Severe childhood uveitis without overt arthritis

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ABSTRACT

Objective. *To look for forme fruste (incomplete) forms of juvenile idiopathic arthritis (JIA)-associated uveitis.*

Methods. *The study involved 6 patients (3 girls and 3 boys) without overt arthritis who had been sent for ophthalmologic and rheumatologic evaluation because of uveitis resembling that seen in JIA.*

Results. *Two patients evinced no evidence of arthritis, 3 had non-specific signs and symptoms such as pains or valgus ankle and one may have had an episode of arthritis. Five patients carried the HLA allele B27 and 4 were positive for antinuclear antibodies. The mean age at diagnosis of uveitis was 8.4 years (range 3.5 - 14.2 years) and the mean follow-up period was 6.2 years (range 3.8 - 7.3 years). All patients had obviously had their uveitis for a long period prior to the first contact with an ophthalmologist. In 3 patients uveitis was asymptomatic when diagnosed, 2 had mild conjunctival injection and one had exacerbation of the disease process. Subsequently the uveitis was asymptomatic and bilateral in all patients.*

Complications of uveitis were common: cataract was found in 4 patients, glaucoma in 1 patient, cystoid macular edema in 4, posterior synechiae in 5 and band keratopathy in 3. The final visual acuity was poor in one eye of 1 patient despite effective treatment of uveitis. Uveitis was still active in all patients at the close of follow-up.

Conclusion. *Asymptomatic uveitis, which is frequently positive for antinuclear antibodies, can occur in children who show no clear evidence of arthritis. Complications occur in consequence of a delay in the diagnosis of insidious uveitis.*

Introduction

Chronic anterior uveitis (CAU) is a serious extra-articular manifestation of juvenile idiopathic arthritis (JIA), formerly called juvenile chronic arthritis or juvenile rheumatoid arthritis. Most studies have reported 10-20% occurrence rates of uveitis, although slightly lower and higher figures have also been published (1, 2). Three main onset types of JIA are recognised: oligoarticular (1 to 4 joints affected) in 40-70% of cases, polyarthritis (≥ 5 joints affected) in 20-40% of cases, and systemic onset arthritis (with fever, rash and at times serositis) in 5-10% of cases in populations of European ancestry (3). Young children with oligoarthritis or rheumatoid factor-negative polyarthritis at the age of 2 to 4 years when diagnosed, and who have antinuclear antibodies (ANA), are at greatest risk of developing CAU (1, 2, 4).

The clinical picture of JIA-associated chronic uveitis is characteristic (1,2). The onset of the disorder is in most cases insidious and the course is chronic, sometimes remitting. Frequently both eyes are affected, either simultaneously or within a few months of each other. In the majority of patients uveitis is non-granulomatous, with a faint flare and only a few cells in the anterior chamber, by no means easy to detect. Keratic precipitates are from small to medium in size, seen mainly in the inferior half of the corneal endothelium. In moderate or severe uveitis, cells in the anterior vitreous and/or posterior synechiae between the iris and lens are seen. The inflammation may also spread to posterior parts of the eye, not infrequently resulting in cystoid macular edema (CME). A serious consequence of chronic uveitis is secondary glaucoma, which may not be amenable to conventional treatment; accordingly, a special mode of filtering surgery is needed (5).

Most often uveitis in JIA is asymptomatic. However, in a minority of patients uveitis is acute anterior, with redness and pain. It tends to occur in older children, often in those with enthesitis-related arthritis (this subtype of JIA corresponds to adult spondyloarthropathy) and positive for HLA B27, most sufferers being boys aged 10 or more (1, 2).

In most instances arthritis precedes CAU; not infrequently it is detected at the first ophthalmologic consultation after the diagnosis of arthritis. In rare cases uveitis is diagnosed before arthritis or later than 7 years after its onset (1,2). There are some old reports on chronic iridocyclitis in children occur-

ring without overt arthritis (6, 7) but no details were given. To the best of our knowledge, however, there are no published reports from more recent years on patients with CAU resembling that seen in JIA who have not developed arthritis. Here we describe 6 patients with chronic uveitis who had been referred for ophthalmologic and rheumatologic evaluation and who have been treated and followed for a mean period of 6.2 (range 3.8 – 7.3) years.

Patients and methods

The study group comprised 6 children with longstanding idiopathic uveitis from different ophthalmologic units in Finland. They were referred to the Rheumatism Foundation Hospital for rheumatologic and ophthalmologic evaluation of eye disease which had proved refractory to previous treatment. In all cases the etiology of the uveitis was unknown. The diagnosis of uveitis was made by ophthalmologists at the central hospital of the patient's district, where a general pediatrician had been consulted in all cases to ascertain the absence of JIA. Sarcoidosis was excluded on the basis of its characteristic ophthalmologic picture. Infectious etiology was looked for by appropriate serological tests, but nothing was found.

The period from the diagnosis of uveitis to the first visit to the Rheumatism Foundation Hospital ranged from 2 months to 5 years (mean 15 months). At the Rheumatism Foundation Hospital the ophthalmologic examination included determination of the best corrected visual acuity, and examination of the eye by biomicroscopy, ocular pressure by tonometry, and the posterior parts of the eye with a Volk lens or by indirect ophthalmoscopy. Complications of uveitis (cataract, synechiae, band keratopathy, glaucoma and CME) were recorded.

A pediatric rheumatologist examined every patient at every visit to the ophthalmologist. The evaluation included an anamnestic inquiry and clinical status with emphasis on joints. X-rays or magnetic resonance imaging of joints were taken if there was even the slightest indication. The laboratory check-up comprised general markers of inflammation such as the erythrocyte sedimentation rate, C-reactive protein, leukocytes, and specific etiological tests including rheumatoid factor, ANA, HLA B27, immunoglobulins A, G and M, and antibodies to various enteric pathogens associated with reactive arthritis. ANA were determined by indirect immunofluorescence using Hep-2 cells; titres ≥80 were regarded as positive.

Results

During the years 1994-1998 six children with chronic idiopathic uveitis without clear evidence of arthritis were referred to the Rheumatism Foundation Hospital for diagnosis and treatment. The patients were at the age of 3-14 years at diagnosis of uveitis. Three of these patients were girls and 3 were boys. The main patient characteristics are described in Table I.

Two of the 3 female patients had no evidence of arthritis and the third had an asymmetrical pes planovalgus. X-rays did not reveal any evidence of arthritis. Two male patients had had vague joint pains and one may have had an episode of arthritis at the age of 3, although in retrospect the diagnosis could not be confirmed. The girls and the youngest boy were positive for ANA (homogeneous pattern) and HLA B27, one boy was HLA B27-positive and one boy was negative for both of ANA and HLA B27. The only patient with a first-degree relative (mother) with a rheumatic disease and HLA B27 positivity was the boy (case 4) with possible arthritis in the past. His mother was HLA B27-positive and she had either mixed connective disease or spondyloarthropathy; she died suddenly of cerebral hemorrhage at the age of 38 before the diagnostic work-up had been completed. None of the other first-degree relatives of the patients had any chronic rheumatic disease.

Details of the ophthalmologic findings are shown in Table II. Uveitis was totally asymptomatic in the female patient (case 1) with unilateral uveitis at the onset. Her visual impairment was detected during a screening at school. Likewise, there were 2 asymptomatic male patients (cases 4 and 5), one of whom had been sent to an ophthalmologist because of decreased visual acuity noted during a school screening (case 4) and the other because of routine evaluation due to epilepsy (case 5). One girl had had transient redness in her eyes for a few months before an ophthalmologic examination (case 2) and another (case 3) had had redness and discomfort in her eyes for 3 weeks before the detection of uveitis. One male patient (case 6) had had redness and aches in his eyes before an ophthalmologic consultation. All patients subsequently experienced asymptomatic CAU during the mean follow-up of 6.2 (range 3.8 – 7.3) years.

The conventional treatment with hourly corticosteroid eye drops and ointment at bedtime and mydriatic drops was instituted in every case. In 5 cases this was supplemented with peroral corticosteroids at some phase of the disease. The systemic immunosuppressive treatment was planned and commenced in close co-operation with a pediatric

Table I. Main patient characteristics of the 6 children with chronic idiopathic uveitis.

Case	Gender	Age at diagnosis of CAU*	HLA B27	ANA#	Joint symptoms or signs
1	female	7.1	+	+ (640)	None
2	female	3.5	+	+ (80)	Pes planovalgus
3	female	14.2	+	+ (5000)	None
4	male	6.9	+	+ (80)	Dfficulties in walking and stiffness at the age of 3
5	male	9.4	+	-	Aches in back and knees
6	male	9.5	-	-	Aches in back and knees, stiffness

*Chronic anterior uveitis; #antinuclear antibodies.

Table II. Characteristics of uveitis in the patients under study.

Case and gender	1 Female	2 Female	3 Female	4 Male	5 Male	6 Male
Number of eyes affected	2	2	2	2	2	2
Visual acuity at diagnosis of uveitis (right/left eye)	1.0 / 0.6	0.6 / 0.6	1.0 / 1.0	0.4 / 1.0	1.0 / 1.0	1.0 / 1.0
Visual acuity at close of follow-up (right/left eye)	1.0 / 0.9	0.5 / < 0.05	0.9 / 1.0	0.8 / 1.0	1.0 / 1.0	1.0 / 1.0
Complicating cataract [eye(s)]	left	both	left	both	none	none
Secondary glaucoma [eye(s)]	none	none	none	both	none	none
Band keratopathy [eye(s)]	left	both	none	both	none	none
Cystoid macular edema [eye(s)]	left	both	left	both	none	none
Posterior synechiae [eye(s)]	left	both	left	both	both	none
Number of surgical eye interventions	1	6	1	4	0	0

rheumatologist.

Uveitis was severe at diagnosis in the 2 female patients with bilateral uveitis (cases 2 and 3) and in the youngest male patient (case 4). Their uveitis was refractory to treatment with local and systemic corticosteroids. In two cases methotrexate (15-30 mg/week) was initiated and cyclosporin A (75-150 mg/day) was subsequently added to the regimen; in the third case this sequence was reversed. The combination therapy alleviated the condition; in one of these cases visual acuity remained poor in one eye. The female patient with unilateral CAU at onset developed mild transient uveitis in the other eye before initiating the treatment with methotrexate (case 1). Her cataract was operated on and she still has mild CME in her left eye requiring continuous local treatment with corticosteroid drops. Two boys (cases 5 and 6) have had mild chronic uveitis after the institution of local treatment supplemented with systemic corticosteroids in one of them. Subsequently both have managed well with minimal topical treatment of their uveitis. Information concerning treatment schedules are summarised in Table III.

Table III. Treatment of uveitis in the patients under study.

Case and gender	1 Female	2 Female	3 Female	4 Male	5 Male	6 Male
Local treatment at the end of follow-up						
Glucocorticosteroid drops or ointment	x5	x4	x3	x3	x1	x3
Mydriatics	x1	x1	x1	x1	x1	0
Anti-inflammatory drugs	0	x3	x2	x2	0	0
Glaucoma medications	0	0	0	x2	0	0
Highest dosage of systemic treatment						
Methotrexate (mg/week)	15	12.5	30	20	0	0
Cyclosporin A (mg/day)	0	50x3	50x2	25x3	0	0
Prednisolone (mg/every 2 days)	5	40	50	20	40	0
Systemic treatment at the end of follow-up						
Methotrexate (mg/week)	15	25	0	7.5	0	0
Cyclosporin A (mg/day)	0	50x3	50x2	25x3	0	0
Prednisolone (mg every 2 days)	5	2.5	10	0	0	0

Discussion

Findings at the first ophthalmologic consultation revealed that all patients had had uveitis for a long period of time. Two had been referred to an ophthalmologist because of impaired vision observed at school and one after a routine evaluation related to epilepsy. Three patients had had redness in the eyes which in these cases indicated severe inflammation. Two patients had evinced no evidence of arthritis and 3 had had non-specific symptoms and signs such as pains or valgus ankle; one male patient may have had a short episode of arthritis 4 years prior to the first ophthalmologic consultation.

The most common immunological abnormality in JIA is positive ANA, which usually exhibits a homogeneous or speckled pattern in the indicator cell. The nature of the antigens responsible for positive ANA in JIA patients has not yet been settled with certainty (4). The frequency of positive reactions depends on the test techniques adopted. On the average, ANA has been detected by immunofluorescence in roughly 30% of children with JIA, most frequently in patients with oligoarthritis, less so in those with rheumatoid factor-seronegative polyarthritis and only seldom in the other subtypes of JIA. Interestingly, ANA-positive patients run a clearly increased risk of CAU (1). Four of the 6 cases in the present series were positive for ANA (pattern homogeneous, titres from 80 to 5000). This bears out the conception that these cases might represent a forme fruste (incomplete) type of JIA-associated CAU. The possibility cannot of course be excluded that some of the patients will in due course develop frank arthritis. Indeed, a legally blind ANA-positive girl with chronic idiopathic uveitis (not included in the study series) had been followed up for 8 years until she developed arthritis in her right knee during the preparation of the present manuscript. The arthritis has persisted for several months.

Five of the 6 patients carried the HLA allele B27. The prevalence of HLA B27 is high in enthesitis-related arthritis and this allele is associated with the occurrence of acute anterior uveitis in both adults and children. However, the uveitis in our patients was entirely different from that seen in HLA B27-associated diseases. The prevalence of HLA

B27 is also slightly increased in oligoarthritis (8) and due to its fairly high background prevalence in Finland (15%), about 25-30% of Finnish JIA patients who do not have enthesitis-related arthritis are positive for it (9).

The study series was collected over a period of 5 years. During this time there were approximately 750 new cases of JIA in Finland and 150 of them may have had CAU (10). A considerable proportion of cases such as those described in the present work are referred to the Rheumatism Foundation Hospital. Accordingly these most likely are fairly rare.

The prognosis of JIA-associated CAU is improving due to prompt and, when needed, aggressive treatment. In a recent Finnish series of 104 patients followed up for a mean of 4.5 years, none developed blindness and only 2 had impaired vision (10). In the present series the complication rate was high and of the 6 patients studied, one had impaired vision in one eye. Quite obviously this was due to a delay in diagnosis. Although the type of disease described here is fairly rare, it has serious consequences for those whom it concerns.

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