The frequency and outcome of uveitis in patients with newly diagnosed juvenile idiopathic arthritis in two 4-year cohorts from 1990-1993 and 2000-2003

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Abstract

Objective

To retrospectively compare the frequency and outcome of uveitis between two cohorts of patients with newly-onset juvenile idiopathic arthritis (JIA) separated by a 10-year interval.

Methods

The diagnosis of JIA was made in 239 patients in 1990-1993 and in 240 patients in 2000-2003 by paediatric rheumatologists at the Rheumatism Foundation Hospital, Heinola, Finland. An ophthalmologist examined all the patients regularly and diagnosed uveitis. The demographics of the patients, type of JIA, frequency, medical treatment and outcome of uveitis were documented.

Results

The main outcome measures were the frequency and outcome of uveitis, the number of complications and the best corrected visual acuity (BCVA), need of corticosteroids and other immunosuppressive treatment.

The frequency of uveitis was higher (25% vs. 18%) in the earlier cohort. The visual outcome was ≥0.5 in all JIA-uveitis patients except one in the earlier cohort. Complications were fewer (21% vs. 35%) and uveitis was milder according to the Standardisation of Uveitis Nomenclature (SUN) criteria in the later cohort. Remission of uveitis (33% vs. 42%) and arthritis (20% vs. 23%) in JIA-uveitis patients was similar in both cohorts after a follow-up of 6.6 and 5.9 years, respectively. Systemic corticosteroids were more commonly used (25% vs. 7%) in JIA-uveitis patients of the earlier cohort but the use of methotrexate was equal in both cohorts (65% vs. 67%).

Conclusion

In this study with early and aggressive treatment and close monitoring the outcome of JIA-uveitis patients was favourable and visual loss was avoided in most cases.

Key words

outcome, frequency, uveitis, juvenile idiopathic arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) is an orphan disease, but it is the most common underlying disease behind childhood uveitis. JIA-associated uveitis affects about 20% of patients and is almost always asymptomatic, bilateral and chronic. Young children with early-onset oligoarthritis and antinuclear antibodies have the highest risk of uveitis. In earlier studies visual impairment from JIA-uveitis was markedly more common (up to 30%) than in recent reports and the frequency of complications was high (cataract, glaucoma, posterior synecchiae, band keratopathy and cystoid macular oedema) already at diagnosis of uveitis (1-5). Meticulous screening, early diagnosis and prompt treatment of uveitis are very important for every child with newly diagnosed idiopathic arthritis to ensure a favourable long-term prognosis. In 90% of patients with JIA, uveitis is detected during the first 4 years after the diagnosis of JIA (6).

The treatment of JIA has changed markedly during the last decades. In the early 90s, methotrexate (MTX) was increasingly introduced and a combination of 2–3 anti-rheumatic drugs was often used in the management of JIA. During the last decade biologic drugs have initiated a new revolution in the treatment strategy of rheumatic diseases (7-9) The treatment of JIA-associated uveitis follows the same lines (10).

In this study we compare two 4-year cohorts of patients with newly diagnosed idiopathic arthritis before the age of 16 years from 1990–1993 and 2000–2003 and analyse the differences in the frequency and outcome of JIA-associated uveitis and the impact of the new changed treatment strategy and differences in medication for uveitis.

Patients and methods

All consecutive patients with a new diagnosis of JIA made at the Rheumatism Foundation Hospital, Heinola, Finland, were collected from two 4-year periods (1990–1993 and 2000–2003) separated by a 10-year interval. All the patients were Finnish Caucasian children. Paediatric rheumatologists examined all patients and made the diagnosis of JIA (according to the criteria of ILAR, International League of Associations for Rheumatology) (11) The patients were as a routine referred regularly after the diagnosis of JIA to an ophthalmologic evaluation every 3 to 6 months until the age of 12 to exclude or to detect uveitis. A careful biomicroscopic examination for detection of uveitis and its possible complications was done, BCVA was measured and treatment of uveitis was initiated when needed. Uveitis was graded retrospectively according to the SUN criteria (12).

The demographic data of the patients were collected; the incidence and outcome of uveitis, the frequency of complications, the number of remissions and final BCVA were recorded.

In this study the remission of arthritis was recorded when there were no symptoms or signs of arthritis without any medication, and remission of uveitis was recorded when no signs or symptoms of uveitis were seen in the absence of any treatment.

Paediatric rheumatologists planned the treatment strategy of arthritis, but the treatment of arthritis and associated uveitis was designed in close cooperation between the paediatric rheumatologists and the ophthalmologists. The medication of the patients was recorded as exactly as possible.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics (Version 20.0; Inc., Chicago, IL.). Chi-squared tests, *t*-tests and analysis of variance (ANOVA) and their 95% confidence intervals (CI) were applied to evaluate statistical differences in distributions between the two cohorts of JIA uveitis patients and the differences within the two cohorts between patients with and without uveitis. Statistically significance threshold was set at $p \leq 0.05$, two-tailed.

Results

The demographic data of the study cohorts are shown in Table I. The sizes of the two cohorts were very similar; 239 and 240 JIA patients with a new diagnosis of JIA. Oligoarthritis was more common (57% *vs*. 30%) in the earlier

Table I. Demographics of the JIA patients of the two cohorts 1990-1993 and 2000-2003 separated by 10 years.

	Patients with uveitis 1990-1993	Patients with uveitis 2000-2003	*p*-value [95%CI]	Patients without uveitis 1990-1993	Patients without uveitis 2000-2003	*p*-value [95%CI]
Number of patients (%)	60 (25)	43 (18)	0.124	179 (75)	197 (82)	0.506
Gender, boys (%)	20 (33)	20 (47)	0.176	59 (33)	72 (37)	0.466
Age at onset of JIA, mean (SD)	4.9 (3.7)	5.5 (4.2)	0.447 [-2.14 - 0.95]	7.1 (4.3)	7.3 (4.4)	0.634 [-1.09 - 0.67]
Age at onset of uveitis, mean (SD)	5.9 (3.7)	5.4 (3.2)	0.494 [-0.90 - 1.86]			
Follow-up, mean (SD)	6.6 (1.3)	5.9 (2.0)	0.042 [0.03 - 1.42]	4.7 (2.2)	5.6 (2.1)	<0.001 [-1.29 - -0.40]
Type of arthritis at the end of the study, n (%)						
Oligoarthritis*	37 (62)	19 (44)	0.079	100 (56)	53 (27)	<0.001
Seronegative polyarthritis	22 (37)	21 (49)	0.217	52 (29)	117 (59)	<0.001
Seropositive polyarthritis	1 (2)	0 (0)	0.395	9 (5)	8 (4)	0.652
Systemic onset arthritis	0 (0)	1 (2)	0.235	12 (7)	5 (3)	0.052
Others**	0 (0)	2 (5)	0.092	6 (3)	14 (7)	0.105
ANA positivity, missing data 5%	44 (73)	28 (70)	0.716	71 (40)	89 (50)	0.044
HLA B27 positivity, missing data 17%	12 (27)	11 (36)	0.411	41 (30)	45 (35)	0.408
Rheumatoid factor, missing data 1%	3 (5)	0 (0)	0.137	12 (7)	12 (6)	0.849

*Extended oligoarthritis is including; **Others including: psoriatic arthritis, IBD-arthritis, enthesitis related, spondyloarthropathy, undifferentiated.

cohort and the most common type of arthritis in the later cohort was polyarthritis (35% *vs*. 61%) but the difference was not significant. There were also no statistically significant differences in the antinuclear antibody (48% *vs*. 54%) and HLA B27 (22% *vs*. 23%) positivity between the cohorts, but all patients were not tested.

Uveitis was more frequent in the earlier (25%) than in the later cohort (18%, p=0.124). Uveitis was diagnosed at first ophthalmologic examination within 3 months after the diagnosis of JIA in 45% (27pts) of 60 uveitis patients (5 patients had complications) in the earlier cohort, and in 56% (24 pts) of 43 patients (4 had complications) in the later cohort. The final BCVA was ≥0.5 in all but one patient (legally blind) in the earlier cohort and in every patient in the later cohort (Table II). The overall frequency of complications was higher in the earlier cohort, 35% (21 patients, p=0.121), compared to the later cohort 21% (9 patients); band keratopathy and synecchiae were rare. The activity of uveitis according to the SUN criteria was milder in the later cohort as shown in Table II, but the difference was not significant. At last visit the anterior cell grade less than 1+ was seen in 67% in the earlier and in 77% in the later cohort.

Table II. The outcome of uveitis in the two study cohorts.

	Patients with uveitis in 1990-1993 (n=60)	Patients with uveitis in 2000-2003 (n=43)	*p*-value
Duration of uveitis, years, [mean (SD)]	5.5 (2.0)	4.9 (3.8)	0.389
Follow up, [mean (SD)]	6.6 (1.3)	5.9 (2.0)	0.042
Uveitis is going on, pts (%)	40 (67)	25 (58)	0.376
Visual acuit, y ≥0.5, n (%)	59 (98)	43 (100)	0.953
Visual acuity, <0.1 n (%)	1 (2)	0 (0)	0.399
Number of patients with 1 or more complications, n (%)	21 (35)	9 (21)	0.121
Cataract, n (%)	21 (35)	8 (19)	0.068
Glaucoma, n (%)	9 (15)	5 (12)	0.622
Bandkeratopathy, n (%)	4 (7)	0 (0)	0.095
CME, n (%)	2 (3)	1 (2)	0.771
AC cells according to the SUN criteria, n (%)*			
0	20 (33)	18 (42)	0.376
0.5+	22 (37)	15 (35)	0.852
1+	14 (23)	6 (14)	0.235
2+	3 (5)	2 (5)	0.935
3+	1 (2)	2 (5)	0.374
Remission of arthritis, n (%)	12 (20)	10 (23)	0.691
Remission of uveitis, n (%)	20 (33)	18 (42)	0.376

*AC cells were measured at last visit.

The mean follow-up of uveitis patients was among 1990 cohort 6.6 years (range, 4–9 years) and among 2000 cohort 5.9 years (range, 0–9 years) (p=0.042, 95% Confidence Interval [CI] 0.03, 1.42), respectively. Among the patients with uveitis, systemic corticosteroid treatment was started in 62% in the earlier and in 42% in the later cohort and 25% and 7% of the patients were on corticosteroids at the end of the follow up, respectively. Accordingly, MTX was initiated in 70% and 91% of uveitis patients and 65% and 67% of patients were on MTX at the end of the follow-up (Table III). Among the JIA-uveitis patients the interval from diagnosis of JIA to the initiation of MTX treatment was mean 3.3 years in the earlier cohort and markedly shorter, mean 0.35 years, in the later cohort. The same interval in JIA patients without uveitis was 2.3 years in the earlier and 0.61 years in the later cohort. In the earlier cohort hydroxyl chloroquine followed by intramuscular or oral gold were started during the first

months/years after diagnosis of JIA, but in the later cohort the first line drug was frequently MTX.

The frequency of remission of uveitis in the two cohorts was 33% and 42%, and remission of arthritis, 20% and 23%, respectively. Biologic drugs were not in use in the earlier cohort but adalimumab had favourable effect in 4 of 5 patients and infliximab in 3 of 7 patients with uveitis in the later cohort.

Among the patients without uveitis the follow-up was 4.7 years (range, 0–9 years) in the earlier and 5.6 years (range, 1–9 years) in the later cohort ($p<0.001$, 95% CI -1.29, -0.40). The remission rate of JIA among these children was 48% and 29%, respectively. The need of systemic corticosteroids and MTX was 34% and 45% in the earlier compared to 45% and 84% in the later cohort at the beginning of JIA, and 18% and 36% compared to 15% and 47% at the end of the study, respectively.

Synthetic DMARDs (sDMARDs) including methotrexate, sulfasalazine or biologics were started within median 0.61 year after diagnosis in patients who were diagnosed JIA without uveitis in period 2000 to 2003. The start of immunosuppressive drugs was even more earlier, median 0.35 years, in patient group which were diagnosed to have JIA and uveitis at the same year period. The more aggressive sDMARD start can be explained by higher ANA positivity. However the use of sDMARDS in the beginning of 2000 was not as rapid as in the latest reports (13).

Table III. The different use of drugs for patients with uveitis in the two study cohorts.

Drug	Patients with uveitis 1990-1993 n=60	Patients with uveitis 2000-2003 n=43	*p*-value	Patients with uveitis 1990-1993 n=60	Patients with uveitis 2000-2003 n=43	*p*-value
	Patients who have used the drug n (%)	Patients who have used the drug n (%)		Patients who still use the drug n (%)	Patients who still use the drug n (%)	
Prednisolone	37 (62)	18 (42)	0.047	15 (25)	3 (7)	0.018
Hydroxychloroquine	55 (92)	32 (74)	0.017	29 (48)	9 (21)	0.004
Methotrexate	42 (70)	39 (91)	0.011	39 (65)	29 (67)	0.796
Cyclosporine A	16 (27)	8 (19)	0.340	8 (13)	3 (7)	0.303
Auranofin	44 (73)	2 (5)	<0.001	11 (18)	0 (0)	0.003
Suphasalazine	19 (32)	5 (12)	0.018	8 (13)	0 (0)	0.013
Azathioprine	8 (13)	1 (2)	0.051	6 (10)	0 (0)	0.033

Discussion

The prevalence of uveitis may reach 20% in children with oligoarticular JIA. JIA associated uveitis is an important cause of childhood uveitis. Because it has typically an insidious onset and chronic course, it carries a high risk for ocular complications and visual loss. According to an earlier study by Kanski the prognosis of JIA uveitis was poor in half of the patients, moderate in 25% and good only in 25% of patients (1). In a recent multicentre study of 327 patients from USA ocular complications and visual loss were common: at presentation 40.3% of 596 affected eyes had a VA of ≤0.5 and 60.2% had at least 1 complication (2). They concluded that increasing uveitis activity was associated with increased risk of visual loss and 1+ or greater grade of anterior chamber cells is a risk for VA loss.

In this study we found that the outcome of JIA-associated uveitis is getting better, when the JIA and associated uveitis are treated actively from the very beginning. With regular and meticulous screening of all JIA patients from the very beginning of arthritis we could detect all the cases with insidious uveitis. This is in accordance with treat-to-target approach in the management of JIA suggested by Consolaro *et al*. (14). Although 8.3% of uveitis patients in the earlier and 9.3% in the later cohort presented with complications, the VA was better than 0.5 in all but 1 patient in the earlier and in all in the later cohort at the end of the study. It is well known that uveitis is found in 75% of JIA-uveitis patients during the first year and in 90% during the first four years after the diagnosis of JIA, but in some cases uveitis may occur in later years. Also, the rate of complications may increase in longer follow-up. At last visit the anterior cell grade less than 1+ was seen in 67% in the earlier and in 77% in the later cohort. In our study the earlier treatment with MTX alone or in combination with other antirheumatic drugs decreased the need for systemic corticosteroids in the later cohort (and accordingly lowered the risk of cataract) as shown in Table III. This was also shown by Pohjankoski *et al*. (8). MTX is a first line medication in JIA patients, especially in those with uveitis. Leflunomide and azathioprine may substitute MTX if it is not effective or if it causes side effects. Cyclosporine is mainly used in combination with other drugs (9-12). The new biologic drugs are increasingly part of the second line of treatment in resistant cases of arthritis and uveitis. The biologic drugs were not available in the follow-up of the earlier cohort. They just came available during the follow-up of the later cohort. Thus, they were rare during the first study years, but etanercept, infliximab and adalimumab were the most common biologics initiated later. With the last two named we got promising results in a few cases with chronic uveitis. In addition, the biologics in addition to other immunosuppressive drugs may decrease the need of corticosteroids. The increasing use of MTX has decreased the use of earlier antirheumatic drugs as sulfasalazine, intramuscular or oral gold and azathioprine, cyclosporine as well as hydroxyl chloroquine (9-12).

Perhaps some cases of uveitis were prevented with early MTX treatment in the later cohort. One male patient developed his first severe uveitis a few years after remission of oligoarthritis and cessation of MTX.

The remission rate without any medication for uveitis or arthritis in JIA-uveitis patients at last visit was very similar (33% *vs*. 35% and 20% *vs*. 23%) in both cohorts, respectively. Oligoarthritis was more common in the earlier cohort and the most common type of arthritis in

the later cohort was polyarthritis but the difference was not significant. The occurrence of uveitis was more frequent in the earlier cohort, but the shift in subtype of arthritis did not influence to the rate of uveitis. In the later cohort the number of patients with chronic polyarthritis was larger and this can partly explain the low incidence of remissions. After the millennium patients with mild oligoarthritis were obviously managed in primary care or with central hospitals and those with uveitis or chronic polyarthritis were more often sent to the tertiary centre at Heinola.

In earlier studies, the rate of blindness was high (even 30%) (1-3). In the majority of patients, uveitis is found during the first 4 years after the diagnosis of JIA (4). JIA-associated uveitis continues into adulthood in about half of the patients and the rate of complications increases with time (6, 12). Early diagnosis and aggressive treatment of uveitis by close screening of the eyes of all patients after the diagnosis of JIA is critical for long-term prognosis. According to our data, this strategy decreases the complications of JIA-uveitis. The patients of this study were examined within a few weeks from the onset of arthritis. Maybe for this reason the rate of complications was very low at the onset of uveitis compared to earlier series. Cataract was more common in the earlier cohort, band keratopathy was rare, but glaucoma and cystoid macular oedema developed quite evenly in both groups. The overall rate of complications was higher in the first group (35% *vs*. 21%) and the outcome of uveitis was better according to SUN criteria in the later cohort, but the results did not reach significance (Table II).

This study was retrospective and the follow-up in a few cases was quite short. However, we were able to show that with effective and early immunosuppressive treatment the visual prognosis is better and the need of systemic corticosteroid treatment is decreasing.

Conclusion

The outcome of JIA associated chronic uveitis seems to be improving because of tight control of the patients and earlier and aggressive treatment of arthritis and uveitis in close cooperation between ophthalmologists and paediatric rheumatologists. The effect of biologic drugs seems promising, but there is still a need for prospective comparative studies.

Aknowlegdements

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