Clinical and therapeutic characteristics of childhood uveitis in a tertiary center in Tunisia

Caracteristiques cliniques et therapeutiques des uveites de l'enfant dans un centre de troisieme ligne en Tunisie

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Abstract

Introduction: Childhood uveitis is a rare condition with various associated diagnostic and therapeutic challenges.
Aim : We proposed to describe the distribution, clinical findings, treatment, complications, and visual outcomes of uveitis in children at a tertiary referral center in Sfax, Tunisia.
Methods: A retrospective study of 33 children (54 eyes) with uveitis collected over the period from January 2009 to December 2018 was carried out at the Ophthalmology Department of Habib Bourguiba University Hospital, Sfax, Tunisia. The data from the clinical examination, the etiological assessment, and the used treatments were collected. Standard diagnostic criteria were used for all uveitic syndromes or entities.
Results: The mean age of the patients was 11.42 years with a male-to-female ratio of 0.74. Uveitis was bilateral in 63% of the patients. The most common anatomical form was intermediate uveitis (39%). Idiopathic cases accounted for 52%. The major complications were posterior synechiae, optic disc edema, cataract, and cystoid macular edema. Anti-infective treatment was prescribed in 24% of the patients. Oral corticosteroid therapy was used in 67% of the patients. 18% of the patients received immunosuppressive therapy and 6% received a biological agent. The mean final visual acuity was 4.6/10.
Conclusion: Childhood uveitis is a serious pathology with frequent and vision-threatening complications. The etiologies are variable and the assessment can remain negative. A rigorous diagnostic approach, an oriented etiological assessment in collaboration with the pediatrician, and an appropriate therapy are necessary for management.

Key words: Childhood uveitis ; Epidemiology ; Etiology ; Corticotherapy ; Immunosuppressive therapy

Résumé

Introduction: L'uvéite de l'enfant est une affection rare avec divers défis diagnostiques et thérapeutiques associés.
Objectif : Décrire la distribution, les aspects cliniques, le traitement, les complications et les résultats visuels de l'uvéite chez les enfants dans un centre de référence de troisième ligne à Sfax, en Tunisie.
Méthodes: Une étude rétrospective de 33 enfants (54 yeux) atteints d'uvéite colligés sur la période de janvier 2009 à décembre 2018 a été réalisée au service d'ophtalmologie du CHU Habib Bourguiba, Sfax, Tunisie. Les données de l'examen clinique, du bilan étiologique et des traitements utilisés ont été recueillies. Des critères diagnostiques standard ont été utilisés pour tous les syndromes ou entités uvéitiques.
Résultats: L'âge moyen des patients était de 11,42 ans avec un ratio homme/femme de 0,74. L'uvéite était bilatérale chez 63 % des patients. La forme anatomique la plus fréquente était l'uvéite intermédiaire (39 %). Les cas idiopathiques représentaient 52 %. Les complications majeures étaient les synéchies postérieures, l'œdème papillaire, la cataracte et l'œdème maculaire cystoïde. Un traitement anti-infectieux a été prescrit chez 24 % des patients. Une corticothérapie orale a été utilisée chez 67 % des patients. 18 % des patients ont reçu un traitement immunosuppresseur et 6 % ont reçu un agent biologique. L'acuité visuelle finale moyenne était de 4,6/10.
Conclusion: L'uvéite de l'enfant est une pathologie grave aux complications fréquentes et menaçantes pour la vision. Une démarche diagnostique rigoureuse, un bilan étiologique orienté en collaboration avec le pédiatre, et une thérapeutique adaptée sont nécessaires à la prise en charge.

Mots clés : Uvéite de l'enfant ; Epidémiologie ; Étiologie ; Corticothérapie ; Thérapie immunosuppressive

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INTRODUCTION

Childhood-onset uveitis are less common than uveitis in adults. They do represent 5 to 16 % of all uveitis (1). Their prevalence is around 30 per 100,000 children and their incidence varies, depending on the location of the study and the age groups, from 0.8 to 6 per 100,000 (2–4). Nevertheless, the disease deserves more attention because of the various diagnostic and therapeutic challenges associated with it. The spectrum of disease, disease manifestations as well as complications, may differ between children and adults.

The purpose of our study was to describe the distribution, clinical findings, treatment, complications, and visual outcomes of uveitis in children at a tertiary referral center in Sfax, Tunisia.

METHODS

This is a retrospective study of children with uveitis examined at the Ophthalmology Department of Habib Bourguiba University Hospital, Sfax, Tunisia from January 2009 to December 2018. We included patients who were 16 years of age or younger at the time of the consultation for uveitis and who were followed up during this period. We excluded pseudo-uveitis especially intraocular tumors, intraocular foreign bodies, Coats disease, hereditary retinal dystrophies, intravitreal hemorrhage, phacoantigenic uveitis, and endophthalmitis, and clinical records that lacked sufficient data to classify uveitis, specify its complications or etiology.

We collected data on gender, age, geographical origin, family and personal history, vaccination status, lifestyle, presenting symptoms, their onset and duration before the first consultation, and other extra-ocular functional signs. Every patient underwent a complete ophthalmic examination. The best corrected visual acuity was evaluated with the decimal scale. Statistical calculations were then based on the conversion into logarithm of the minimum angle of resolution (logMAR) units. Slit-lamp biomicroscopy, measurement of the intraocular pressure by Goldmann applanation tonometer, and dilated fundus examination were performed in all children. Fundus photography, fluorescein angiography, indocyanine green angiography, optical coherence tomography, visual field test, and ultrasonography were performed when needed. The “International Uveitis Study Group” criteria were used to classify uveitis anatomically into anterior, intermediate, posterior, or panuveitis. We also divided the uveitis into groups of granulomatous or non-granulomatous uveitis. The course of ocular inflammation was defined as acute, recurrent, or chronic. The etiological classification included infectious uveitis, uveitis associated with a non-infectious systemic disease, uveitis associated with a specific ocular entity, and idiopathic uveitis. The etiological assessment was based on a detailed medical history, an extensive review of systems, complete ophthalmic and physical examinations, and appropriate laboratory and ancillary tests. In the absence of an etiological orientation, a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), syphilis serology, tuberculin skin test (TST) and/or Quantiferon blood test, and a chest x-ray were performed. According to the clinical suspicion, other serologic and immunologic tests and further ancillary testing including radiology and biopsy were performed when indicated. Patients were co-managed by pediatricians according to the clinical situation. Standard diagnostic criteria were employed for all uveitic syndromes or entities.

We reviewed the medical, physical, and surgical treatments the patient received to treat either the uveitis or its complications or its causative systemic disease. Statistical analysis was performed using the statistical package for social sciences (version 20; SPSS Inc., Chicago, IL).

RESULTS

The clinical and demographic characteristics of our patients are shown in Table 1. A total of 33 children (54 eyes) were included in the study. The age of the patients ranged from 4 to 16 years, with a mean age at diagnosis of 11.42 years and a standard deviation of 3.79 years. The male-to-female ratio was 0.74. The most common reasons for consultation were decreased vision (61 %), eye redness (49 %), and pain (36 %). Uveitis was bilateral in 21 patients (63 %). Initial best-corrected visual acuity ranged from counting fingers at 10 cm to 10/10 (mean: 3.2/10). The most common anatomical form was intermediate uveitis (13 cases, 39 %) followed by anterior uveitis (12 cases, 36 %) then posterior uveitis (4 cases, 12 %) and panuveitis (4 cases, 12 %). Non-granulomatous uveitis occurred more frequently (18 cases, 55 %) than granulomatous uveitis (15 cases, 45 %).

Table 1. General characteristics and distribution of the patients

Parameter	Values {mean (range) or No (%)}
Mean age	11.42 years (range: 4–16 years)
Sex	
Male	14 (42 %)
Female	19 (58 %)
Site	
Anterior uveitis	12 (36 %)
Intermediate uveitis	13 (39 %)
Posterior uveitis	4 (12 %)
Panuveitis	4 (12 %)
Ocular involvement	
Unilateral	12 (36 %)
Bilateral	21 (64 %)
Chronology	
Acute	11 (33 %)
Recurrent	10 (30 %)
Chronic	12 (36 %)
Type of inflammation	
Granulomatous	15 (45 %)
Non granulomatous	18 (55 %)

Seventeen cases (52 %) were idiopathic in our series. An etiology was identified in 16 children (49 %). Infectious uveitis was found in eight cases (24 %); uveitis associated with non-infectious systemic disease was found in five cases (15 %) and uveitis associated with a specific ocular entity was found in three cases (9 %). The distribution of the etiological forms of uveitis varied according to the anatomical form and the difference was statistically significant (p = 0.035). We found in our series that herpetic uveitis and Vogt-Koyanagi-

Harada (VKH) disease were the most common specific etiologies identified. Table 2 lists anatomic and etiologic diagnoses. For the course of ocular inflammation, we found acute uveitis in 11 patients (33 %), recurrent uveitis in 10 patients (30 %), and chronic uveitis in 12 patients (36 %). We also found in our series a statistically significant variation (p = 0.049) in the course of uveitis depending on the etiological form. It was especially acute for infectious uveitis and uveitis associated with a specific ocular entity when it was mostly chronic or recurrent for uveitis associated with a non-infectious systemic disease and idiopathic uveitis.

Table 2. Prevalence of uveitic diagnoses

Anatomic diagnosis	Specific diagnosis	Number of patients	Total cases (%)
Anterior		12	36
	HSV	3	9
	VZV	1	3
	JIA	1	3
	Crohn's disease	1	3
	VKH	1	3
	Idiopathic	5	15
Intermediate		13	39
	Tuberculosis	1	3
	Systemic lupus erythematosus	1	3
	Multiple sclerosis	1	3
	Idiopathic	10	30
Posterior		4	12
	Toxoplasmosis	2	6
	Rickettsiosis	1	3
	VKH	1	3
Panuveitis		4	12
	Behçet's disease	1	3
	VKH	1	3
	Idiopathic	2	6

Complications were described in 44 eyes (82 %) in our series. They included posterior synechiae (50 %), cataract (24 %), and ocular hypertension (13 %) for the anterior segment and optic disc edema (41 %) and cystoid macular edema (17 %) for the posterior segment. The ocular complications described are summarized in Table 3. Anti-infective treatment was prescribed in eight patients (24 %). Corticosteroid therapy was used topically in 27 patients (82 %). Locoregional corticosteroid therapy was prescribed in four patients (12 %) including three intermediate idiopathic uveitis complicated by unilateral cystoid macular edema. Oral corticosteroids were used in 22 patients (67 %) who presented with intermediate or posterior uveitis and/or severity signs, especially with bilateral involvement. Corticosteroid dependence was found in 18 % of cases. Immunosuppressive therapy was initiated in six patients (18 %), in case of insufficient corticosteroid therapy, onset of corticosteroid dependence, or looking for corticosteroid sparing. Ciclosporin was used for VKH disease, methotrexate for juvenile idiopathic arthritis (JIA) and idiopathic uveitis, and azathioprine for Behçet disease and idiopathic uveitis. Two patients (6 %) received a biological agent. We used adalimumab for refractory cases with JIA and idiopathic uveitis.

Table 3. Ocular complications of uveitis

Complications		Number of eyes (Total=54)	Percentage (%)
Anterior segment	Cataract	13	24
	Band keratopathy	4	7
	Corneal opacities	2	4
	Ocular hypertony	7	13
	Posterior synechiae	27	50
	Pupillary seclusion	9	17
	Other complications	6	11
Posterior segment	Macular edema	9	17
	Optic disc edema	22	41
	Epiretinal membrane	8	15
	Retinal ischemia	2	4
	Choroidal neovascularisation	1	2
	Retinal or chorioretinal scars	2	4
	Rhegmatogenous retinal detachment	1	2
	Vitreoretinal tractions	4	7
	Vitreous organization	6	11
	Vasoproliferative tumour	1	2
	Other complications	5	9

Retinal pan-photo coagulation was performed in one patient (3 %) with Behçet's disease presenting with extensive retinal ischemia. Peripheral YAG laser iridectomy was performed in two patients (6 %) and surgical peripheral iridectomy was performed in one patient (3 %). One patient (3 %) underwent cataract surgery. Intra-vitreous injections of anti-VEGF were performed in one patient (3 %) for choroidal neovascularization complicating a macular toxoplasmosis scar. Intra-vitreous injections of anti-VEGF and cryo-application were performed in one patient (3 %) for vasoproliferative tumor complicating intermediate idiopathic uveitis.

The average follow-up was 21.18 months (range: 1-74 months). The final visual acuity ranged from the absence of light perception to 10/10 with an average of 4.6/10. A final visual acuity <1/10 (legal blindness) was found in five eyes (9 %). Causes of blindness in our patients included optic disc edema and/or atrophy, posterior synechiae, cataract, and vitreous organization.

DISCUSSION

It is difficult to accurately determine the exact frequency of childhood uveitis due to the different recruitment biases in studies. Nevertheless, according to a review of the literature (1) a frequency of 5 to 16 % of all uveitis can be retained. In Tunisia, a frequency of 9.8 % was described in a study by Khairallah et al (5) and 8.75 % in a study by Chebil et al (6). In our series, the mean age at diagnosis was 11.42 years. It is comparable to the results of most international and national series where the mean age varies between 7.8 and 12.4 years (5-12). We found a slight female predominance with a male-to-female ratio of

0.74. Some series in the literature have found concordant results (5,7,11) while a slight male predominance has been described in other series (6,8-10,12) that may be explained by a higher frequency of JIA in males. The laterality of involvement in childhood uveitis differs from one author to another. We noted in our series a predominance of bilateral forms in concordance with several series in the literature (4,7,13,14) whereas in other series unilateral forms were more frequent than bilateral forms (5,10,12). This finding may be related to the influence of identified etiologies in each series. The initial visual acuity in our series with a mean of 3.2/10 is close to that reported in the literature (5,7,8). The frequency of anatomical forms of uveitis in children is variable in the different series depending on the origin of the patients and their mode of recruitment. As in adults, anterior uveitis is, in a majority of studies, the most frequent form (30 to 58.4 % of cases), followed by posterior uveitis (13.8 to 50 %), intermediate uveitis (10 to 27.7 %) then panuveitis (5 to 21 %) (15). Some authors found an equivalent or a higher frequency of intermediate form than that of anterior uveitis such as Khairallah (31.25 % of anterior uveitis and 31.25 % of intermediate uveitis) and Abdellatif (27.1 % of anterior uveitis and 30 % of intermediate uveitis) (5,8). We found in our series a similar result with a slight predominance of intermediate uveitis compared to anterior uveitis (39 % and 36 % respectively). On reviewing the literature, we also note a modification of the anatomical distribution pattern of uveitis in children over time with a stronger predominance of anterior uveitis now than in the 1960s (15). Cunningham (15) reported a predominance of posterior uveitis (40 % to 50 % of cases) compared to anterior uveitis (30 % to 40 % of cases) in the child. Holland (16), Smith (13), and Kump (17) reported however a predominance of anterior uveitis. Kump (17) suggests that the higher proportion of anterior uveitis currently can be explained by a more frequent diagnosis of complications of JIA and that the decrease in the proportion of posterior uveitis is explained by a decrease in the frequency of toxoplasmic chorioretinitis through the development in the prevention, diagnosis, and treatment of toxoplasmosis, especially in congenital infections. 56% of the uveitis in our series were non-granulomatous. Khairallah (5) found a comparable result with a greater occurrence of non-granulomatous uveitis (71.8% of cases) against granulomatous uveitis (28.2% of cases) while granulomatous uveitis was predominant in the series of Loukil (12) (67.4% of cases).

The diagnostic strategy to adopt in childhood uveitis must follow a logical and systematic approach to avoid delayed care (18). The medical interview must be as precise as possible. It should be specified both during the first consultation and during the surveillance or recurrence: the anatomical form of the uveitis, the laterality, the granulomatous character or not, if it is a first episode or a recurrent form, and whether there is associated hypertonia, hypopyon or ocular complications. Associated systemic manifestations should be sought. It is then relevant to examine the child by a pediatrician when the diagnosis of uveitis is made. Before starting the etiological research and considering any treatment (especially corticosteroid therapy), it is necessary to eliminate pseudo-uveitis. They are mainly retinoblastoma, acute leukemia, metastases, juvenile xanthogranuloma, Von Recklinghausen's disease, Coats disease, hereditary retinal dystrophy, intraocular foreign body or intravitreal hemorrhage (19-21). Indeed, the visual or vital prognosis may be involved if these pathologies are ignored. The first step of the etiological assessment is then guided by the results of clinical examination to research orientation elements. When they are present, the complementary examinations will be oriented. In the absence of an etiological orientation, a minimal initial assessment will be practiced. It will include CBC, ESR, CRP, Antinuclear antibodies (ANA), HLA-B27 typing in non-granulomatous uveitis, Angiotensin-converting enzyme (ACE) assay, syphilis serology, TST and chest x-ray (12,21). A more in-depth para-clinical assessment will be carried out when this first assessment turns out to be negative. We also propose a diagnostic approach adapted according to the anatomical form of uveitis. The results of our series support the utility of this approach. We found that the etiological forms of uveitis in the child varied in a statistically significant way depending on the anatomical form. The difference in the incidence of presumed or defined etiologies of uveitis at different ages is probably the cause of a better classification of uveitis in children than in adults (22). In our series, an etiology was identified in 49 % of cases and was idiopathic in 52 % of cases. This result is close to that reported by many series in the literature where more than 50 % of childhood uveitis were idiopathic (4,7,17,22,23). In our series, uveitis was infectious in 24 % of cases. The proportion of infectious causes is still very different between Western countries and Middle Eastern or undeveloped countries. Ferrara reported in its series 3.49 % of infectious uveitis in the USA (7) while 26.83 % of children were diagnosed with infectious uveitis in the series of Gautam in India (9) and 25 % in the series of Khairallah in Tunisia (5). Two specific etiologies were the most frequent in our series, herpetic uveitis, and Vogt-Koyanagi-Harada disease. This result differs from one series to another. Anterior uveitis associated with JIA has indeed been reported as the most commonly identifiable specific cause of childhood uveitis in northern European countries and the United States (23). The vast majority of our patients have experienced one or more complications (82 % of eyes), in agreement with the proportions previously reported in other studies, confirming the higher percentage of complications in children than adults (5,7,14). Children can be at particular risk of complications, as the inflammation is often chronic and the diagnosis is often delayed due to the absence of expressed symptoms. In addition, children are more difficult to examine and treat. When the uveitis diagnosis is done on time and appropriate treatment is started early, only the initial severity of uveitis is a predictor of progression to complications according to Edelsten (24). The complications of the anterior segment most encountered in our series as well as in the literature were posterior synechiae, cataract, and ocular hypertonia (5,7,8,10,12). The rate of band keratopathy was however a little less. Macular complications (macular edema, epiretinal membrane) and optic nerve complications (optic disc edema, optic atrophy, optic disc neovascularization) were the most common posterior segment complications in our series as well as in the literature (5,7,8,10,12).

The cause should always be treated when it has been defined, particularly in the case of infectious uveitis. Anti-infective treatment should always be started before corticosteroid therapy. In the case of non-infectious uveitis, the choice of treatment will depend on the anatomical form of uveitis, its etiology, visual acuity, complications (including macular edema), the laterality of the involvement, and response to different treatments. Escalation therapy is carried out on a case-by-case basis depending on the course of ocular inflammation and under the direction of the ophthalmologist. Of course, collaboration with the pediatric team is essential for implementing and monitoring

treatment and its side effects (21,25,26). Surgical treatment is aimed at complications of uveitis. It is important to choose the ideal time to operate given the increased risk of surgery on inflammatory eyes but also to know the indications in time under penalty of intervening late and risking to have a poor functional result.

Vision loss has been described as more common in childhood uveitis than in that of adults (14). The frequency of legal blindness was 9 % in our series. This frequency can reach 26 % of eyes with pediatric uveitis in the literature (27). Several authors have examined the prognosis factors of childhood uveitis. And it has been shown that the young age at the beginning of uveitis, the severity of uveitis on the initial eye examination including the presence of initial complications, a longer duration of the course of uveitis, a longer delay before referral to a specialist, the anatomical form: posterior uveitis or pan-uveitis, and certain etiologies, especially JIA were all factors associated with a poor prognosis for childhood uveitis (13,14,18).

The retrospective nature of the study is one of the limitations of our study. In addition, the collection of data from only a tertiary referral establishment does not reflect the distribution of pediatric uveitis in the wider community. Indeed, a single episode of uncomplicated acute uveitis or common infectious uveitis, such as toxoplasmosis, is usually easily managed by the ophthalmologist in the community without the need to refer the patient to a specialized center. This bias is however common to most studies of childhood uveitis.

In conclusion, we will retain the diversity of childhood uveitis, in the mode of presentation, the characteristics of the disease, and its evolution mode. Most cases are idiopathic. Early and adequate diagnosis, rigorous ophthalmic and pediatric monitoring, and correct therapy are mandatory for good visual outcomes.

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