EXTENDED REPORT

Uveitis in children and adolescents

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Aims: To study the relative occurrence of uveitis (intraocular inflammation) and its causes in children and adolescents.

Methods: Patients with uveitis examined and followed during a period of 10 years were categorised by age and sex. All underwent ocular examination and an individually tailored battery of laboratory tests. The intraocular manifestations were classified according to the anatomical location of the inflammation and their most probable cause. The final diagnosis was based on typical clinical ocular and extraocular symptoms and signs and on the results of specific laboratory investigations.

Results: Out of 821 patients, 276 (33.1%) were 18 years of age or younger with a male to female ratio of 1 to 1. In these 276 children and adolescents, 70.3% had bilateral ocular involvement. Intermediate uveitis was the most frequent anatomical diagnosis. In many cases, symptoms were mild despite the prominent signs and marked decrease of vision. The underlying cause for the uveitis was evaluated as non-infectious in 184 cases (66.7%) and infectious in 92 cases (33.3%). A potential aetiology and/or a definite clinical diagnosis were established in 74.6% of the cases and only 25.4% of the 276 patients were classified as idiopathic. Juvenile idiopathic arthritis (JIA) was the most common systemic disease association diagnosed in 14.9% of these children. Parasite infestation was the most common infectious association.

Conclusions: Uveitis in children and adolescents is not as low as previously reported. Parasite infestation on the one hand and JIA on the other hand are the most common aetiologies associated with the uveitis in these young patients.

Intraocular inflammation affecting the uvea (uveitis) occurring in childhood has been reported at a much lower incidence than in adults.[1] Children with uveitis comprised 2.2% to 10.6% of the total number of uveitis patients examined and followed in specialised adult clinics.[2–6] It is interesting that the same authors within the same organisation reported a large variability in the prevalence of uveitis in children when the studies were carried out during different periods.[4 5]

When examining the causes of uveitis in the general population, a marked variability in the incidence and/or prevalence of the different entities has been observed.[6–10] These differences were influenced by factors such as recognition of new clinical entities, the introduction of newer and more sophisticated diagnostic tools, and eradication of certain infectious diseases. Environmental and genetic factors along with a heightened awareness of previously unsuspected entities also played an important part in the reported incidences of specific diseases in various countries.[9 11] In children, juvenile idiopathic arthritis (JIA) has been reported as the accompanying systemic manifestation in 81% of children with uveitis[12] and in 95% of children with anterior uveitis.[13] More recently, JIA was found to be the associated systemic manifestation in 41.5% of 130 children with uveitis.[14] 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."[8 14]

We observed and followed a large cohort of 276 children and adolescents and report our findings regarding the pattern and most probable aetiology of the intraocular inflammation in these patients.

PATIENTS AND METHODS

Patients

From March 1989 to February 1999, 821 consecutive patients with intraocular inflammation (uveitis) were diagnosed in the immuno-ophthalmology and uveitis clinic of the Hebrew University Hospital, Jerusalem, Israel. The follow up ranged between 1 and 10 years with a mean of 51 months for the entire group. All patients were of white (Semite) origin: Arabs and Jews.

Table 1 Main site of intraocular inflammation

Uveitis	No	%
Anterior	37	13.4
Intermediate	115	41.7
Posterior	39	14.1
Panuveitis	85	30.8
Total	276	100.0

Clinical examination

History of possible systemic disease and ocular manifestation were carefully reviewed. All patients underwent a complete ocular examination during their first visit. This examination included assessment of the visual acuity using Snellen charts or illiterate E charts and/or familiar pictures for the younger and verbal children. In a few of the very young and preverbal children, the pattern of fixation for near and distance and the elicitation of optokinetic nystagmus were used to assess their visual functions.[15] Slit lamp biomicroscopy, fundus examination, and assessment of refractive errors in both eyes were performed in all cases. The intraocular pressure (IOP) using the Goldmann applanation tonometer or the Tonopen was obtained in all cooperative children. In a few complicated and

Abbreviations: BCVA, best corrected visual acuity; CBC, complete blood count; CRP, C reactive protein; DUSN, diffuse unilateral subacute neuroretinitis; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis

Table 2 Presenting symptoms, signs, and visual acuity

Symptoms	Patients No	%	BCVA* (mean (SE))
None	80	29.0	0.30 (0.1)
Tearing, photophobia	67	24.3	0.20 (0.2)
Red eye	44	15.9	0.80 (0.2)
Drop of vision	33	12.0	0.40 (0.3)
''Funny behaviour''	26	9.4	0.60 (0.4)
Strabismus	15	5.4	0.10 (0.1)
Leukocorea	11	4.0	0.05 (0.0)

*BCVA, best corrected visual acuity of affected eyes.

poorly cooperating cases, IOP assessment, fundus examination, and refraction data were obtained after general anaesthesia.

Ocular movement abnormalities, the presence or absence of strabismus, and the binocular functions were also assessed.

Laboratory tests

Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) tests were performed in all cases. According to the clinical observations and the results of these routine preliminary examinations, a tailored more arduous battery of tests was designed for each case as deemed necessary.[16]

Classification of uveitis

The type of intraocular inflammation (uveitis) was classified according to the anatomical site of the major inflammatory manifestations and the most probable aetiological factors associated with this reaction as described earlier.[16 17] Anatomical classification of ''anterior uveitis'' (anterior segment intraocular inflammation) was made only when the intraocular inflammatory signs were confined to the anterior chamber with less than 10 inflammatory cells observed in the anterior vitreous. In the presence of more than 10 inflammatory cells in the anterior or mid-vitreous and/or in the presence of ''snowballs,'' a diagnosis of ''intermediate uveitis'' (intermediate intraocular inflammation) was made. Diagnosis of ''posterior uveitis'' (posterior segment intraocular inflammation) was made in the presence of inflammatory cells within the posterior vitreous with retinal vasculitis and/or retinal or choroid infiltrates. In eyes harbouring anterior and posterior segment intraocular inflammatory signs, a diagnosis of ''panuveitis'' (panintraocular inflammation) was made.[16] The intraocular inflammation was further subdivided according to whether it was associated with an infectious or non-infectious process and whether it was strictly confined to the eyes or it was associated with a systemic disease.[17 18] Systemic disease association was determined according to established sets of criteria.[9 19–21]

Table 3 Aetiology

Diagnosis	No	%
Non-infectious*	114	41.3
Infectious	92	33.3
''Idiopathic''†	70	25.4
Total	276	100.0

*With a definite disease entity.
†Also non-infectious, without a definite entity classification.

RESULTS

Out of the 821 patients with uveitis, 276 patients (33.1%) were 18 years of age or younger; 249 were younger than 16 years of age and 27 patients (9.8%) were 16–18 years old. The male to female ratio was one to one (49.6% boys and 50.4% girls). A bilateral involvement was detected in 70.3% of the cases and only 29.7% had either only the left or the right eye involved. Thus, a total number of 470 eyes with intraocular inflammation are evaluated in this study.

The uveitis was characterised as strictly anterior only in 37 patients (13.4%) while intermediate uveitis was diagnosed in 41.7%. Posterior uveitis was found in 14.1% of the cases and a diagnosis of panuveitis was observed in 30.8% of the cases (table 1).

In 80 children (29.0%), subjective ocular symptoms were not reported despite a very poor visual acuity detected during a routine testing in school or kindergarten (table 2). Tearing and photophobia were the presenting symptoms in 24.3% of the cases while a ''red eye'' was the cause for referral in 15.9% of the cases. A drop of vision reported by the child was the symptomatic cause of referral in only 12% of the cases. Leukocorea and strabismus were the presenting signs in 4.0% and 5.4% of the children, respectively. These signs were observed in children less than 6 years of age and in all cases were associated with extremely poor vision and the presence of deep amblyopia (table 2).

The intraocular inflammation was associated with an infectious agent in 92 (33.3%) of the cases while a non-infectious aetiology was determined in 184 (66.7%) of the 276 cases (table 3). Seventy children (25.4%) with a non-infectious aetiology and signs strictly confined to the eyes were classified as ''idiopathic'' because no specific cause was found. In the other 114 children with non-infectious aetiology (41.3% of the 276 patients), a specific ocular diagnosis or a systemic disease association were unveiled (table 3).

Bacteria were the direct and indirect cause for the intraocular inflammation in 18 children, 19.6% of the infectious causes and 6.5% of all causes (table 4). Toxoplasma was diagnosed in 20 and *Toxocara* in 13 children. In 10 additional children, visceral larva migrans other than *Toxocara* were found. In all, an antihelminthic regimen combined with a short course of oral corticosteroids (prednisone 1.25 to 1.5 mg/kg/day as starting dose tapered to discontinuation over 6 weeks) had marked beneficial therapeutic effects. Three additional children presented the typical ocular manifestation of diffuse unilateral subacute neuroretinitis (DUSN). In one child with Down's syndrome, the typical fundus manifestations of DUSN were observed in both eyes and were associated with the presence of *Oxyuris* larvae in the stools. Thus, in 26 out of the 276 (9.4%) children and adolescents with uveitis, visceral larvae migrans was the only associated finding and the most probable aetiology for the intraocular inflammation.

Table 4 Incidence of specific infectious aetiologies

Infectious agent	Specific	No of patients	Percentage	
			Infectious (92)	All cases (276)
	Toxoplasma	20	21.7	7.2
	Toxocara	13	14.1	4.7
	DUSN	3	3.3	1.1
	Others*	10	10.9	3.6
Parasites	Total	46	50.0	16.6
	Herpes	10	10.9	3.6
	ARN	2	2.2	0.7
	Varicella	2	2.2	0.7
	EBV	7	7.6	2.6
	CMV	5	5.4	1.8
	Adenovirus	2	2.2	0.7
Viruses	Total	28	30.5	10.1
	Lyme disease	5	5.4	1.8
	Cat scratch	4	4.3	1.4
	Staphylococci†	3	3.3	1.1
	Klebsiella‡	3	3.3	1.1
	Tuberculosis	2	2.2	0.7
	Yersenia‡	1	1.1	0.4
Bacteria	Total	18	19.6	6.5

DUSN, diffuse unilateral subacute neuroretinitis probably associated with a larva parasite. In one of these cases, the manifestation was bilateral; EBV, Epstein-Barr virus; CMV, cytomegalovirus.
*In these cases, the uveitis was associated with the presence of visceral larva migrans other than *Toxocara* (*Oxyuris* or ascariasis). The presence within the eye of living larvae was not documented in any of these cases.
†These bacteria were isolated from the anterior chamber in children with unilateral disease and were probably associated with an unsuspected antecedent penetrating trauma in these eyes.
‡The bacteria were isolated from the urine of children suffering from chronic urinary tract infection and bilateral uveitis.

Viruses were the cause of uveitis in 28 children (30.4% of the infectious aetiologies and 10.1% of the 276 patients (table 4).

Of the 184 children and adolescents with non-infectious uveitis, in 74 (40.2%) an associated systemic disease was detected while in 110 cases (59.8%) the inflammatory processes were strictly confined to the eyes (table 5).

Of the 110 children and adolescents with a non-infectious aetiology and manifestations confined to the eyes, 70 (63.7%) were classified as idiopathic. This diagnosis, however, comprised only 25.4% of all children and adolescents included in this study. Blunt trauma, sympathetic ophthalmia, and Fuchs' heterochromic cyclitis were diagnosed in 10, eight, and seven cases respectively. Manifestations confined to the eyes and demonstrating an important component of white dots (multifocal choroiditis, multiple evanescent white dot syndrome, presumed ocular histoplasmosis-like manifestation, acute posterior multifocal placoid pigment epitheliopathy and punctate inner choroidopathy) were diagnosed in 13 cases (table 6).

Of the 74 children with an associated systemic disease, JRA was diagnosed in 41 children. This is a prevalence of 55.4% among children with non-infectious aetiology and an associated systemic disease. JRA association however, comprised 22.3% of all non-infectious cases and only 14.9% of the entire group (table 7). Ocular Behçet's disease was diagnosed in 13 cases, 17.6% of 74 patients with associated systemic disease, 7.1% of 184 children with uveitis of non-infectious origin and 4.7% of the entire group. Other less frequent diagnoses are detailed in table 7.

DISCUSSION

In our study, 33.1% of patients (276 out of 821) diagnosed with intraocular inflammation (uveitis) during a period of 10 years were 18 years of age or younger. Although in most other studies patients up to 16 years of age were considered as ''children,'' we opted in the present study for an age extension up to 18 years and label this group as ''children and adolescents.'' We believe that this definition may be more appropriate. In Israel, this grouping also had practical aspects as the majority of 17–18 years olds undergo medical check ups including a thorough ophthalmology examination before their enlistment into the army. The one third ratio of children and adolescents with intraocular inflammation is much higher than that of previous reported estimates.[1–6] In our 276 patients (249 of whom were less than 16 years of age), 137 were boys and 139 were girls. The higher prevalence of girls in other studies may have resulted from the fact that in these reports, JIA was the most common cause for the uveitis.[14]

During the entire period of follow up, intraocular inflammation remained strictly restricted to one eye only in 29.7% of the cases while 70.3% either presented with a bilateral involvement or developed it later.

Routine visual acuity screening in kindergarten and school was the principal factor for referral of the younger children. This finding highlights the importance of periodic vision screening in schools.

An intraocular inflammation strictly confined to the anterior segment was observed only in 13.4% of the patients, a figure lower than that found in adult series[7–9 22] and much

Table 5 Non-infectious causes of all types

Organ involvement	No	Percentage	
		Non-infectious (184)	Total (276)
Eye only	110	59.8	39.8
Eye +*	74	40.2	26.8
Total	184	100.0	66.6

*The uveitis in these cases was associated with a definite systemic disease.

Table 6 Non-infectious causes affecting the eyes only

Diagnosis	No	Percentage		
		Eye only (110)	Non-infectious (184)	Total (276)
Idiopathic	70	63.7	38.0	25.4
Blunt trauma	10	9.1	5.4	3.6
Sympathetic ophthalmia	8	7.3	4.3	2.9
Fuchs' iridocyclitis	7	6.4	3.8	2.5
Multifoc. choroiditis	4	3.6	2.2	1.4
MEWDS	3	2.7	1.6	1.1
PIC	3	2.7	1.6	1.1
APMPPE	2	1.8	1.1	0.7
RP-Coats'-like	2	1.8	1.1	0.7
POHS-like	1	0.9	0.5	0.4
Total	110	100.0	59.6	39.8

lower than the figures published for children with uveitis.[1 14 23–25] These findings may derive from the strict limitation of definitions according to the anatomical classification of uveitis and the fact that the majority of our patients had a chronic condition when initially examined. On the other hand, panuveitis was observed in 30.8% of the cases, a figure comparable with that observed by others.[24]

In the present study, we were able to reach a workable diagnosis in 206 out of 276 (74.6%) of the children and adolescents with uveitis. An idiopathic diagnosis was made in only 70 (25.4%) of these patients (table 6). This relatively low incidence of an ''idiopathic'' diagnosis was, most probably, due to the tailored and individualised diagnostic approach.[18 19]

JIA as the associated aetiology of uveitis was ascertained in only 14.9% of these 276 children and adolescents with uveitis. This prevalence of JIA association seems a more realistic figure than the findings of 95% or even 40% as reported by others.[12–14 23] Despite the reported variations of JIA associated disease among children with uveitis, it is unanimously observed that girls are more affected than boys and the ocular complications and morbidity are high. In the present study, most severe ocular complications were associated with a female sex, an age of less than 4 years old when uveitis is detected and a pauciarticular manifestation (paper in preparation). In our group of patients, the prevalence of toxoplasmosis was much lower than that reported by others.[4 6 26 27] These differences may derive from the social and environmental factors of the patients included in the various studies. Diffuse unilateral subacute neuroretinitis (DUSN) has been suspected as another form of parasite involvement and cause of intraocular inflammation.[28 29] Involvement of parasites as an associated cause for uveitis, in our study, was based on suggestive laboratory results, clinical ocular manifestations and exclusion of any other potential cause for the intraocular inflammatory manifestations. In our population of children, *Oxyuris* and *Ascaris* infestation were identified as possible associated causes for the intraocular inflammation. Attempts to corroborate these clinical observations and associations are now under investigation in experimental animals.

Bacteria were a rare aetiology for the intraocular inflammation in our studied group. Although cat scratch disease (CSD) is associated with *Bartonella henselae*[30] and in rare instances to *Rochalimaea*,[31] the possible involvement of chlamydia was also raised. *Chlamydia* infection is a very rare cause of intraocular inflammation. They have been (and still are) suspected as being the infective agents responsible for the Reiter's syndrome (including uveitis). Furthermore, sporadic reports implicating *Chlamydia pneumonia* as the causative agent of uveitis have been published while a high frequency of IgA antibodies to Cpn Hsp60 have been interpreted to indicate a role of *Chlamydia pneumonia* in the pathogenesis of uveitis.[32]

Unlike the high incidence of HIV associated uveitis observed by others[8 33 34] none of our 276 children suffered from uveitis associated HIV disease. These findings illustrate best the possible discrepancies which may occur when patients from different countries and/or different cultures are compared.

Gaucher's disease as an underlying cause for uveitis is a rare association reported earlier.[35] The presenting symptom in

Table 7 Non-infectious, systemic disease-associated

Diagnosis	No	Percentage		
		Systemic (74)	Non-infectious (184)	Total (276)
JIA	41	55.4	22.3	14.9
Behçet's	13	17.6	7.1	4.7
TINU	4	5.4	2.2	1.4
Masquerade*	4	5.4	2.2	1.4
VKH	3	4.1	1.6	1.1
Sarcoidosis	2	2.7	1.1	0.7
Gaucher	2	2.7	1.1	0.7
Reiter's disease	2	2.7	1.1	0.7
Spondylitis	1	1.4	0.5	0.4
Juvenile psoriasis	1	1.4	0.5	0.4
Juvenile polychondritis	1	1.4	0.5	0.4
Total	74	100.2	40.2	26.8

*Three of these patients had acute lymphoblastic leukaemia (ALL) and were in remission when the ''uveitis'' was detected. Systemic examination disclosed a recurrence of the disease. Treatment induced remission of the systemic disease and ''clearing'' of the intraocular findings. The fourth case in this group had Langerhans cell histyocytosis.

one of the two children included in this study was bilateral uveitis and spontaneous hyphaema in one eye. The underlying Gaucher's disease was unveiled during the systemic evaluation of the child because of the unusual ocular presentation.

Our present study is in line with the possibility that the cause for the variable incidences of specific aetiologies for the intraocular inflammation reported in different studies is due to a ''pattern of changes in uveitis diagnosis'' rather than to ''changes in the pattern of uveitis.''[8 14]

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