95% CI, 3.0–8.0) for polyarticular onset JRA patients.

For studies providing the mean length of follow-up, there was no correlation between mean length of follow-up and cumulative incidence of uveitis (Spearman $R=-0.31$, $P=0.622$). Similarly, there was no correlation between year of publication of a study and the cumulative incidence of uveitis in the total group of JRA patients ($R=0.35$, $P=0.13$) or pauciarticular onset JRA patients ($R=0.17$, $P=0.51$). This was also true considering US-based series alone (to avoid confounding from geographic variation).

Geographic variation in the cumulative incidence of JRA-associated uveitis

As seen in Table 3, the cumulative incidence of uveitis in JRA patients from US-based series was lower than in Scandinavian series ($P<0.0001$) but higher than in series from East Asia ($P<0.0001$) or India ($P<0.0001$). The cumulative incidence of uveitis for pauciarticular onset patients in US series was similar to that of Scandinavian series ($P=0.3965$) but higher than series from East Asia ($P=0.0050$) or India ($P<0.0001$). Finally, polyarticular onset JRA patients from Scandinavian series had the highest incidence of uveitis, followed by patients from the US, India and East Asia ($P=0.0189$, $P<0.0001$, $P=0.0028$). Differences in the cumulative incidence between studies from East Asia and India did not reach statistical significance.

Table 5 Effect of presence of ANA on the cumulative incidence of uveitis

	JRA patients[a]		Pauciarticular JRA patients[b]		Polyarticular JRA patients[c]	
	n	Cumulative incidence of uveitis % (95% CI)	n	Cumulative incidence of uveitis % (95% CI)	n	Cumulative incidence of uveitis % (95% CI)
ANA positive	633	17.7 (14.8–20.9)	412	17.2 (13.7–21.2)	163	8.0 (4.3–13.3)
ANA negative	757	6.3 (4.7–8.3)	373	7.5 (5.1–10.7)	231	4.3 (2.1–7.8)
P-value	–	<0.0001	–	<0.0001	–	0.134
Odds ratio	–	3.18 (2.22–4.54)	–	2.57 (1.62–4.07)	–	1.92 (0.82–4.48)

[a]References: [1, 11, 13, 34, 35, 37, 40, 61]
[b]References: [1, 11, 13, 35, 37, 40, 61]
[c]References: [1, 11, 13, 35, 37, 61]

Table 6 Complications and visual outcome of JRA-associated uveitis

Study	Country	Patient cohort	Mean years of follow-up (range)	JRA uveitis Patients	JRA uveitis Eyes	Cataracts Patients (%)	Cataracts Eyes (%)	Glaucoma Patients (%)	Glaucoma Eyes (%)	Band keratopathy Patients (%)	Band keratopathy Eyes (%)	Adverse visual outcome
[11]	USA	Population based series	12.5 (1–36)	3	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[35]	Finland		n/s	18	36	3 (17)	4 (11)	2 (11)	2 (5.5)	0 (0)	0 (0)	1 (5.5)
[39]	NZ		9.3	1	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[8]	USA	Series from multiple cen-	3.8 (1.4–6.6)	5	10	1 (20)	2 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
[9]	USA	ters	5	60	—	—	—	—	—	—	—	a
[13]	USA		n/s	71	—	10 (14)	—	8 (11)	—	12 (17)	—	8 (11)
[41]	USA		4.6(0.5–23)	10	—	1 (10)	—	2 (20)	—	2 (20)	—	0 (0)
[1]	USA	Tertiary referral series	n/s	5	10	3 (60)	4 (40)	0 (0)	0 (0)	3 (60)	—	0 (0)
[24]	USA		n/s	—	72	—	13 (18)	—	—	—	—	—
[23]	USA		>2 years	69	128	—	—	21 (30)	30 (23)	—	—	—
[34]	USA		4 (0–13.8)	39	78	7 (18)	11 (14)	4 (10)	4 (18)	—	—	b
[40]	Korea		7.0	7	—	—	—	—	—	—	—	2 (28)
[43]	Italy		6.6	42	84	16 (38)d	24 (29)d	13 (31)	19 (23)	10 (24)d	12 (14)d	c
[51]	Canada		6.0 (1–9)	35	—	6 (17)	—	—	—	3 (8.6)	—	d
[54]	USA		5.9	13	—	—	—	—	—	—	—	e
[60]	USA		12.7 (>1)	—	102	—	41 (40)	—	24 (24)	—	26 (25)	—
Pooled data		Cataracts		Patients (n=229)	Eyes (n=400)	20.5% (95% CI: 15.5–26.3)	24.7% (95% CI: 20.6–29.2)					
		Glaucoma		Patients (n=264)	Eyes (n=456)			18.9% (95% CI: 14.4–24.2)	17.3% (95% CI: 14.0–21.1)			
		Band keratopathy		Patients (n=191)	Eyes (n=240)					15.7% (95% CI: 10.9–21.7)	15.8% (95% CI: 11.5–21.1)	
		Adverse visual outcome		Patients (n=120)								9.2% (95% CI: 4.7–15.8)

a Four patients with "some loss of vision in one eye" and eight patients with "some loss of vision in both eyes"

b All eyes except one had visual acuity better than 20/60

c 33% of eyes presented with vision worse than 20/33 and at last follow-up 35% of eyes had vision worse than 20/33

d Specific information not provided but it is mentioned that nine children had less than 20/60 vision in one or both eyes

e Specific information not provided but reported that "none experienced significant visual loss"

Effect of JRA onset type on the cumulative incidence
of uveitis

Considering the series which provide cumulative incidence
for uveitis in both pauci- and polyarticular onset JRA
patients (Table 2), the odds risk ratio (OR) of uveitis in
pauciarticular onset JRA patients compared to polyarticular
onset JRA patients is 3.20 (95% CI, 2.36–4.33).

Effect of gender on the cumulative incidence of uveitis

The cumulative incidence of JRA-associated uveitis in girls
was 10.2% (95% CI, 8.3–12.3%) compared to 6.3% (95%
CI, 4.2–9.0%) in boys (OR=1.70, 95% CI, 1.09–2.62).
Differences in the cumulative incidence of JRA-associated
uveitis between the two genders in pauci- or polyarticular
onset JRA patients were not statistically significant (P=
0.391 and P=0.734, respectively). It should be emphasized
that not all the studies that provided data on cumulative
incidence of JRA-associated uveitis provided data on each
subgroup of patients (Table 4).

Gender differences in the cumulative incidence of JRA-
associated uveitis were not statistically significant when
the data from series from tertiary referral centers were
excluded (P=0.0545). These comparisons did not take into
account ANA status.

Effect of ANA on the cumulative incidence of uveitis

The cumulative incidence of uveitis in ANA positive
patients was 17.7% (95% CI, 14.8–20.9%) compared with
6.3% (95% CI, 4.7–8.3%) of ANA negative patients,
(OR=3.18, 95% CI, 2.22–4.54), as shown in Tables 5 and 6.
In pauciarticular onset patients, the cumulative incidence
of uveitis in ANA positive patients was 17.2% (95%CI
13.7–21.2%) compared with 7.5% (95% CI, 5.1–10.7)
in ANA negative patients (OR=2.57, 95% CI, 1.62–4.07).
There was no statistically significant difference in the
cumulative incidence of uveitis between ANA positive
and ANA negative polyarticular onset patients (OR=1.92,
95%CI, 0.82–4.48). The results were similar considering
data from Scandinavia or North America alone (data not
shown).

Cumulative incidence of adverse visual outcome
and complications of uveitis

The cumulative incidence of adverse outcome was 9.2%
(95% CI: 4.7–15.8). The cumulative incidence of cataract
development was 20.5% (95% CI: 15.5–26.3), of glaucoma
18.9% (95% CI: 14.4–24.2) and of band keratopathy
15.7% (95% CI: 10.9–21.7). The cumulative incidence of
adverse visual outcome and of complications of uveitis was

not statistically different if series from single tertiary
referral centers were excluded or if only series reporting on
US-based patient cohorts were considered. There were no
data on adverse visual outcome or complications of uveitis
in studies from East Asia or India.

Discussion

Our meta-analysis suggests that the cumulative incidence
of JRA-associated uveitis in pauciarticular patients 12.4%
(95% CI: 10.9–13.9) was at the low end of the 10–30% rate
that is commonly quoted in reviews of JRA-associated
uveitis [2, 45]. Similarly the cumulative incidence of JRA-
associated uveitis in polyarticular patients (4.3%, 95% CI
3.3–5.5%) was lower than 7–37% [2]. It may be argued that
this may have been the result of pooling studies with
variable follow-up times and that discussion of "incidence"
without reference to time-at-risk is problematic: since the
vast majority of cases of uveitis occur within the first 4
years after onset of arthritis [2, 45], we analyzed pooled
data exclusively from series with 4 or more years of mean
follow-up, and results were not statistically different.
Finally, in order to exclude referral bias, we analysed
pooled data exclusively from series from population based
studies or studies involving multiple centers: the results
were not statistically different.

It has been suggested that the cumulative incidence of
JRA-associated uveitis has decreased over the years.
Indeed, a study comparing the cumulative incidence of
JRA-associated uveitis between 1989 and 1975 at a major
tertiary referral center in Seattle supported this finding,
even though this study did not attempt to control for
possible changes in referral patterns [54]. Additionally, it
is widely believed that the more prevalent use of
methotrexate for control of active arthritis in JRA has
caused the incidence of JRA-associated uveitis to decline
[1]. We did not find a decrease in the cumulative incidence
of JRA-associated uveitis in studies published more
recently, although some recently published studies cover
such long periods of time so that their results likely include
patients from the era when methotrexate use was not
prevalent.

The cumulative incidence of uveitis was found to vary
depending on the country of origin of the study, being
significantly greater in Scandinavian series, followed by
series from the US, East Asia and finally India. Access to
health care and patterns of over- or under-diagnosis of
JRA or uveitis (ascertainment bias) might in part account
for this finding. Additionally, no study from East Asia or
India specified a length of follow-up; follow-up times in
these studies may have been shorter than in studies from
Scandinavia or the USA. However, genetic differences
(e.g. frequency of HLA haplotypes) or environmental
influences acting by modulating the immune response or
modulating the virulence pattern of a putative causative

agent may also partly account for the geographic variation.

JRA onset type is an established major risk factor for development of JRA-associated uveitis. Pauciarticular onset tripled the risk compared to polyarticular onset. It is noteworthy that in the series included in our meta-analysis there were no patients from Europe or North America with systemic onset JRA who developed JRA-associated uveitis.

The presence of ANA was shown to be a strong risk factor for the development of JRA-associated uveitis, nearly tripling the risk of pauciarticular onset patients (OR 2.57, 95% CI 1.62–4.07). ANA determination in the child diagnosed with JRA is therefore an important consideration for the appropriate risk stratification of that child.

Unexpectedly, female gender alone was only a weak risk factor (OR 1.69, 95% CI 1.09–2.62) for the development of uveitis in JRA patients and did not reach statistical significance when onset-type was considered. While it is possible that female gender may be associated with a higher incidence of pauciarticular disease and not be an independent risk factor for JRA-associated uveitis, it is more likely that the lack of association between female gender and uveitis after considering onset type may result from smaller sample sizes as well as the proportionately larger contribution from the East Asian cohorts to these samples [25, 40]: it is possible that female gender is not a risk factor for the development of uveitis in East Asian patients. The data presented in these series are not sufficient to allow a meaningful multivariate analysis to determine whether female gender is or not an independent risk factor after accounting for onset-type and/or ANA positivity.

A minority of studies provided data for visual outcome. Nonetheless, the adverse visual outcome cumulative incidence of 9.2%, although highly undesirable, is lower than commonly perceived [2]. It should be noted that no study reported on visual field deficits or measures of visual function other than visual acuity. Given a cumulative incidence of JRA-associated uveitis of 8.3%, it follows that the probability of a child with JRA developing an adverse visual outcome is less than 1%. However, it must be emphasized that this is the probability of the patient having vision of less than 20/40 OU and that individual eye visual impairment was not considered. Nevertheless, this is a valid outcome measure, since vision of 20/40 or better is consistent with a relatively good level of visual function.

The glaucoma and cataracts were complications in approximately one-fifth of patients with JRA-associated uveitis. Although definitions for these complications vary between studies and the severity of these complications may vary between patients, this is a useful estimate of the risk of development of either complication that may be quoted to the parents of a patient with JRA-associated uveitis. Since these complications both result from severe uveitis, it may be expected that they may be encountered together more often than by chance; there are insufficient data to support or refute this concept.

Our findings support the overall rationale of the current screening guidelines [2], with a slight modification. Currently, it is recommended that ANA positive pauci- and polyarticular onset JRA patients diagnosed before 7 years of age should undergo ophthalmologic examinations every 3–4 months (high risk) while ANA negative, pauci- or polyarticular onset JRA patients undergo ophthalmologic examinations every 6 months (medium risk)[2]. However, our results suggest that pauciarticular onset, ANA negative patients have the same risk of developing JRA associated uveitis (7.5%, 95%CI, 5.1–10.7%) as polyarticular onset, ANA positive patients (8.0%, 95% CI, 4.3–13.3); therefore, we suggest that consistency of screening recommendations between these two groups be considered.

Integration of immunogenetic data, [17, 28] with clinical and laboratory risk factors for occurrence of JRA-associated uveitis (such as JRA disease onset subtype, female gender, age of onset of arthritis, ANA positivity, serum concentrations of inflammatory markers) into a model that predicts patients who will develop uveitis would be highly desirable. Although prognosticators for adverse visual outcome in JRA-associated uveitis have been identified [16, 62] and a model that predicts JRA-associated uveitis severity has been developed [60], there exists no model that predicts which patients will develop JRA-associated uveitis. Until such a model is available, it is reasonable and advisable to continue to subject children with JRA to frequent ophthalmological examinations for early diagnosis of uveitis, although only a small proportion develop it.

Any analysis of the literature is subject to the limitations of each of the studies under analysis. A large, prospective population-based study of JRA patients would certainly best determine the incidence and outcomes of JRA associated uveitis. However, the relative rarity of the disease and its complications make it impractical, if not impossible to employ this strategy to answer these important questions. It is hoped that this analysis of the current literature provides a guide for physicians as they care for these patients, and discuss possible outcomes with the patients and their parents and caregivers.

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