Risk Factors for the Development of Cataract Requiring Surgery in Uveitis Associated with Juvenile Idiopathic Arthritis

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• PURPOSE: To identify the possible risk factors for the development of cataract requiring surgery in children with juvenile idiopathic arthritis (JIA)-associated uveitis.

• DESIGN: Retrospective cohort study.

• METHODS: Data of 53 children with JIA-associated uveitis, of whom 27 had undergone cataract extraction (CE), were obtained. The main outcome measure, the interval between the onset of uveitis and the first CE (U–CE interval), was examined in relation to clinical and ophthalmologic characteristics and treatment strategies before CE.

• RESULTS: A shorter U–CE interval was found for children with posterior synechia vs those without posterior synechia (hazard ratio [HR], 3.57; 95% confidence interval [CI], 1.33 to 10.00). No significant difference was found for children in whom the uveitis was the first manifestation of JIA vs those in whom arthritis was the first manifestation of JIA (HR, 1.59; 95% CI, 0.63 to 4.00) and children treated with periocular corticosteroid injections vs those not treated with periocular corticosteroid injections (HR, 3.23; 95% CI, 0.95 to 11.11). Children treated with methotrexate (MTX) had a longer U–CE interval than children not treated with MTX (HR, 0.29; 95% CI, 0.10 to 0.87).

• CONCLUSIONS: The risk factor for development of early cataract requiring surgery in children with JIA-associated uveitis is the presence of posterior synechia at the time of diagnosis of uveitis. However, early treatment with MTX is associated with a mean delay in the development of cataract requiring surgery of 3.5 years. (Am J Ophthalmol 2007;144:574–579. © 2007 by Elsevier Inc. All rights reserved.)

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CATARACT REPRESENTS A MAJOR COMPLICATION of uveitis in childhood. It occurs in approximately 35% (range, 20% to 70%) of the cases of juvenile idiopathic arthritis (JIA)-associated uveitis.[1] Cataract can be caused by systemic and local corticosteroid treatment and the intraocular inflammation itself.[2] The risk of cataract formation in JIA-associated uveitis increases when posterior synechia are present at the initial examination and with treatment with a high dose of systemic corticosteroids.[3] Previously, the visual outcome of cataract surgery in JIA-associated uveitis was poor. Since new surgical techniques have been recommended, the results of cataract extraction (CE) have improved, but surgery in uveitic eyes of children still remains challenging.[4]

The aim of our study was to evaluate which factors accelerate the development of cataract requiring surgery in JIA-associated uveitis. Therefore, clinical and ophthalmologic characteristics and the treatment strategies in children with JIA-associated uveitis were investigated in relation to the interval between the diagnosis of uveitis and the first cataract extraction (U–CE interval).

METHODS

WE REVIEWED THE MEDICAL RECORDS OF 53 CHILDREN with JIA-associated uveitis (n = 51) or antinuclear antibody (ANA)-positive uveitis without arthritis (n = 2) diagnosed before the age of 16 years. These children represent all children with JIA-associated uveitis identified in a complete database search of the FC Donders Institute of Ophthalmology, University Medical Center, Utrecht, The Netherlands, from January 1990 through June 2006 (53 of 240 children with uveitis). Our center combines a secondary and a tertiary referral function. Children were referred by the ophthalmologists of secondary referral hospitals or by the pediatric rheumatologists of our medical center. The pediatric rheumatologists referred all children with JIA for uveitis screening according to the criteria of the American Academy of Pediatrics in cases of JIA.[5] The parents of the children gave permission for all the treatment.

In this study, we investigated the clinical data of the first eye that underwent cataract surgery per patient. Cataract

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TABLE 1. The First Manifestation of Juvenile Idiopathic Arthritis, the Presence of Posterior Synechia, and the Treatment with Methotrexate and Periocular Corticosteroid Injection(s) in Children with Uveitis Associated with Juvenile Idiopathic Arthritis in Relation to Clinical Characteristics and Treatment Strategies

	Children with Uveitis Associated with JIA (n = 53)											
	First Manifestation of JIA (n = 53)			Posterior Synechia at the Time of Diagnosis of Uveitis (n = 48*)			Treatment with MTX (n = 42†)			Treatment with Periocular Corticosteroid Injection(s) (n = 49‡)		
Clinical Characteristics	Uveitis (n = 12)	Arthritis (n = 41)	*P* value	Yes (n = 15)	No (n = 33)	*P* value	During the First Year after the Diagnosis of Uveitis (n = 17)	Never Treated with MTX (n = 25)	*P* value	During the First Year after the Diagnosis of Uveitis (n = 7)	Never (n = 42)	*P* value
Mean age (yrs) at diagnosis of uveitis (median)	4.7 (4.3)	5.6 (4.8)	.750	5.3 (4.5)	5.5 (5.0)	.956	6.3 (3.4)	5.3 (4.8)	.431	5.0 (4.1)	5.7 (4.9)	.547
Female-to-male ratio	5:7	30:11	.080	8:7	23:10	.276	12:5	16:9	.747	3:4	29:13	.217
Uveitis as the initial manifestation of JIA	N.A.	N.A.	N.A.	7/15	4/33	.022	0/17	10/25	.003	3/7	9/42	.340
ANA positive§	10/12	35/40	.656	12/15	30/33	.360	15/17	22/24	1.000	7/7	34/41	.573
HLA-B27 positive§	1/8	2/11	1.000	0/8	3/9	.206	1/3	0/10	.231	0/1	3/18	1.000
Presence of posterior synechia at time of diagnosis of uveitis‖	7/11	8/37	.022	N.A.	N.A.	N.A.	4/17	9/21	.207	5/6	10/38	.013
Lens opacity at time of diagnosis of uveitis‖	1/9	2/36	.497	1/5	2/36	.330	1/17	2/18	1.000	1/5	2/36	.330
Treatment with MTX during the first year after the diagnosis of uveitis	0/12	17/41	.005	4/15	13/33	.387	N.A.	N.A.	N.A.	2/7	13/42	1.000
Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis	3/12	4/41	.183	5/15	1/33	.008	2/17	5/25	.681	N.A.	N.A.	N.A.
Treatment with systemic corticosteroids during the first year after the diagnosis of uveitis	0/12	1/41	1.000	1/15	0/33	.313	1/17	0/25	.405	1/7	0/42	.143
Glaucoma surgery before CS or the end of follow-up	1/12	8/41	.665	1/15	8/33	.239	3/17	1/25	.286	1/7	5/42	1.000

ANA = antinuclear antibody; CS = cataract surgery; HLA = human leukocyte antigen; JIA = juvenile idiopathic arthritis; MTX = methotrexate; N.A. = not applicable.

*For five patients, no information about posterior synechia at time of diagnosis of uveitis was available.

†Eleven patients were treated with methotrexate more than one year after the onset of uveitis.

‡Four patients were treated with periocular corticosteroid injection(s) more than one year after the onset of uveitis.

§The ANA and HLA-B27 status were not available for all children.

‖Data about posterior synechia and lens opacity at diagnosis of uveitis was not available for all children.

TABLE 2. Hazard Ratios (Crude and Adjusted) for Cataract Requiring Surgery in Children with Uveitis Associated with Juvenile Idiopathic Arthritis

Variable	Crude HR (95% CI)	Adjustment for	Adjusted HR (95% CI)
Uveitis as the initial manifestation of juvenile idiopathic arthritis (uveitis vs arthritis)	2.44 (1.09 to 5.26)	The presence of posterior synechia at time of diagnosis of uveitis	1.59 (0.63 to 4.00)
Gender (boys vs girls)	1.64 (0.71 to 3.85)		
ANA status (positive vs negative)	0.88 (0.30 to 2.63)		
Posterior synechia at time of diagnosis of uveitis (yes vs no)	4.55 (1.82 to 11.11)	Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis and the course of juvenile idiopathic arthritis	3.57 (1.33 to 10.00)
Systemic treatment with methotrexate during the first year after the diagnosis of uveitis (yes vs never)	0.29 (0.10 to 0.87)		
Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis (yes vs never)	5.26 (1.89 to 14.29)	The presence of posterior synechia at time of diagnosis of uveitis	3.23 (0.95 to 11.11)

ANA = antinuclear antibody; CI = confidence interval; HR = hazard ratio.
The HR was defined to be significant if one did not fall into the 95% confidence interval.

surgery to the second eye was not included in this study because possible personal predispositions may interfere with the results. If no CE was performed before the end of follow-up, the data of the first affected eye was included. We recorded the following clinical and ophthalmologic data for each patient: gender, age at diagnosis of uveitis and arthritis, the course of JIA (arthritis or uveitis as the first manifestation of JIA), ANA status, adherent posterior synechia and lens opacity at the time of the diagnosis of uveitis, age at first cataract surgery, all intraocular surgeries before CE, and age at last visit to our clinic. Furthermore, we noted all treatment in the first year after the diagnosis of uveitis and before CE or final visit and paid special interest to treatment with methotrexate (MTX), systemic corticosteroids, and periocular corticosteroids. We compared children with the above-mentioned treatment strategies during the first year after the onset of uveitis with children who had never been treated with those drugs. Treatment during the first year was chosen because after more than one year, cataract formation might have developed as a result of other factors. The treatment with corticosteroid drops was not specifically investigated because this treatment method was used in all children.

All intraocular surgeries before CE (n = 9) were registered, and all were found to be glaucoma related (trabeculectomy with or without mitomycin C). Cataract surgery was performed if the visual acuity was 20/63 (Snellen) or less. The U–CE interval in the first operated eye was taken as the outcome parameter time until development of cataract requiring surgery. All patients who underwent CE were seen for follow-up. In this study, the follow-up period was defined as the time period between the diagnosis of uveitis and the last ocular examination or CE. The mean follow-up was 3.4 years (range, 0.2 to 14.1 years). Uveitis was classified and categorized according to the criteria of the Standardization of Uveitis Nomenclature Working Group.[6] The diagnosis of JIA was made according to the criteria from the International League against Rheumatism.[7,8] In cases of presumed JIA, the diagnosis was confirmed by a pediatric rheumatologist.

Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS, Inc, Chicago, Illinois, USA). The interquartile range (IQR) was used to show the range between the first and third quartile. The Chi-square test or the Fisher exact test were used to compare categorical data. The independent samples *t* test was used to compare the means of two groups. The mean U–CE interval was calculated with the Kaplan-Meier survival analysis, which corrects for patients who did not undergo CE before the end of follow-up. The Kaplan-Meier survival analyses were quantified using multivariate Cox proportional hazard analysis (i.e., time-to-event analysis) in which we submitted all variables with a $P < .05$ in univariate analysis.[9] The hazard ratio (HR) was defined to be significant if one did not fall into the 95% confidence interval.

RESULTS

• **GENERAL CHARACTERISTICS:** Of all the children investigated in this study, 27 of 53 (51%) underwent CE before the end of follow-up. The mean follow-up of children with and without CE was 3.8 years (IQR, 1.2 to 5.0 years; n = 27) and 3.1 years (IQR, 1.0 to 4.1 years; n = 26), respectively ($P = .593$). The mean age at onset of uveitis of children with and without cataract surgery was 4.6 years (IQR, 3.4 to 5.1 years) and 6.2 years (IQR, 3.2 to 8.5 years), respectively ($P = .088$). The uveitis was chronic

and bilateral in all cases, except for two girls who had chronic unilateral uveitis. Data concerning the first manifestation of JIA, the presence of posterior synechia, and the treatment with MTX and periocular corticosteroid injection(s) in relation to clinical characteristics and treatment strategies are shown in Table 1.

• **CLINICAL CHARACTERISTICS IN RELATION TO CATARACT REQUIRING SURGERY:** Children in whom the diagnosis of uveitis was the initial manifestation of JIA (CE, 11/12 [92%]) had a significantly shorter mean U–CE interval than children in whom arthritis preceded uveitis (3.5 years vs CE, 16/41 [39%]; 6.6 years, respectively; Table 2). In the group in which uveitis was the first manifestation of JIA, there were no children treated with MTX in the first year after the diagnosis of uveitis (Table 1). Therefore, adjustment was performed only for the presence of posterior synechia at the time of diagnosis of uveitis. After adjustment, the difference between arthritis and uveitis as the initial manifestation of JIA did not reach significance (Table 2). If we limit our data to only those patients who had arthritis as the initial manifestation of JIA (n = 41), no statistically significant difference was found for the U–CE interval between children treated with MTX during the first year after the diagnosis of uveitis (n = 17) and children never treated with MTX (n = 15; HR, 0.46; 95% confidence interval [CI], 0.13 to 1.61).

In addition to the course of JIA, we also examined the gender and ANA status of the patients. No statistically significant difference was found for the mean U–CE interval between boys (CE, 11/18 [61%]) and girls (CE, 16/35 [46%]; 4.9 and 5.8 years, respectively; HR, 0.61; 95% CI, 0.26 to 1.41), nor between ANA-positive children (CE, 22/45 [49%]) and ANA-negative children (CE, 4/7 [57%]; 6.2 and 5.9 years, respectively; HR, 1.13; 95% CI, 0.38 to 3.34; Table 2). In one additional child with cataract, the ANA status was unknown.

• **OPHTHALMOLOGIC CHARACTERISTICS IN RELATION TO CATARACT REQUIRING SURGERY:** The presence of adherent posterior synechia at the time of diagnosis of uveitis (CE, 12/15 [80%]) resulted in a significantly shorter mean U–CE interval than when no posterior synechia were present (CE, 10/33 [30%]; 3.0 vs 8.5 years, respectively; Table 2). After adjustment for treatment with periocular corticosteroid injections in the first year after the diagnosis of uveitis and for the course of uveitis, the difference between the two groups remained significant (Tables 1 and 2). In five children, no information about posterior synechia at time of diagnosis of uveitis was available.

Three children were observed with lens opacity at the time of diagnosis of uveitis. Because of this small number, the relation between lens opacity and the development of cataract requiring surgery was not evaluated.

Children with CE who previously had undergone glaucoma surgery (n = 7) and children without previous glaucoma surgery (n = 20) had a mean U–CE interval of 5.4 and 3.2 years, respectively. The mean period between the diagnosis of uveitis and glaucoma surgery was 4.2 years, and the mean period between glaucoma surgery and CE was 0.8 years. Between these two groups, no significant differences were found concerning treatment in the first year after the diagnosis of uveitis with MTX and periocular corticosteroid injections (P = 1.000 and P = 1.000, respectively).

• **SYSTEMIC TREATMENT WITH MTX:** Children who started MTX treatment during the first year after the diagnosis of uveitis (CE, 5/17 [29%]) had a significantly longer mean U–CE interval than children who were never treated with MTX (CE, 16/25 [64%]; 7.0 vs 3.5 years, respectively; Table 2). In 11 patients, MTX was started more than one year after the onset of uveitis. The indication for starting MTX treatment was uveitis not responding to topical corticosteroid treatment in five children and arthritis in 12 children. In the group treated with MTX during the first year after the diagnosis of uveitis, significantly fewer children had uveitis as the initial manifestation of JIA than children never treated with MTX (P = .003; Table 1). Adjustment could not be performed for the course of uveitis, because there were no children with uveitis as the initial manifestation of JIA in the MTX-treated group. If we limited our data to only those patients who were never treated with MTX (n = 25), then children with uveitis as the initial manifestation of JIA (CE, 9/10 [90%] after 1.8 years) had a significantly shorter U–CE interval than children who had arthritis as the first manifestation (CE, 7/15 [47%] after 5.1 years) with an HR of 3.13 (95% CI, 1.08 to 9.09).

• **SYSTEMIC TREATMENT WITH CORTICOSTEROIDS:** The relation between systemic corticosteroid treatment and the development of cataract could not be evaluated because there was only one child who had started systemic corticosteroid treatment during the first year after the diagnosis of uveitis.

• **TREATMENT WITH PERIOCULAR CORTICOSTEROID INJECTIONS:** Seven children were treated with periocular corticosteroid injection(s) in the first year after the diagnosis of uveitis. Of these, five children received one injection (including one child not operated on for cataract) and one child received five injections, and for one child, the number of injections in the first year after the diagnosis of uveitis was unclear. These children (CE, 6/7 [86%]) had a significantly shorter U–CE interval than children never treated with periocular corticosteroid injections (CE, 17/42 [40%]; 1.8 vs 7.1 years, respectively; Table 2). Adjusting for the presence of posterior synechia at the time of diagnosis of uveitis did not reach signifi-

cance, but there was still a trend toward earlier cataract formation in children treated with corticosteroid injections (Tables 1 and 2). Four patients were treated with periocular corticosteroid injection(s) more than one year after the onset of uveitis.

DISCUSSION

THIS STUDY DEMONSTRATES THAT THE PRESENCE OF ADherent posterior synechia at the time of diagnosis of uveitis is strongly associated with the early development of cataract requiring surgery in JIA-associated uveitis and that treatment with MTX in the first year after the diagnosis of uveitis is associated with a delay in cataract surgery. Previous studies have demonstrated that the presence of posterior synechia at the time of diagnosis of uveitis is associated with a poor visual prognosis in JIA-associated uveitis.[3] Because of the association with poor visual outcome, detection of uveitis before the formation of posterior synechia development is recommended. Therefore, screening of uveitis should occur shortly after the onset of arthritis. Chia and associates have advocated for more intensive screening for uveitis in the first year after the diagnosis of JIA in the hope of reducing the rate of complications.[10] In concordance with Chia and associates, we believe that more intensive screening in the early phase of JIA may result in less frequent development of posterior synechia and therefore less early development of cataract. When uveitis is diagnosed, prompt, careful follow-up should ensue, especially in cases where posterior synechia already are present. However, in children in whom uveitis precedes arthritis, early detection of uveitis is not possible because these children have the intraocular inflammation without notice. Furthermore, one can speculate that the presence of posterior synechia may be an indication for early treatment with MTX because this drug was associated with a delay proceeding to cataract surgery. In this study, the presence of posterior synechia was equal in both groups treated with MTX in the first year and in the group never treated with MTX.

In addition to the presence of posterior synechia, treatment with periocular corticosteroid injections in the first year after the diagnosis of uveitis showed a trend, although not a significant one, toward a more rapid cataract requiring surgery development. In our series, we do not know the duration of uveitis before the diagnosis. Therefore, we cannot determine whether this is of influence on the early development of cataract requiring surgery. Whether the differences found for children with posterior synechia and children treated with periocular corticosteroid injections were caused by a more intense uveitis or whether this difference is removed after adjustment for the unknown duration of uveitis before diagnosis is unclear.

We could not investigate the effect of treatment with systemic corticosteroids in our series because there was only one child who had received this treatment in the first year. However, literature reports that systemic corticosteroids enhance cataract formation.[3]

The only modifiable factor that may be associated with a delay in the development of cataract requiring surgery was early treatment with MTX. If MTX treatment was started during the first year after the diagnosis of uveitis, the development of cataract was not accelerated, but rather was postponed by a mean of 3.5 years. Because cataract development in JIA-associated uveitis is caused by various factors, it is difficult to determine the specific importance of a single factor. Unfortunately, adjustment for the course of uveitis (first manifestation of JIA) was not possible, because there were no children with uveitis as the initial manifestation of JIA in the group treated with MTX. Referral bias cannot be excluded because our uveitis clinic is a combined secondary and tertiary center. However, patients with uveitis as well as arthritis as the initial manifestation of JIA were referred by their ophthalmologist. A possible explanation for the lack of children with uveitis as the initial manifestation of JIA may be that presently, MTX is not (yet) administered as the first treatment of choice for uveitis when there are no signs of arthritis. Treatment with topical corticosteroids initially is indicated, and only severe cases are treated with MTX. So if the cases who received MTX have a higher baseline risk of developing cataract requiring surgery, the benefit of MTX in delaying cataract surgery may have been reduced artificially, and the benefit may be even greater than what we observed. However, the delay in cataract surgery is still a remarkable observation, because the other treatment strategies were associated with a shortening of the U–CE interval. A delay in cataract formation is very favorable for several reasons. It is well known that CE in children is complicated because of anatomic and functional characteristics, which include the small globe size, increased tissue reactivity, lower scleral rigidity, changing axial length, and the risk of amblyopia.[11,12] Furthermore, with a delay in cataract formation, it will be easier to treat secondary posterior capsule opacification, to measure axial length and keratometry, and to perform capsulotomies. If cataract development can be postponed, the visual prognosis may improve, especially in young children in whom the period in which management to prevent amblyopia is necessary will be shortened. The protective mechanism responsible for the delay of development of cataract requiring surgery in children treated with MTX may include better control of the intraocular inflammation with possibly fewer flare-ups during the course of the disease. Another explanation may be that treatment with MTX diminishes the need for treatment with topical or systemic corticosteroids. However, both hypotheses need further investigation.

A limitation of this study is the relatively small number of patients available for statistical analysis, especially of some subgroups. Because of these small numbers, no analysis could be carried out on lens opacity and systemic corticosteroids in relation to the development of cataract requiring surgery. Furthermore, no patients were included

who had been treated with MTX and who had uveitis as the initial manifestation of JIA, so adjustment for the course of JIA could not be performed in this subgroup. Another limitation is the possible bias resulting from the time of cataract surgery. All children had a visual acuity of 20/63 (Snellen) or less before CE. However, the final decision to perform cataract surgery is not based solely on visual acuity, but on a combination of visual acuity, the risk of amblyopia, clinical findings, and the symptoms and preferences of patients and parents. So the different time schedules adopted for performing CE may well have influenced the results.

What is positive about this study is that it included only children with JIA-associated uveitis, which means it is based on a homogeneous population. Furthermore, all the children were seen in the same institute, and the different analyses were all performed on one relatively large study group with a relatively long median follow-up of 3.4 years. For further study, it may be interesting to compare early treatment (during the first year after the diagnosis of uveitis), late treatment (treatment after more than one year after the onset of uveitis), and no treatment with MTX, periocular corticosteroid injections, or both in a large patient series.

In conclusion, development of cataract requiring surgery in JIA-associated uveitis is caused by various factors. The presence of adherent posterior synechia at the time of diagnosis of uveitis is strongly associated with the early development of cataract requiring surgery in children with JIA-associated uveitis. This is in contrast with early treatment with MTX, which is associated with a delay in the development of cataract requiring surgery. So the beneficial effect of early treatment with MTX on the development of cataract requiring surgery may be expected in cases with posterior synechia. These observations are of value for ophthalmologists treating chronic severe uveitis in children with JIA.

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Biosketch

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