



Ocular Involvement in Chronic Inflammatory Disease in Children: About 55 Cases

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Abstract

Inflammatory ocular involvement is a frequent pathology in pediatrics, which is mainly associated with juvenile idiopathic arthritis, Behçet's disease and granulomatosis. Our study was conducted on a series of 55 cases, with ocular involvement associated with different chronic inflammatory diseases, collected in the department of pediatric rheumatology of the Children's Hospital of Rabat over a period of 15 years (2003-2018). The age at diagnosis of ocular involvement was 7.5 years for JIA and 8.8 years for Behçet. The sex ratio was 1.03, with a female predominance in oligoarthritis and a male predominance in Behçet's disease and juvenile spondyloarthropathy. Uveitis appears to be the type of ocular involvement most incriminated in the development of ocular complications as well as in the progression to blindness. The evolution was favorable in 69% of cases. The aim of this work is initially to highlight the epidemiological, clinical, biological, therapeutic and evolutionary particularities of this condition in order to better understand the clinical approach to the treatment of ocular involvement and to prepare training plans for residents and pediatricians with the aim of improving the quality of health care.

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Introduction

Ocular involvement is common in chronic inflammatory diseases of children. It is dominated by uveitis. It is a potentially serious pathology whose ophthalmological sequelae may jeopardize the visual prognosis of the child, not to mention the non-negligible impact on schooling and family life. The diseases involved are dominated by Juvenile Idiopathic Arthritis (JIA), essentially juvenile oligoarthritis, Behçet's disease and granulomatosis. Oligoarthritis is the most common form of JIA. The evolution of chronic uveitis is dreadful, and can lead to ophthalmological sequelae that can severely compromise the visual prognosis of the child. Ocular involvement is a serious element of the disease.

The aim of this work is firstly to highlight the epidemiological, clinical, biological, therapeutic and evolutionary particularities of this condition through 55 cases and then to compare our results with the data of the literature while noting the particularities of our series.

Methods

This is a retrospective, descriptive and analytical study of 55 cases of chronic inflammatory diseases including 24 cases of oligoarthritis, 23 cases of Behçet's disease, 5 cases of juvenile spondylarthropathy, 2 cases of articular polyarthritis without rheumatoid factor and 1 case of articular polyarthritis with rheumatoid factor, diagnosed in the pediatric IV department



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and in the pediatric rheumatology consultation of the Children's Hospital of Rabat over a period of 15 years (2003-2018).

Results

Our series is composed of 28 girls and 27 boys with a sex ratio (M/F) of 1.03 with a female predominance in oligoarthritis and a male predominance in Behçet's disease and Juvenile Spondyloarthropathy (JPS).

The most affected age group was between 6 and 10 years of age, and constituted 44% of the population. The average age at onset of the first symptom of the disease was 5.9 years and 8 years for JIA and Behçet's disease respectively. The average age at diagnosis of ocular involvement was 7.56 and 8.8 years for JIA and Behçet's disease respectively.

Ocular involvement was bilateral in 71% of Behçet's cases and in 56% of JIA cases. It was symptomatic in 81% of cases of Behçet's disease, whereas it was asymptomatic in 72% of cases of JIA. Ophthalmic signs included decreased visual acuity (25%), ocular redness (18%), tingling (7%), visual fog (5%), photophobia (4%), ocular pain (4%), diplopia (2%), and myodesopsia (2%).

Uveitis was the main ocular involvement, found in 74% of cases, and was essentially anterior in JIA, whereas it was generally posterior or total in Behçet. Optic neuropathy and retinal vasculitis were found specifically in Behçet's cases, in 24% and 20% of cases respectively.

Ocular complications were found in 52.7% of cases, of which 20% had Behçet's and 33% had JIA. They were inaugural in 30% of cases, of which 17% had JIA and 13% had Behçet's. While they were subsequent in 21% of cases. Ocular complications included iridocrystalline synechiae (31%) (Figure 1), maculopathy (18%), cataract (16%), glaucoma (9%), pupillary seclusion (3.6%) (Figure 2), chorioretinal atrophy (3.6%), optic atrophy (3.6%), vitreous opacities (1.8%), strip keratopathy (1.8%) (Figure 3), ocular hypotony (1.8%), vitreous hemorrhage (1.8%), retinal detachment (1.8%), retinal ischemia (1.8%), and vitreous detachment with collapse (1.8%). Blindness was found in 16% of cases. The age of onset of ocular involvement was younger in children with complications, as well as in cases that progressed to blindness. Male children appeared to be more likely to develop ocular complications as well as to progress to blindness than female children.



Figure 1: LAF photograph showing iridocrystalline synechiae in a child in our series with oligoarthritis.

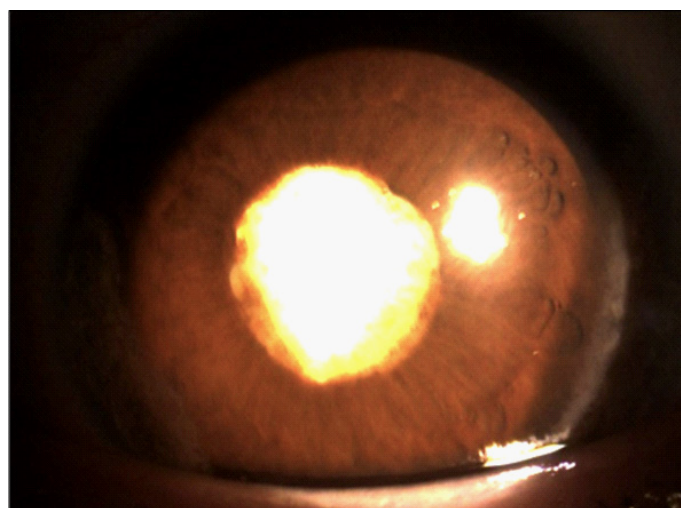


Figure 2: AFL photograph showing a complicated cataract with pupillary seclusion in a child in our series with oligoarthritis.

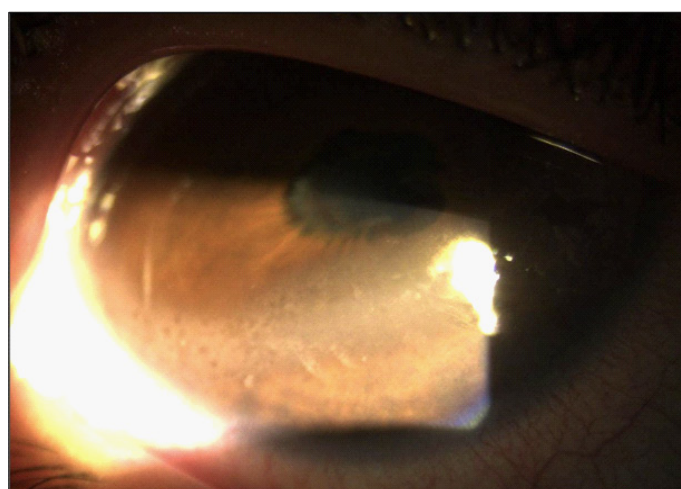


Figure 3: LAF photograph showing band keratopathy in a child in our series with oligoarthritis.

In terms of biology, an inflammatory workup was requested from all patients at the time of hospitalization. It was present in 85% of cases. HLA B51 and B15 typing was performed in 9 cases of Behçet, of which 1 case had a positive HLA B51 typing and 1 case had a positive HLA B5 typing. HLA B5 typing was performed in 3 Behçet cases, and it was negative. HLA B27 typing was performed in 4 cases of SPJ, of which 2 cases had positive typing. Fluorescein angiography performed in 7 children, showed papilledema in 2 cases, macular edema in 2 cases, vasculitis in 4 cases, retinal ischemia in 1 case, and macular atrophy in 1 case. Ocular ultrasonography performed in 3 children revealed vitreous detachment with collapse in 1 case, hypotonia with risk of phthisis in 1 case, and retinal detachment in 1 case. Optical coherence tomography performed in 3 children showed a large nonspecific macular lesion in 1 case. Other radiological and endoscopic explorations were performed according to the type of disease and extraocular manifestations (articular, neurological, vascular, digestive).

All Behçet cases received colchicine from the onset of the disease, 87% of whom also received platelet-aggregating acetyl salicylic acid. NSAIDs were prescribed in 62% of cases to treat joint inflammation. Systemic corticosteroid therapy was prescribed in 65% of cases, including 36% of Behçet cases, and 29% of JIA cases. Local ocular corticosteroid therapy was prescribed in 16% of cases. Local corticosteroid therapy by intra-auricular

infiltration was performed in 9% of cases with JIA, at the Pediatric Rheumatology Unit. Immunosuppressants were administered in 49% of the cases, of which 43% of the cases had Behçet and 53% of the cases had JIA. They were based on methotrexate, cyclophosphamide, azathioprine and cyclosporine A. Biotherapy based on anti TNF α (adalimumab and etanercept) and anti IL1 (anakinra) was prescribed in 29% of the cases, including 9% of the cases with Behçet's and 44% with JIA. Combined surgery of both eyes with implantation, trabeculotomy and application of mitomycin C was performed in 1 child with JIA. Whereas, surgery for cataract was indicated in some cases that had developed a cataract, but which will be performed in a lull period to avoid amblyopia. The evolution of ocular involvement had improved in 38% of cases, stabilized in 33%, and worsened in 20% of cases. The general evolution was marked by a remission in 16% of cases and a relapse in 29% of cases. It was favorable in 69% of cases. Ocular complications were developed in 52.7% of cases, whereas blindness was found in 16% of cases.

Discussion

Pediatric uveitis accounts for approximately 5% to 10% of all uveitis. Several studies in the United States, Europe, and the United Kingdom have reported an incidence of pediatric uveitis between 4.3 and 6 per 100,000, with a prevalence between 27.9 and 30 per 100,000. [1,2].

Antinuclear antibody (ANA) status in JIA appears to be independent of the development of ocular complications. Children who had an initial Tyndall in the anterior chamber more frequently developed ocular complications. An initial visual acuity of less than 2/10 would be a risk factor for the development of ocular complications, especially inaugural ones, as well as for the progression to cancer. The long duration of the evolution of the ocular disease would be a risk factor for the development of subsequent complications. The occurrence of ocular complications, particularly inaugural ones, would be a risk factor for progression to blindness. In our series, the extraocular manifestations of Behçet cases were dominated by cutaneomucosal manifestations, followed by articular, neurological, vascular, digestive, ureterological, and cardiac manifestations. In JIA cases, extraocular manifestations were dominated by articular manifestations.

In oligoarthritis, there is a female predominance with a sex ratio (F/M) of 2.4. Whereas, in Behçet's disease, the predominance was male with a sex ratio (M/F) of 2.2 [3].

Ocular involvement can occur from a few months to a few years (7 months to 8 years) before the onset of the disease in 6 to 12% of cases in the chronic inflammatory diseases studied. It can mark the beginning of the disease in 31 to 77% of cases. While it can develop during the course of the disease in 15 to 87% of cases, with a greater frequency in the first three years.

According to different series of studies, ocular involvement in Behçet's disease is bilateral in 44 to 100% of cases; While in JIA, ocular involvement is bilateral in 41 to 84% of cases [3].

In Behçet's disease, the inflammatory involvement of the anterior segment is mainly manifested by visual disturbances, ocular redness, periorbital or global pain, photophobia, and lacrimation; whereas, the inflammatory involvement of the posterior segment is usually manifested by decreased visual acuity with myodesopsias [4].

Juvenile oligoarthritis and rheumatoid factor-negative poly-

arthritis are characterized by inflammatory ocular involvement of chronic and insidious onset, irrespective of the severity of the uveitis [5]. In both forms of JIA, the dominant form of ocular involvement is chronic anterior uveitis, which is usually asymptomatic or occurs at a very young age for the child to reliably express the visual disturbances experienced. Often, uveitis is discovered only after complications have set in, following ocular symptoms such as ocular pain and/or redness, photophobia, vision changes, and headaches; or, by the parents' observation of an abnormal ocular appearance due to band keratopathy, cataract, or strabismus [6].

SPJ is characterized by acute and highly symptomatic ocular inflammatory involvement [7]. Acute anterior uveitis is the typical form of ocular involvement in PJS. It usually manifests as ocular pain and/or redness, photophobia, vision changes, and headache [6,7].

The most widely used classification is the one recommended by the IUSG (International Uveitis Study Group) in 1987, and also used by SUN Working Group (Standardization of Uveitis Nomenclature) in 2005. This classification is based on the anatomical location of the inflammation [8].

JIA is the most common systemic condition associated with pediatric uveitis, likewise Behçet's disease is a major cause [9]. In our series, uveitis was the most frequent ocular manifestation in all rheumatologic diseases studied, with a percentage of 74%.

Anterior uveitis was predominant in JIA, occurring in 78% of cases, whereas posterior uveitis and panuveitis were predominant in Behçet's disease occurring in 80% and 75% of cases, respectively. Intermediate uveitis did not exceed 12% of cases in the different diseases studied. These results are consistent with the literature, with minimal differences related to the geographic distribution of the chronic inflammatory diseases studied.

According to different series of studies performed mainly in regions where Behçet's disease is endemic, total uveitis is the most predominant form of uveitis, occurring in 24 to 100% of uveitis cases. While isolated posterior or anterior uveitis is less frequently encountered, occurring in 8 to 66% of cases [10].

Severe, chronic uveitis that is difficult to control is often accompanied by ocular complications and sequelae, which burden the child's visual functional prognosis, putting the child at risk of amblyopia or even blindness. These complications usually include iridocrystalline synechiae, cataract, glaucoma, maculopathy, strip keratopathy, and ocular hypotonia. Other rare complications are possible, depending on the chronic inflammatory disease involved, such as: vitreous opacities, retinal detachment, vitreous hemorrhage and retinal ischemia.

According to several studies, risk factors for the development of ocular complications as well as progression to blindness include male sex, young age at disease onset, young age at ocular involvement, short time between disease onset and ocular involvement, bilaterality of ocular involvement, initial visual acuity less than 2/10, initial presence of Tyndall in the anterior chamber, initial presence of ocular complications, chronicity of uveitis and disease [11-14].

Patients with JIA or Behçet's often present with a nonspecific inflammatory syndrome; Accelerated SV, increased CRP, PNN-predominant hyperleukocytosis, moderate inflammatory

anemia, thrombocytosis, or hyper fibrinogenemia. These biological parameters are of interest in monitoring the disease; the acceleration of the SV indicates the activity of the disease, and the CRP rises during relapses.

HLA B51-positive typing has been discussed as a prognostic marker of ocular involvement in Behçet. Some authors have found a frequently associated HLA B5 group with greater severity of ocular involvement. HLA B5/B51 typing during Behçet predisposes to a greater risk of ocular involvement [15]. The typical phenotype of HLA B27-positive uveitis is that of acute unilateral anterior uveitis, with a strong tendency to recurrence. Ocular complications are often associated with it. According to several studies carried out in different regional reference centers, more than 65% of the cases of HLA B27 positive uveitis had ocular complications [16].

Fluorescein angiography is the key examination to analyze the posterior segment elements. It allows the demonstration of retinal vasculitis, as well as its vascular complications (occlusive, ischemic, hemorrhagic and neovascularization). It allows the evaluation of macular and papillary damage, as well as the early detection of papilledema at the subclinical stage. It also allows visualization and description of retinal foci [17].

B-mode ocular ultrasound allows the visualization of two-dimensional sections of the eyeball. It becomes essential in the case of an inaccessible fundus, such as in the case of dense hyalitis, totally obturating cataract, or vitreous hemorrhage [18]. Optical coherence tomography should be requested in the presence of any stigma of posterior uveitis in search of macular lesions.

Inflammatory ocular pathology is a potentially serious condition, which can jeopardize the visual prognosis. It represents a major therapeutic challenge, particularly in the pediatric population. Treatment is based on local and general corticosteroid therapy, followed by immunosuppressants. Immunosuppressive drugs are indicated in cases of severe visual or vital prognosis, in cases of recurrent or chronic uveitis, for cortisone sparing or in cases of cortico-resistance or cortico-dependence. These treatments are prolonged and have the potential for significant toxicity, notably digestive, hematological or infectious. They therefore require close collaboration between ophthalmologists and pediatricians for the implementation and monitoring of treatments, their efficacy and their side effects [19].

Biotherapy now represents a therapeutic option in the management of uveitis refractory to conventional treatments, threatening visual function.

Biotherapy has revolutionized the management of pediatric inflammatory uveitis. It has marked a real turning point in the prognosis of certain severe forms, refractory to corticoids and immunosuppressants. It has transformed, also, the prognosis of children for whom conventional treatments were contraindicated or poorly tolerated.

In 2018, Adalimumab was granted marketing authorization for the treatment of chronic non-infectious anterior uveitis associated with JIA in children aged 2 years and older and adolescents, in cases of insufficient response or intolerance to conventional therapy or in whom conventional therapy is inappropriate [20].

The efficacy of Adalimumab (ADA) in the treatment of JIA-related uveitis, is amply demonstrated by multicenter, double-blind, placebo-controlled randomized trials, including, the

French ADJUVITE trial and the British SYCAMORE trial in 2017. The ADJUVITE trial confirms the efficacy and safety of ADA in JIA-related uveitis in failure of Methotrexate and local corticosteroid therapy and yet shows variable response kinetics [21]. Etanercept appears to be less effective due to less ocular penetration and is therefore not recommended in the treatment of pediatric uveitis. Adalimumab has better efficacy and tolerability compared with Infliximab in the treatment of refractory JIA-related uveitis in the medium term [22].

The course of ocular involvement depends on the inflammatory activity of the ocular involvement, the initial visual acuity, the presence or absence of ocular complications, and the degree of severity of the disease.

Behçet's disease in pediatrics, is characterized by total or posterior uveitis with retinal vasculitis, and manifests as a generally noisy picture. However, some uveitis is asymptomatic and only becomes symptomatic after the development of ocular complications, which may jeopardize the visual prognosis of the child. Therefore, when Behçet's disease is suspected, an ophthalmologic examination is necessary to detect any ocular involvement and ensure proper therapeutic management as early as possible.

JIA, particularly the oligoarticular form, is characterized by an often anterior, chronic, and insidious uveitis, which delays the diagnosis of ocular involvement and adequate therapeutic management. Therefore, all juvenile oligoarthritis must benefit from well-managed ocular surveillance in order to avoid the silent evolution of anterior uveitis towards total uveitis or even towards sequential ocular complications that can be blinding.

Conclusion

In order to provide an effective and well-conducted diagnostic and therapeutic approach to the child, a close collaboration between the pediatric rheumatologist and the ophthalmologist is required. Uveitis is a blinding pathology, which requires early detection, regular systemic follow-up especially for OA, given the insidious onset and evolution of uveitis, as well as effective, intense and timely therapeutic management. Biotherapy represents today a very interesting therapeutic option in the management of uveitis refractory to conventional treatments threatening visual function.

References

1. Guex-Crosier Y, Vaudaux J, Hofer M. Management of pediatric uveitis. *Paediatrica*. 2015; 26: 10-14.
2. Thorne JE, Suhler E, Skup M, et al. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. *JAMA Ophthalmol*. 2016; 134: 1237-1245.
3. Stoffel PB, Sauvain MJ, Vigier ROV, Beretta-Piccoli BC, Bianchetti MG, et al. Noninfectious causes of uveitis in 70 Swiss children. *Acta Paediatr*. 2000; 89: 955-958.
4. Reiff A, Kadayifcilar S, Özen S. Rheumatic inflammatory eye diseases of childhood. *Rheum Dis Clin N Am*. 2013; 3: 801-832 .
5. Petty RE, Rosenbaum JT. Uveitis in Juvenile Idiopathic Arthritis. *Textbook of pediatric rheumatology*. 7th edition. 2016; 11: 274-284.
6. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Best Practice & Research: clinical rheumatology*. 2018; 1-18.

7. Heidary G , Kazlas M, Pavan-Langston D. Manual of ocular diagnosis and therapy 6th ed. 2008; 11: 293-336.
8. Petty RE, Rosenbaum JT. Uveitis in Juvenile Idiopathic Arthritis. Textbook of pediatric rheumatology. 7th edition. 2016; 11: 274-284.
9. Foster CS. Diagnosis and treatment of juvenile idiopathic arthritis-associated uveitis. *Curr Opin Ophthalmol*. 2003; 14: 395-398.
10. Moal L, Rousseau A, et al. Pediatric uveitis in French ophthalmological and rheumatological referral centers: descriptive analysis of 61 children. *Oral communications / Revue du Rhumatisme*. 2016; 83: A81-A162.
11. Sabri K, Saurenmann RK, Silverman ED, Levine AV. Course, complications, and outcome of juvenile arthritis-related uveitis. *J AAPOS*. 2008; 12: 539-545.
12. Kone-Paut I. Behçet's disease in children, an overview. *Pediatric Rheumatology*. 2016; 14: 10.
13. Angeles-Han ST, McCracken C, Yeh S, Jenkins K, et al. Characteristics of a cohort of children with JIA and JIA-associated Uveitis. *Pediatric Rheumatology*. 2015; 13: 19.
14. Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with Juvenile Idiopathic Arthritis *Am J Ophthalmol*. 2007; 143: 647-655.
15. Maldini C, Cheminant M, Guillevin L, Lavalley MP, Mahr A. Impact of HLA-B5/B51 on the clinical phenotype of Behçet's disease: Systematic review of the literature and meta-analyses of genotype-phenotype correlations.
16. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol*. 2005; 50: 364-388.
17. Khairallah M, Ben Yahia S, R Kahloun, I Khairallah-Ksiasa, R Messaoud. Eye and Behçet's disease. *French Journal of Ophthalmology*. 2012; 35: 826-837.
18. Guex-Crosier Y, Vaudaux J, and Hofer M. Management of pediatric uveitis. *Paediatrica*. 2015; 26: 10-14.
19. N Stolowy, E Zanin, A Comet, Al Jurquet, C Benso, et al. Immunosuppressive therapy in severe or chronic pediatric uveitis: Review of the literature. 2021; 44: 252-258.
20. Hiyama T, Harada Y, Doi T and Kiuchi Y. Early administration of adalimumab for paediatric uveitis due to Behçet's disease. *Pediatric Rheumatology*. 2019; 17.
21. Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, et al. ADJUVITE: A double blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis*. 2017; 77: 1003-1011.
22. Cecchin V, Zannin ME, Ferrari D, Pontikaki I, Miserocchi E, et al. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2018; 45: 1167-1172.