# Uveitis and juvenile idiopathic arthritis: A cohort study

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**Objective:** Assess the incidence of intraocular inflammation (uveitis) and ocular complications in children with various types of JIA in a single cohort of patients.

**Patients:** Included are 172 children (35 boys and 137 girls) diagnosed with JIA. All underwent thorough initial ophthalmologic examination and were followed for a minimum of 3 years.

**Results:** Of 172 children with JIA, 152 (88.4%) presented with arthritis. Uveitis was detected in 14 of the152 children (9.2%) during the first ophthalmic examination. In 17 additional patients of this group (11.2%), uveitis developed during the follow up period of up to 15 years. Twenty children out of the total of 172 (11.6%) presented initially with uveitis. In children developing uveitis before or along with arthritic manifestations, the ocular disease was chronic with a high rate of secondary complications (band keratopathy, glaucoma, posterior synechiae and cataract). In all affected eyes the initial ocular inflammation was typically confined to the anterior segment. On longer follow up however, most children developed binocular disease and posterior segment involvement. Dense cataract and amblyopia were the major cause of severe visual disabilities.

**Conclusion:** Pauciarticular JIA is associated with intraocular inflammation (uveitis) early during the arthritic disease course. The ocular disease course is unpredictable. Therefore education of parents regarding its signs and symptoms is of utmost importance. To preserve functional vision, secondary ocular complications and amblyopia should be avoided.

**Keywords:** arthritis, eye, JIA, uveitis, intraocular inflammation, visual acuity, cataract, glaucoma

Juvenile rheumatoid arthritis (JRA) or juvenile idiopathic arthritis (JIA) is a frequent systemic disease of childhood which is associated with intraocular inflammation (uveitis). JIA has been reported as the accompanying systemic manifestation in 81% of children with uveitis (Kanski and Shun-Shin 1984) and in 95% of those with anterior uveitis (O'Brien and Albert 1989). More recently, JIA was detected as the associated systemic manifestation in 41.5% of 130 children with uveitis (Tugal-Tutkun et al 1996). A prospective study carried out for a period of 10 years in our specialized uveitis clinic demonstrated that only 14.9% of 276 children and adolescents with uveitis had JIA (BenEzra et al 2005). These different incidences of the most prevalent causes for uveitis in children and those observed in adults have been attributed to "changing patterns of uveitis" (Henderly et al 1987; Tugal-Tutkun et al 1996). Despite all management care and modern treatment modalities, JIA remains an important cause of vision loss and blindness in most developed countries worldwide (Kanski et al 1990; Akduman et al 1997; Dollfus 1998; BenEzra and Cohen 2000; Kotaniemi et al 2001; Grassi et al 2007; Henligenhaus et al 2007). While the reported relative prevalence of JIA-associated ocular disease varies markedly among children with uveitis, the most severe ocular complications are observed in young girls with the pauciarticular type and bilateral eye involvement. This group of children therefore deserves special clinical and surgical

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treatment considerations aiming at minimizing the severe ocular complications leading to rapid non-reversible loss of vision (BenEzra and Cohen 2000).

In the present study, the ocular complications and relative incidence of intraocular inflammation in a cohort of 172 children with various types of JIA were evaluated during a period of 15 years with a minimum follow up of 3 years for each included patient.

## Patients and methods

Children diagnosed with JIA were referred by pediatricians to our Immuno-Ophthalmology Unit for ophthalmic examination. Children 10 years old or younger presenting to our clinic with intraocular inflammation were referred for pediatric consult to verify a possible JIA association. Included in this study is a cohort of 172 children with JIA who were examined with the slit lamp at least on three consecutive visits and followed for a minimum of 3 years and a maximum of 15 years after the original referral visit. At the time of initial examination, the children's age ranged between 30 months and 15 years. These included 35 boys and 137 girls. All were diagnosed by pediatricians as having JIA either prior to their initial ophthalmic examination (152 patients) or after pediatric consult was sought following the initial detection of intraocular inflammation (20 patients). All 172 children fulfilled the criteria for the diagnosis of JIA: Children with arthritis of at least 3 months duration, less than 16 years old at the time of first arthritic manifestation and without any other detectable cause for the arthritis.

### Clinical examination

History of possible systemic disease and ocular manifestations were carefully reviewed with the patients and parents. All patients underwent an ocular examination which included assessment of the visual acuity using the Snellen charts or the illiterate E charts and/or familiar pictures for the young verbal children. In a few of the very young and pre-verbal children, the pattern of fixation for near and distance and the elicitation of optokinetic nystagmus were used to assess their visual functions (BenEzra and Rose 1990). Slit lamp biomicroscopy, thorough fundus examination and assessment of refractive errors in both eyes were performed in all cases. The intraocular pressure (IOP) using the Goldman applanation tonometer was obtained in cooperative children. In a few of the very young children with early ocular complications the IOP assessment, fundus examination and refraction data were obtained after sedation or general anesthesia. Ocular movement abnormalities, the presence or absence of strabismus and the binocular functions were also routinely assessed.

### Ocular medical treatment

Ocular medical treatment consisted on instillations of corticosteroids and cycloplegic eye drops when the intraocular inflammation was confined to the anterior segment. The frequency of eye drops instillations in these cases was arbitrarily modulated for every affected eye according to the intensity of inflammatory reaction in the aqueous humor as assessed at the slit lamp.

Systemic corticosteroids (up to 1.0 mg/Kg/day) and/or Methotrexate (up to 25 mg once a week) were prescribed if the intermediate and posterior segments demonstrated active inflammatory process or at the advice of the treating rheumatologist for the control of severe arthritic manifestations.

### Laboratory tests

Complete blood count (CBC), sedimentation rate (ESR), C reactive protein (CRP), urine culture, kidney and liver function tests were performed in all cases. According to the clinical observations and the results of these routine preliminary examinations, a tailored individual more arduous battery of tests was designed as necessary (Dick and Forrester 1999).

### Classification of uveitis

The type of intraocular inflammation (uveitis) was classified according to the anatomical site of the major inflammatory manifestations following the intraocular inflammation society guidelines (Forrester et al 1998; BenEzra et al 2000). The intraocular inflammation was further subdivided to whether the disease was strictly ocular or it was associated with a systemic disease. Systemic disease associations were determined according to established sets of criteria (Bloch-Michel and Nussenblatt 1987; Weiner and BenEzra 1991; Dollfus 1998; Forrester et al 1998; BenEzra et al 2000; BenEzra et al 2005).

## Results

Of the 172 children with JIA, 152 were referred by pediatricians for ocular examination after the diagnosis of JIA was ascertained. In 20 children, intraocular inflammation was the presenting symptom while JIA disease was established later by a pediatrician. Of the 152 children with the presenting symptom of arthritis, 18 (11.8 %) had the systemic type of JIA, 87 (57.2%) had the pauciarticular type and 47 (30.9%) had the polyarticular type. Of the 152 children presenting with

**Table 1** Incidence of uveitis among JRA children presenting with articular disease

| | No. (Percent) | | Ocular Involvement | | | | % of type | | % of all types |
|---|---|---|---|---|---|---|---|---|---|
| Type | | | 1st Visit | | Later | | | | |
| | | | No. | (%) | No. | (%) | No. | (%) | – |
| Pauci | 87 | (57.2) | 12 | 13.8 | 8 | 9.2 | 20 | 23.0 | 64.5 |
| Poly | 47 | (31.0) | 1 | 2.1 | 6 | 12.8 | 7 | 14.9 | 22.6 |
| Systemic | 18 | (11.8) | 1 | 5.6 | 3 | 16.7 | 4 | 22.2 | 12.9 |
| TOTAL | 152 | 100 | 14 | 9.2 | 17 | 11.2 | 31 | – | 100.0 |

all types of JIA arthritic manifestations, in 14 children (9.2%), the intraocular inflammation (uveitis) was diagnosed during the first ophthalmic examination (12/14 had clinical evidence for the pauciarticular type of JIA). All these 14 children had a recent history (3 to 9 months) of arthritic disease. Ten additional children developed uveitis less than three years of the initial ocular examination and, in 7 children the uveitis was detected 3 to 7 years later (Table 1). Among the 20 children presenting initially with uveitis, 19 developed clinical manifestations compatible with the pauciarticular type of JIA. A systemic type of JIA was confirmed two months after the diagnosis of uveitis in one out of these 20 children (Table 2). Thus, out of a total of 172 children with JIA, 51 children had an associated intraocular inflammation (uveitis). Thirty nine of these 51 children (76.5%) had the pauciarticular type of JIA. In 32 of these 39 children (82%), the uveitis was either the presenting symptom or it was detected during the initial ophthalmic examination.

On initial examination, the intraocular inflammation processes were confined to the anterior segment in 45 of the 51 (88.2%) affected children. In 5 of the affected children (9.8%), a few cells were also observed in the anterior vitreous and in one child (2%), a marked vitritis with peripheral retinal vasculitis was observed in one eye. On further follow up however, only in 4 out of the 51 patients (7.8%), the inflammatory processes remained strictly confined to the anterior segment. Thus, with time, a tendency towards the involvement of the intermediate and posterior segments was observed. On last ophthalmic examination (3 to 15 years after initial diagnosis), in 22 patients (43.1%) the inflammatory signs were detected in all eye segments (pan uveitis) and in 24 children (47%), the inflammatory reaction involved the anterior and intermediate segments.

When the intraocular inflammation was initially diagnosed, it was uniocular in 29 of the 51 children (56.9%). On further follow up, the intraocular inflammation remained uniocular only in 8 of the 51 patients (15.7%) while in 43 children (84.3%) there was involvement of both eyes. When both eyes were affected, the intensity of intraocular inflammation was unequal in the majority of patients. The eye with more severe inflammation showed invariably a poorer visual acuity and more prominent secondary ocular complications.

The ocular complications observed in the 94 affected eyes of the 51 children are illustrated in Table 3. More severe and early complications were observed in girls manifesting the intraocular inflammatory processes when 4 years of age or younger.

In 46 of the 94 eyes with uveitis (48%), a band-shaped keratopathy developed. In most, the keratopathy was mild and did not interfere with vision. In 5 eyes (5.3%), the keratopathy was dense, encroached on the visual axis and affected the visual acuity.

An increased IOP above 24mmHg and possible development of glaucoma was detected in 24 of the 94, (25%) affected eyes. Medical treatment consisting of beta blockers and carbonic anhydrase inhibitor drops along with a decrease in the instillation frequency of corticosteroid eye drops induced a decrease of IOP below 20 mmHg in all cases.

Posterior synechiae and irregular pupil were observed in 64 eyes (68%).

Lens opacity interfering with the visual acuity (cataract) was recorded in 56 of the 94 affected eyes (59.6%). In eyes developing severe lens changes (dense cataract) accompanied by band keratopathy, marked impairment of the visual functions interfering with the daily activity and/or inducing amblyopia were observed (Table 4). In 30 of the eyes (32%) it was assessed that the lens opacity and/or the ensuing amblyopia were the main cause for the decrease of vision to a level lower

**Table 2** Type of JRA in children presenting initially with uveitis

| Type of arthritis | Ocular No. | Involvement (%) |
|---|---|---|
| Pauci | 19 | (95) |
| Poly | 0 | (0) |
| Systemic | 1 | (5) |
| TOTAL | 20 | (100) |

**Table 3** Ocular complications observed in 94 eyes of the 51 affected children

| Complication* | No. Children | (%) | No. Eyes | (%) |
|---|---|---|---|---|
| Band keratopathy | 30 | (59) | 46 | (48) |
| Glaucoma | 13 | (25) | 24 | (25) |
| Post. synechia | 43 | (84) | 64 | (68) |
| Cataract | 22 | (43) | 56 | (59.6) |

*More than one complication was observed in most eyes. Each of these complications is tabulated separately. Therefore, the total number of observed secondary complications (190) is higher than the total number of eyes.

than 0.05 (6/120 or 20/400) (Table 4). Therefore, surgery of the cataract was advised in these cases. Twenty nine of these eyes underwent lensectomy combined with anterior vitrectomy while in one case, the parents declined surgical intervention. An intraocular lens (IOL) was implanted in 19 eyes (pseudophakia) while 10 eyes remained aphakic. Glasses or contact lenses were prescribed for the correction of aphakia in these 10 eyes.

## Discussion

A definite association exists between the articular and ocular manifestations in children with JIA. The reported incidences of this association vary markedly with lower incidences and less severe ocular disease being reported more recently (Sherry et al 1991; Oren et al 2001; Sim et al 2006; Saurenmann et al 2007). A close look at these published differences reveals that the severity of ocular affection in the various studies is probably associated with population selection and referral trends in specific medical environments. It appears that the severity of ocular complications is higher when the study authors are ophthalmologists. This tendency is increased further when the papers originate from tertiary clinics specializing in uveitis and surgery of its complications.

Noteworthy is the fact that 20 of the 51 children with JIA and uveitis in our cohort presented with severe intraocular inflammation. The diagnosis of JIA was made only after these children were referred specifically for pediatric examination to assess the possible presence of JIA. In most of these 20 children the articular disease was of little concern to the children or their parents. They did not seek pediatric care and did not attend a pediatric clinic. Thus, a study regarding the incidence of uveitis in JIA carried out by pediatricians will not include these children biasing the incidence as well as the severity of ocular inflammation.

Concomitant with other reports (Sim et al 2006; Grassi et al 2007; Henligenhaus et al 2007), we observed in our present study that the highest associated incidence of arthritis and ocular manifestations is found in the group of children with the pauciarticular type. We have also noted that, in many cases, the articular and ocular clinical disease severity do not parallel. In many children, we observed severe ocular exacerbations during quiescent periods of arthritic manifestations and vice versa.

An interesting aspect of our study is the observation that during the initial phase of the ocular disease, the inflammation is strictly restricted to the anterior segment. Later during the follow up however, the intermediate and posterior segments become involved in the intraocular inflammatory processes. These observations may result from a "spill over" of the chronically stimulated inflammatory cells from the anterior segment to the posterior structures "dragging" them to react following the release of inflammatory cytokines.

The major points of clinical interest which can be derived from our study are:

1. Thirty nine of the 51 children with uveitis in our study group (76.5%) had the pauciarticular type of JIA.
2. The majority of children with pauciarticular JIA developing intraocular inflammation harbor signs of ocular disease either before or shortly after the development of arthritic manifestations.
3. Most children with polyarticular or systemic JIA types do not present signs of intraocular inflammation during the first three years following the initial arthritic manifestations.
4. The potential for a child with JIA to develop de novo ocular inflammation, at any time during the ophthalmic follow up, is low. The majority of children within all JIA types who devolop an associated uveitis harbor ocular signs on initial examination. Only a minority of these children develop the uveitic signs and symptoms later. Therefore, frequent ophthalmic visits for all children with JIA seems unjustified.
5. Nearly all children presenting with ocular disease and developing later JIA characteristics, had a mild arthritis involving only one or two joints.

**Table 4** Best corrected visual acuity (BCVA) in relation to the lenticular changes in the 94 affected eyes*

| Lenticular changes | No. Eyes | (%) | BCVA** |
|---|---|---|---|
| None | 38 | (40.4) | $0.7 \pm 0.2$ |
| Mild/Moderate | 26 | (27.7) | $0.4 \pm 0.3$ |
| Severe | 30 | (31.9) | $0.02 \pm 0.02$ |

*Recorded on last visit before any corrective surgery was carried out.
**BCVA: best corrected visual acuity expressed as decimal scale units eg, 1.0 is a visual acuity of 6/6 or 20/20 and 0.01 is 6/600 or 20/2000. In practical terms, we recorded 0.01 visual acuity level as the ability to perceive light with accurate projection and 0.02 as the ability to perceive hand movements in front of the affected eye.

From our present study observations, it can be concluded that rigorous and very frequent ophthalmic exams for JIA children are not obligatory if during the first ophthalmic examination ocular inflammatory signs are not detected. Furthermore, from our experience, a rigorous time frame for "regular" follow up visits for these children as suggested (Rosenberg and Oen 1986) seems unnecessary and, in our opinion, may be counterproductive for the following reasons: (a) uveitis may be detected during the ophthalmic examination only if the inflammatory signs are already present, (b) there are no "predictive signs" for the potential development of intraocular inflammation in these children, and (c) an intraocular inflammation may develop 24 or 48 hours after the "regular" periodic visit. In these cases, parents may be reluctant to seek again ophthalmic consultation (even if they suspect a problem) until serious complications develop. Therefore, education of the parents about the ocular disease, its potential evident signs and symptoms should be the main line of conduct for follow up instead of regular frequent ophthalmic visits. A drop of vision affecting the child's daily behavior can be noticed by parents. Also, parents can be taught to perform a visual acuity test at home when playing with the child. These measures in our experience are more effective, practical, easily carried out and have the highest possible cost/benefit ratio.

In this study we confirm, as published earlier (BenEzra and Cohen 2000) and also reported by others (Wolf et al 1987; Akduman et al 1997; Woreta et al 2007) that, severe complications with loss of vision are still to be feared in children with JIA who are developing uveitis. Most severe ocular complications have been observed in children 4 years of age or younger who presented first with ocular disease or had an ocular involvement detected during the initial ophthalmic examination. Young children with unilateral ocular affection or bilateral unequal involvement may develop amblyopia. If not treated early, loss of vision may ensue in these cases even if successful control of the intraocular inflammation is achieved but proper anti amblyopic measures are not applied early.

Last but not least, in the management of JRA associated ocular inflammation, surgery should be considered despite the potential for complications. In properly selected cases, beneficial outcomes may be obtained and restoration of vision achieved. Early surgery may even be considered in children with severe visual impairment in one eye due to band keratopathy, seclusion of the pupil by inflammatory membranes and/or dense cataract. In these cases, adequate surgical procedure of the cataract combined with intraocular lens implantation is to be considered and can result in good restoration of vision (BenEzra and Cohen 2000; Khotaniemi and Penttila 2006).

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