Ocular Immunology and Inflammation, 13:33–38, 2005

ISSN: 0927-3948 print; 1744-5078 online
DOI: 10.1080/09273940590909220

Taylor & Francis
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ORIGINAL ARTICLE

Visual Outcome of Juvenile Rheumatoid Arthritis-Associated Uveitis in Adults

Pinar Ç. Özdal,
Raul N. G. Vianna,
and Jean Deschênes
McGill University, Department of Ophthalmology, Uveitis Service, Montréal, Canada

ABSTRACT *Purpose:* Juvenile rheumatoid arthritis (JRA) is the systemic disease most frequently associated in childhood uveitis. The disease may cause several ocular complications, visual impairment, and blindness. Recent studies revealed a more favorable ocular prognosis. Our purpose was to analyze the long-term visual outcome of JRA-associated uveitis. *Methods:* Ocular complications and visual outcome in adult patients with JRA-associated uveitis were evaluated. Among 18 patients included in the study, uveitis was bilateral in 12 (66.7%) and unilateral in six (33.3%), for a total of 30 eyes with ocular involvement. *Results:* The mean durations of JRA and its associated uveitis were 24.9 and 20.5 years, respectively. All eyes (100%) had at least one ocular complication. The most frequently observed ocular complications were cataract (83.3%), band keratopathy (60%), posterior synechia (46.7%), glaucoma (33.3%), hypotony (16.7%), and macular pathology (13.3%). Final visual acuity was impaired in 40% of the eyes, poor in 20%, and totally lost in 10%. Therefore, 70% of the eyes were either visually handicapped or totally blind. Most eyes underwent at least one surgical procedure. Inflammation was active at last examination in 63.3% of eyes. All patients were still treated topically and with systemic NSAID. Sixty-one percent of the patients were using an immunosuppressive agent. *Conclusion:* JRA-associated uveitis still has a severe course and blinding potential. Patients suffer from uveitis and its complications even during the adulthood period. However, because our series represents a more severe subset of the disease, the outcome may be poorer than that of some other outcome studies.

KEYWORDS Adults; juvenile rheumatoid arthritis; prognosis; uveitis; visual outcome

INTRODUCTION

Pediatric uveitis makes up 6% of all uveitis cases. As in adults, uveitis in children may be a primary intraocular process or may be associated with a systemic disease.[1] Juvenile rheumatoid arthritis (JRA) is the systemic disease most frequently associated systemic disease in childhood uveitis.[2] Up to 80% of all pediatric anterior uveitis cases are associated with JRA.[1] Diagnosis of the disease is based on the clinical evidence of chronic arthritis

Accepted 20 August 2003.

Correspondence to: Pinar Ç. Özdal, Sehit Cevdet Ozdemir Mah. Seftali S. K. 74/17, 06460-Dikmen, Ankara, Turkey, e-mail: pinarozdal@hotmail.com

of at least three-months duration in a child younger than 16 years old, when other causes of arthritis have been excluded.[3] The peak age at onset of JRA is between two and four years and the disease is more common in girls.[4] The incidence of uveitis has been reported to be 9.3% by Chalom et al.,[5] 20% by Kanski,[6] and 34% by Chylack.[7] The risk factors for developing uveitis in JRA are pauciarticular type (involvement of $\leq$4 joints), early age at onset of arthritis, positivity of antinuclear antibodies (ANA), negativity of rheumatoid factor, and female gender.[8–11] In 80% of these patients, uveitis has an insidious, asymptomatic onset and can lead to blindness when left untreated.[10] JRA-associated uveitis has been reported to result in visual loss in up to 58% of the cases, depending on the severity of the inflammation.[11] On the other hand, several studies have stated that if diagnosed and treated early, visual prognosis in JRA-associated uveitis is relatively good.[5,9–13] Moreover, some pediatric rheumatologists have the impression that visual prognosis of these patients has improved since 1985.[5] Our clinical experience, however, shows that even with a regular follow-up by an ophthalmologist and the use of immunosuppressive agents, ocular complications and blindness can still occur in chronic cases. We therefore aimed to analyze the long-term visual outcome of our adult patients with JRA-associated uveitis.

MATERIALS AND METHODS

From 1986 to 2003, 36 eyes of 18 adult patients who had been diagnosed with JRA during their childhood were included in the study. All patients were followed for at least two years by one of the authors (JD) because of ocular involvement. JRA patients without ocular involvement, patients with another type of arthritis, patients with a follow-up period of less than two years, and patients younger than 18 years of age were excluded. The charts of included patients were retrospectively reviewed. Ocular examination consisted of uncorrected and best-corrected visual acuity with Snellen chart, slit-lamp biomicroscopy, applanation tonometry, and ophthalmoscopy. The presence of cells or keratic precipitates with or without flare was considered as active inflammation, and graded from 1+ (mild) to 4+ (very severe). The age at onset of arthritis, age at onset of uveitis, laterality, sex, follow-up period, localization of uveitis, grade of inflammation, best-corrected visual acuity at initial and last examinations, presence of any ocular complication associated with the disease, performed surgeries, presence of immunological markers, and treatment strategies were recorded. Secondary glaucoma, posterior synechia, cataract, band keratopathy, hypotony, macular pathology, and phthisis bulbi were considered ocular complications. The course of the ocular disease was categorized as chronic inflammation, recurrent inflammation, and acute monophasic disease course. The initial and most recent best-corrected visual acuities were classified into four groups: good visual acuity (equal to or better than 20/40), impairment in visual acuity (20/50 to 20/100), poor visual acuity (equal to or less than 20/150), and total blindness (no light perception). A change of one line in visual acuity was considered significant.

In the case of active inflammation, our principal treatment strategy was to start with topical corticosteroid, mydriatic agent, and systemic non-steroidal anti-inflammatory drug (NSAID). In the presence of intractable anterior uveitis or intermediate or posterior uveitis, a posterior subtenon injection of triamcinolone acetonide (40 mg) was our first choice. In more severe cases, oral prednisone and/or immunosuppressive agents were added.

Chi-square and Fisher's exact tests were used for the statistical analysis and p values less than 0.5 were considered significant.

RESULTS

Of the 18 patients included in the study, 17 (94.4%) were female. The mean duration of JRA and its associated uveitis was 24.9 ± 8.3 (range: 12–42) and 20.5 ± 9.6 (range: 8–35) years, respectively. The mean ophthalmologic follow-up period was 8.8 ± 3.8 (range: 2–17) years. The mean age of the patients at last examination was 29.6 ± 8 (range: 18–48) years. The mean age at onset of arthritis and uveitis was 4.6 ± 1.7 (range: 2–8; median: 4.5) and 8.9 ± 5.5 (range: 3–23; median: 7) years, respectively. Therefore, the onset of arthritis preceded the onset of uveitis by a mean period of 4.3 ± 6.2 (-1 to 21) years. Uveitis was diagnosed one year before the arthritis in one (5.6%), at the same time in five (27.7%), and 1–21 years later in 12 (66.7%) patients. Arthritis was of the pauciarticular onset type in 15 (83.3%) patients, the polyarticular onset type in two (11.1%), and the systemic onset type in one (5.6%). ANA was positive in 13 patients (72.2%) and rheumatoid factor was positive in four (22.2%).

Uveitis was bilateral in 12 (66.7%) patients and unilateral in six (33.3%), for a total of 30 eyes with ocular involvement. Inflammation was nongranulomatous in 28 eyes (93.3%) and granulomatous in two (6.7%). Inflammation affected primarily the anterior segment in 21 (70%) eyes and all segments (panuveitis) in nine (30%). Its course was chronic in 19 (63.3%) eyes, recurrent in nine (30%), and acute monophasic in two (6.7%). Of these 30 eyes, three (10%) were already phthisic at the time of presentation at our Uveitis Service. Other ocular complications related to JRA-associated uveitis included: cataract (25 eyes, 83.3%); band keratopathy (18 eyes, 60%); posterior synechia up to 360° (14 eyes, 46.7%); glaucoma (10 eyes, 33.3%); hypotony (5 eyes, 16.7%); macular pathology (scar, cystoid edema, or hemorrhage; 4 eyes, 13.3%); peripheral anterior synechia, pupillary membrane, and optic atrophy (3 eyes each, 10%); and retinal gliosis (1 eye, 3.3%). All 30 eyes (100%) with ocular involvement had at least one ocular complication.

Performed surgeries and interventions included cataract extraction in 22 eyes (73.3%; 13 of which were without and 9 with intraocular lens implantation), YAG laser capsulotomy in nine eyes (30%), Ahmed valve implantation in three eyes (10%), intraocular viscoelastic injections and laser iridotomy in two eyes each (6.7%), vitrectomy, trabeculectomy and Holmium laser sclerostomy in one eye each (3.3%).

The status of visual acuity at initial presentation to our Uveitis Service and at the most recent examination is presented in Table 1. At last examination, the number of patients with visual acuity 20/150 or worse in at least one eye was nine (50%). Compared with the initial examination, visual acuity was improved in nine of the 30 eyes (30%), decreased in 12 (40%), and the same in nine (30%; 3 of which were already phthisic).

There was no statistically significant relationship regarding ANA positivity between patients whose last visual acuity was 20/150 or less and whose visual acuity was better than 20/150 ($p > 0.5$). Having poor visual acuity was not correlated with age at arthritis onset equal to or younger than 4.5 (median age) and older than 4.5 years ($p > 0.1$). Furthermore, having poor visual acuity was not correlated with age at uveitis onset equal to or younger than 7 (median age) and older than 7 years ($p > 0.5$). Additionally, because all eyes with uveitis had at least one ocular complication, the presence of a complication was not correlated with visual acuity equal to or less than 20/150 ($p > 0.05$). However, five of six patients (83.3%) in whom the diagnosis of uveitis was made at the same time or before the onset of arthritis and four of 12 patients (33.3%) in whom the diagnosis of uveitis was made after the onset of arthritis had poor visual acuity. This difference was considered statistically significant ($p < 0.05$).

TABLE 1 **The status of visual acuity at initial and last examinations.**

	Initial examination	Last examination
Good visual acuity	13 (43.3%)	9 (30%)
Impaired visual acuity	8 (26.7%)	12 (40%)
Poor visual acuity	6 (20%)	6 (20%)
Total blindness	3 (10%)	3 (10%)

Of 30 eyes with ocular involvement at the most recent ophthalmologic examination, 19 (63.3%) still had active inflammation; it was mild in seven, moderate in three, severe in seven, and very severe in two. Inflammation was stable in eight eyes (24%). As mentioned before, three eyes were phthisic and six were free of inflammation since their first visit. All 18 patients were using topical treatment consisting of corticosteroids and/or nonsteroidal anti-inflammatory agent ± mydriatic agent. Six patients were also using topical antiglaucoma medication. Again, all of them were given a systemic NSAID. Rofecoxib or celecoxib, which are specific cyclooxygenase-2 enzyme inhibitors, were the first choice as NSAIDs. Other NSAIDs included piroxicam, diclofenac, naproxen sodium, and indomethacin. Eleven patients (61.1%) still required the use of a systemic immunosuppressive agent. Methotrexate was the most often used immunosuppressive (8 patients) followed by azathioprine (2 patients) and cyclosporine (2 patients, one of whom received it together with methotrexate). Two patients used systemic corticosteroids, three hydroxychloroquine, and two methazolamide. Twelve patients underwent several posterior subtenon injections (Table 2).

DISCUSSION

JRA-associated uveitis is usually a nongranulomatous uveitis that affects primarily the anterior segment of the eye.[1] It is bilateral in 67–89% of the cases.[2] Inflammation is chronic in 93% of the cases, recurrent in 5%, and acute monophasic in 2%.[8] The majority of patients develop uveitis within 4–7 years after JRA onset. In some patients, however, the interval between the onset

TABLE 2 **Medical management of the patients at last examination.**

Patient	CS*	NSAID*	Mydr.*	Antigl.*	NSAID	MTX	Azath	CsA	CS	h.chloroq.	Methazol.	Post ST
1	+	+	+	+	+		+					+
2	+			+	+	+					+	
3	+	+	+		+	+						+
4	+		+	+	+		+			+	+	
5	+	+	+	+	+	+						+
6	+	+	+		+							
7	+		+	+	+	+						+
8	+	+			+	+						+
9	+				+							+
10	+	+	+		+			+		+		+
11	+			+	+							
12	+		+		+	+						+
13		+			+							
14	+				+	+						+
15	+				+							+
16		+			+							
17	+		+		+					+		+
18	+		+		+	+		+				+

*Topical agents.

CS, corticosteroids; NSAID, non-steroidal anti-inflammatory drug; antigl., antiglaucoma, MTX, methotrexate; Azath., azathioprine; CsA, cyclosporine-A; h.chloroq., hydroxychloroquine; Methazol., methazolamide; Post ST, posterior subtenon injections.

of arthritis and that of uveitis may exceed 20 years.[4] The average age at the time of uveitis' diagnosis varies from 4.3 to 13 years.[5,6,8,11,14,15] Our results are in accordance with those mentioned above: inflammation was bilateral in 66.7% of the eyes, nongranulomatous in 93.3%, and affected primarily the anterior segment in 70%. Its clinical course was chronic persistent in 63.3% of the eyes, recurrent in 30%, and acute monophasic in 6.7%. The mean age at onset of uveitis was 8.9 years and the mean interval between onset of arthritis and onset of uveitis was 4.3 years. Uveitis occurred 21 years later in one patient.

Our study confirmed the known risk factors for developing uveitis in JRA. Female predominance (94.4%), young age at onset of arthritis (4.6 years), ANA positivity (72.2%), rheumatoid factor negativity (77.8%), and pauciarticular onset of arthritis (83.3%) were the main characteristics of our patients.

JRA-associated uveitis has a blinding potential which is often under appreciated.[1] Past experiences have shown that one-third of the affected eyes develop visual impairment and one-tenth become blind.[16] The visual prognosis is closely correlated with ocular complications.[17] The degree of inflammation and visual acuity found on initial examination and the duration of uveitis are also responsible for the severity of visual loss.[5,11] It is believed that patients whose uveitis precedes arthritis have a worse prognosis than those in whom uveitis follows arthritis.[1,2,5,11] This could be related to the fact that patients without arthritis are less likely to be referred for an ophthalmologic evaluation and thus present with a more advanced eye disease.[1,8] Uveitis preceded or was diagnosed at the same time as arthritis in 33.3% and followed the arthritis in 66.7% of our patients. The poor visual outcome was significantly higher in the first group ($p < 0.05$). According to Chalom and colleagues, ocular complications are more common in children who are ANA-negative.[5] We did not find any relationship between the presence of ANA and poor visual prognosis. Likewise, having poor final visual acuity did not differ between two groups created according to age at onset of arthritis and uveitis.

The rate and the definition for poor visual acuity and the frequency of ocular complications vary from one study to another (Tables 3 and 4). In our study, 70% of the eyes were either visually handicapped or totally blind at the most recent examination and all eyes had at least one complication. Our results concurred with the high rates of complications reported by Wolf et al.,[11] Dana et al.,[5] and Tugal-Tutkun et al.[18]

On the other hand, some studies reported more favorable results explained by early detection and prompt treatment of uveitis. According to Sherry and

TABLE 3 **The occurrence of ocular complications in JRA-associated uveitis: comparison with some of the previous studies.***

	Cataract	BK	Posterior synechia	Glaucoma	Hypotony	Macular disease	Phthisis bulbi
Özdal et al., 2003	83.3	60	46.7	33.3	16.7	13.3	10.3
Dana et al., 1997[8]	70	64	ND	21	17[a]	33	
Chalom et al., 1997[5]	14	17	10	11	ND	ND	ND
Tugal-Tutkun et al., 1996[18]	71	66	ND	30	19	37	ND
Cabral et al., 1993[10]	21	17	24	12	ND	ND	1
Rosenberg, 1987[14,b]	37.7	33.6	20.7	15.5	ND	ND	6.7
Wolf et al., 1987[11]	81	77	100	45	ND	ND	13
Kanski, 1977[19]	42.1	41.2	ND	18.8	ND	ND	ND

*Except for the Chalom et al. study which reported % of patients, values represent % of affected eyes.
[a]Includes eyes with phthisis bulbi.
[b]Results are a compilation of five previous studies.
BK, band keratopathy; ND, not described.

colleagues, not only the prevalence, but also the severity of chronic uveitis has decreased in recent years.[13] Comparing patients with pauciarticular JRA seen in 1975 to those seen in 1989, the prevalence of eye disease decreased from 45% to 13% and severe visual loss from 21% to none.[13] Chalom and co-workers emphasized that the outcome of children with JRA who developed uveitis was excellent 95% of the time.[5] Similarly, Kotaniemi et al.[9] reported ocular complications in 24% and good visual prognosis in 97% of their patients with JRA-associated uveitis. However, their study covered only new cases of JRA and uveitis was still active in most patients, which means that an increase in the frequency of complications is expected.[9] The occurrence of ocular complications and visual impairment was reported to be 33% and 15%, respectively, in the study by Cabral's group.[10] Their study suggested that impaired vision occurs in the presence of ocular complications only. We do not have comparable results because all eyes with uveitis had at least one complication whether or not vision was impaired. In the series by Oren's group, the final visual acuity of all children was better than 20/30 after a mean follow-up period of 55 months.[12] With the frequency of ocular complication(s) (100%) and the rate of visual acuity equal to or less than 20/50 (70%), we are not as optimistic as they were with regard to the long-term visual outcome in JRA-associated uveitis. In addition, most eyes underwent at least one surgical procedure, inflammation was still active in 63.3%, and all patients were still treated topically and systemically. Moreover, 61.1% of the patients were still using at least one immunosuppressive agent. These relatively unfavorable results might be explained by several factors. (1) JRA-associated uveitis is usually asymptomatic with insidious onset.[1,16] Because the ocular symptoms are mild, patients are frequently managed by general ophthalmologists, and only complicated, difficult-to-manage patients are referred to uveitis specialists. By the time we saw these patients at our referral center, most of them had severe eye disease, including phthisis bulbi in three, and a visual acuity already worse than 20/150 in 30%. (2) In 63.3% of the eyes, inflammation had a chronic persistent course. This concurs with studies demonstrating that patients with a chronic course of uveitis have a higher frequency of complications.[10]

TABLE 4 **Visual outcome in JRA-associated uveitis: comparison with some of the previous studies.***

	Good vision[a]	Impaired vision[b]	Poor vision[c]	Total blindness[d]
Özdal et al., 2003	30	40	20	10
Kotaniemi et al., 2001[9]	97	3	ND	None
Dana et al., 1997[8]	43	32	25	ND
Tugal-Tutkun et al., 1996[18]	44.4	30.1	20.6	4.7
Cabral et al., 1993[10]	85	5	10	ND
Wolf et al., 1987[11]	61	17	18	4
Cassidy et al., 1977[20]	55*	21*	16*	ND

*Except for the studies by Kotaniemi's and Cassidy's groups which reported % of patients, values represent % of affected eyes.
[a]Good vision was 20/20-20/60 in the Kotaniemi et al. study and 20/20-20/40 in the other studies.
[b]Impaired vision was less than 20/60 in Kotaniemi et al., 20/50-20/400 in Cassidy et al., 20/50-20/200 in Tugal-Tutkun et al., and 20/50-20/100 in the other studies.
[c]Poor vision was defined as less than 20/400 in Cassidy et al., 20/150 or less in ours, 20/300 or less in Tugal-Tutkun et al., and 20/200 or worse in the other studies.
[d]No light perception.
ND, not described.

(3) Previous studies presented ophthalmologic results of children with JRA and were mostly performed in pediatric rheumatology or ophthalmology clinics. Because our patients were adults, the mean durations of the disease (24.9 years) and its associated uveitis (20.5 years) were much longer and demonstrated the visual outcome and complications in the long term. We think that pediatric rheumatologists might not be familiar with the long-term ocular prognosis of the disease.

Even though the visual outcome in JRA-associated uveitis is still guarded, complications do not necessarily result in a poor outcome. This fact is closely correlated with awareness and better screening of risk factors, proper use of systemic treatment, and development of microsurgical techniques. Chalom and colleagues reported 20/40 or better vision in 73% of the children with complications.[5] In our study, although all eyes had at least one complication, vision was 20/40 or better in 30% of the eyes and the presence of complications was not correlated with poor visual acuity.

In conclusion and contrary to studies reporting an improvement in visual outcome in recent years, our study suggests that the long-term prognosis of ocular involvement is still poor and patients continue to suffer from JRA-associated uveitis in adulthood. This major finding of our study is not always accepted by pediatric rheumatologists and ophthalmologists who are not specialized in uveitis. However, because our series represents a more severe subset of disease, the outcomes may be poorer than some other outcome studies. Further improvement of visual outcome depends on a good knowledge of prognostic factors, a close follow-up planned according to the risk factors, early referral to a specialist on uveitis, and proper and timely administration of systemic treatment. We agree with Nguyen and Foster[4] and also with Tugal-Tutkun et al.[18] that cooperation among specialists caring for patients with JRA will help to reduce ocular morbidity and blindness due to ocular involvement.

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