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Uveitis In Children

Marieta Dumitrache[1*], Miruna Cioboată[2], M. Manea[3], Rodica Lascu[4]

[1]*Carol Davila" University of Medicine and Pharmacy, Bucureşti.*
[2]*Bucharest Ophthalmological Emergency Clinical Hospital.*
[3]*Carol Davila" University of Medicine and Pharmacy, Bucureşti.*
[4]*Misan Med Clinic, Sibiu*

***Corresponding Author**: *Marieta Dumitrache*, Carol Davila" University of Medicine and Pharmacy, Bucureşti

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Abstract

Uveitis in children is rarer than in adults, has variable clinical aspects, depending on etiopathogenesis, many forms are asymptomatic, and there can be difficulties in diagnosis and treatment. Uveitis in children can cause significant eye morbidity, with vision loss in 25/30% of cases, through complications, such as: cataract, glaucoma, band keratopathy. Uveitis in children is more frequently bilateral, with persistent, recurrent chronic evolution, resistant to conventional treatment and can be anterior, intermediate, posterior, panuveitis, acute or chronic. Juvenile idiopathic arthritis (JIA) is the most common cause of anterior uveitis in children 60% (girls, under 6 years old), in which uveitis is unilateral, non- granulomatous, with chronic evolution, associated with positive ANA. Uveitis in JIA has multiple complications and sequelae, with decreased vision. The prognosis of the disease is dependent on the establishment of an adequate early treatment in which the first line of therapy is topical, periocular, systemic, intravitreal corticotherapy, with possible side effects of steroid medication. Immunosuppressive treatment – the second line of therapy, is instituted if children do not respond to steroids, are cortico-dependent or have ocular and/or systemic complications – Methotrexate, Azathioprine, Cyclophosphamide, Cyclosporine, Chlorambucil, antiTNF alfa which are administered to patients at high risk of decreased vision – Infliximab, Adalimumab. The objective remains the treatment of complications: phacoemulsification in cataract with/without IOL (per primam, per secundam), medical and surgical treatment of glaucoma. Intermediate uveitis in children (10-25%) is manifested by myodesopsia, with a white eye, the most common etiology being idiopathic intermediate uveitis. Posterior uveitis represents almost 30% of cases, with multiple etiology, infectious inflammatory diseases (bacterial, viral, parasitic) non-infectious diseases (sarcoidosis, Behcet, VKH). Panuveitis in children may be present in acute tubulointerstitial nephritis in adolescents. Pseudouveitis is uveitis in retinoblastoma, leukemia. Uveitis in children is a serious disease, in which the diagnosis must be established quickly, with an appropriate (even aggressive) treatment, because the complications and sequelae present in the prolonged evolution of uveitis are accompanied by decrease/loss of vision. Ocular and systemic monitoring and screening of the disease are necessary for a favourable prognosis of the disease

Keywords: *anterior; intermediate; posterior uveitis; panuveitis, JIA; Behcet's disease; sarcoidosis; spondylarthropathies; corticosteroids; immunosuppressants; biological agents*.

Introduction

Uveitis is an inflammation of the uvea (iris, ciliary body, choroid), sometimes with a serious evolution, which can be associated with inflammation of the adjacent eye structures (cornea, sclera, retina, vitreous) and can be potentially disabling by reducing/losing vision.

Uveitis is an important cause of ocular morbidity and for a favourable prognosis it is necessary to establish a correct positive diagnosis and an adequate treatment to reduce ocular complications and sequelae, to preserve visual function.

SUN (Standardisation of uveitis nomenclature) classifies uveitis according to the anatomical criteria

in: anterior uveitis (iritis, anterior cyclitis, iridocyclitis), intermediate uveitis (pars planitis, hyalitis, posterior cyclitis), posterior uveitis (focal, multifocal choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis) and panuveitis with/without retinal, arterial or venous vasculitis. (1)

Evolutionarily, uveitis is acute (under 6 weeks), chronic (persistent over 6 weeks) and recurrent (repeated episodes of uveitis, separated by inactive periods of time ≥ 3 months, without treatment). (2)

Uveitis in children, with an average incidence of 5%, is rarer than in adults, 10-17%, and is a heterogeneous group of bacterial (staphylococcus, Klebsiella, TB, Lyme), viral (HSV, RNA, varicella, CMV) infectious inflammatory eye diseases, parasitic (toxoplasma, toxocara) and non-infectious of strictly ocular cause (idiopathic, sympathetic ophthalmia, Fuchs', Coats' disease) or associated with systemic diseases (JIA, Behcet, VKH, sarcoidosis), immune-mediated, some with genetic determinism. (3)

Table 1: Etiology of uveitis in children

Infectious - inflammatory uveitis			**Inflammatory uveitis**	**Idiopathic uveitis**
Bacterial	***Viral***	***Parasitic***		
Lyme	*HSV*	*Toxoplasmosis*	*JIA*	*30% of uveitis have unidentified etiology*
TB	*HZV*	*Toxocariasis*	*Spondyarthropathies / juvenileand ankylosing*	
Streptococcus, Staphylococcus	*Varicella*	*Onchocerciasis*	*Reiter's syndrome*	
	Rubella		*Psoriatic arthritis*	
			Sarcoidosis	
			Behcet, VKH	

Peculiarities of uveitis in children

Uveitis in children has variable aspects, depending on etiopathogenesis, and there may be difficulties in diagnosis and treatment.

The child with uveitis can be asymptomatic, even in the presence of severe eye inflammation, with the significant decrease in vision. This is the reason for which certain forms of uveitis can be discovered through an incidental ophthalmic check-up, or by parents who notice a decrease in vision or the presence of eye changes: cataracts, band keratopathy, which are irreversible eye complications. (4)

The decrease in vision in uveitis in children is greater than in adults, many forms of uveitis being more aggressive.

The diagnosis of uveitis in a child can be delayed as a result of insufficient communication abilities of the child and difficult clinical examination.

In children, anterior uveitis is more frequently encountered, but it can also be intermediate, posterior, panuveitis, uveitis producing significant ocular morbidity, with a decrease in vision in 25-30% of cases, through complications and sequelae. (5)

Uveitis in children is more frequently bilateral, often has a chronic, persistent, recurrent, treatment-resistant evolution, requiring adaptation of the treatment to the evolution of the disease and permanent monitoring for durable remission of the eye disease, without steroids, to reduce the risk of complications under treatment. (6)

The diagnosis of uveitis is confirmed by OCT, AFG, automatic perimetry, serology, radiology, microbiology, microscopic cytology, culture, PCR (polymerase chain reaction). Uveitis in children poses multiple diagnostic and treatment problems and requires early diagnosis and aggressive treatment to reduce the potential risk of complications and vision loss. (6) Unilateral uveitis in children carries a risk of amblyopia that must be identified and treated in a timely manner by therapeutic occlusion.

Early detection of uveitis and appropriate treatment reduce the potential risk of ocular complications: cataract, hypotony or glaucoma, band keratopathy, macular edema, papillary edema, choroidal neovascularisation.

The therapeutic management of the child with uveitis requires prolonged duration of treatment with the risk of side effects of the therapeutic administration – corticosteroids, immunosuppressants. Administering corticosteroids locally can induce cataracts, glaucoma, and systemically can have serious side effects: weight gain, hyperglycemia, osteoporosis, growth retardation, psychosis. (5,7,9)

Early positive clinical diagnosis is absolutely necessary in every child with uveitis, with the assessment of the stage of the disease, the appropriate treatment, but also the prevention of complications in the evolution of uveitis, with serious, definitive sequelae, with vision loss. (6,10)

In pediatric uveitis, a multidisciplinary therapeutic algorithm is necessary, through the clinical-therapeutic collaboration of ophthalmologist, pediatrician, rheumatologist, infectious disease specialist. (8)

A psychologist is recommended for the child and the family.

Table 2: Clinical forms of uveitis in children

IDIOPATHIC UVEITIS	**INFECTIOUS UVEITIS**			**NON-INFECTIOUS UVEITIS**	
	Bacterial	***Viral***	***Parasitic***	***Ocular***	***Associated with systemic diseases***
	Staphylococcus	HSV	Toxoplasmosis	Ankylosing spondylitis	JIA
	Klebsiella	CMV	Toxocariasis	Sympathetic ophthalmia	VKH
	TB	ARN		Post traumatic	Sarcoidosis
		Adenovirus		Coats' disease	Reiter's syndrome
		Chicken pox		MEWDS	
				POHS	

Table 3: Frequent forms of uveitis in children

TODDLER	**SCHOOL-AGE CHILDREN**	**ADOLESCENT**
HSV	*JIA*	*JIA*
Toxocariasis	*Toxoplasmosis*	*Parsplanitis, Toxoplasmosis*
	Toxocariasis	*HLA-B 27*
Retinoblastoma-RB	*VKH, Leukaemia*	*Behcet's disease*
		Intraocular foreign body
		Sarcoidosis (Blau syndrome)

Table 4: Anterior uveitis

ANTERIOR UVEITIS					
ACUTE			**CHRONIC**		
Unilateral		**Bilateral**	**ANA+**	**ANA-**	
HLA-B27+	*HSV*	*Interstitial nephritis*	*Non-granulomatous Idiopathic*	*Non-granulomatous Sarcoidosis*	*Granulomatous*
JIA	*Trauma*				*Sarcoidosis*
Psoriatic arthritis			*JIA*	*HSV*	*TB*

Table 5: Anterior uveitis in children (30-60%)

ACUTE	CHRONIC	
NON-GRANULOMATOUS	***NON-GRANULOMATOUS***	***GRANULOMATOUS***
Idiopathic	*JIA*	*Sarcoidosis*
Associated HLA-B 27	*Behcet's disease*	*Inflammatory bowel disease*
JIA		*HSV*
HSV varicella		*TB*
Psoriatic arthritis		*Behcet's disease*

Table 6: Intermediate, posterior uveitis

INTERMEDIATE	POSTERIOR	
	Without vasculitis	***With vasculitis***
Idiopathic	*Toxocariasis*	*CMV*
Parsplanitis	*Toxoplasmosis*	*HSV*
JIA	*Laukemia*	*Behcet's disease*
Sarcoidosis	*TB*	*LES*
	Intraocular foreign body	*Sarcoidosis*
	VKH	*Polyarteritis nodosa, Wegener's disease*

Table 7: Differential diagnosis, non-granulomatous, granulomatous uveitis

SYMPTOMS	NON-GRANULOMATOUS	GRANULOMATOUS
Onset	*Acute*	*Insidious*
Pain	*Important +++*	*Minimal absent*
Photophobia	*+++*	*Minimal*
Decreased VA	*Moderate*	*Important*
Perikeratic hyperemia	*+++*	*Minimal, absent*
Precipitates	*Fine, white*	
Pupil	*Small, irregular*	*Wide, gray "mutton fat"*
Posterior synechiae	*Thin, fine*	*Variable*
CA	*Mobile filaments, variable in number and size*	*Thick*
Iris nodules	*Rare, absent*	*+++*
Cloudy vitreous	*Absent*	*+ / -*
Eye fundus	*Diffuse edema*	*Nodular lesions*
Evolution	*Acute*	*Chronic*
Prognostic	*Good*	*Sometimes reserved*

Etiologically, the most common uveitis forms in children are: JIA, idiopathic uveitis, autoimmune, post-infectious, infectious uveitis, sarcoidosis, Blau syndrome, masked syndrome (retinoblastoma,

leukemia), traumatic uveitis.

Clinical therapeutic aspects of uveitis in children

Anterior Uveitis

Juvenile idiopathic arthritis JIA includes all forms of arthritis of unknown cause, occurring before the age of 16, with a minimum duration of 6 weeks. It is not hereditary, but may have genetic susceptibility with various trigger factors (possibly infectious). In JIA, HLA-DR 17% risk for the oligoarticular form was identified. HLA-A21, HLA DRB1-11, 1-08, related to the seronegative polyarticular form. (10)

JIA in children has a frequency of 4.9-6.9%, up to 13-30

Children under 7 years have a reserved visual prognosis.

Treatment requires the use of periocular, systemic steroids, which can reduce inflammation, but may have ocular and systemic side effects.

Discontinuous treatment with Infliximab, single or associated, favours disease remission.

Untreated or poorly treated intermediate uveitis has reserved visual potential with irreversible vision loss. (6)

Posterior Uveitis

It is the inflammation of the choroid, retina, +/- optic nerve and represents 25-30% of uveitis, the most common etiology being: toxoplasmosis, toxocariasis, CMV, Lyme, non-infectious uveitis in systemic diseases: sarcoidosis, Behcet's disease, VKH, idiopathic retinitis, tubulointerstitial nephritis. (9)

Sarcoidosis is a multisystemic disease of unknown etiology, present in the 8–15-year-old children (sporadically), characterized by the formation of granulomas at tissue level, ocularly associated with anterior chronic granulomatous uveitis, with "mutton fat" precipitates, with moderately severe inflammation of the vitreous, with intermediate uveitis. Children under 5 years old often have anterior uveitis, skin lesions, elbow-hand arthritis. Older children have adult-like uveitis. Intermediate uveitis can be present with moderate vitreous inflammation, snow ball, snow bank, exudates, choroidal granulomas (sarcoid), periphlebitis "headlight in the fog". (11)

Ocular manifestations in sarcoidosis are present in 20-30% of cases (2,3)

The anterior pole in sarcoidosis may present:

- nongranulomatous anterior uveitis, unilateral, with sudden onset, with adenopathy and erythema nodosum
- granulomatous, chronic, bilateral uveitis, with "mutton fat" precipitates, associated with chronic sarcoidosis, with pulmonary fibrosis uveopapillitis, Heerdfort syndrome, bilateral, granulomatous panuveitis, parotid gland involvement, cranial nerve palsy, rash, fever other ocular manifestations: conjunctival granulomas: dry eye, scleral nodules, cataract, glaucoma, papilledema, optic neuritis, muscle paralysis, proptosis

The posterior pole in sarcoidosis shows:

- retinal periphlebitis, retinal vascular occlusions
- granulomas in the choroid, retina, papilla, preretinal (Landers sign)
- retinal neovascularisation, CME

The treatment of ocular manifestations in sarcoidosis is complex and adapted to the evolving clinical aspect.

- Uveitis treatment – topically -mydriatic, cyclopegic, steroid therapy
- periocularly–subtenon Triamcinolone, 40mg, every 4 weeks
- systemically -oral steroid, prednisone 1mg/kg/day
- immunosuppressants – Methotrexate, Azathioprine, in recalcitrant forms, with chronic evolution and prolonged inflammation;

Ciclosporin in steroid-refractory forms.

- CME treatment – Epinephrine (drops), Acetazolamine, NSAIDs (orally, topically), topical, systemic, subtenon steroids (Metylprednisolone 80mg/ml, 0.5ml)
- medical-surgical treatment of neovascularisation, of glaucoma, differentiated according to the type of glaucoma (inflammatory, open-angle, post steroid, neovascular, closed-angle glaucoma).

Familial, juvenile, systemic granulomatosis – Blau syndrome. It is an autosomal dominant condition, characterized by glanulomatous polyarthritis, skin rash, granulomatous anterior uveitis. In young children, it can be considered infantile sarcoidosis.

Behcet's disease is a chronic, recurrent, multisystemic, rare inflammatory disease in children, with immunological determinism (autoimmune) in the possible presence of an infectious trigger.

The ocular manifestation in Behcet's disease is the anterior uveitis (iridocyclitis) with hypopyon, acute, recurrent, accompanied by serious sequelae and complications that cause vision loss. (19)

- posterior uveitis can be a determining factor for decreased vision, with progression to blindness, can be isolated or associated with: anterior uveitis (panuveitis), arterial or venous vasculitis, with

vascular occlusions generating retinal ischemia and neovascularisation, retinal hemorrhages, inflammatory or papillary ischemic edema, uni/bilateral, macular edema, CME.

The evolution of ocular manifestations in Behcet's disease is long (sometimes years), multiple, severe, recurrent, accompanied by complications.

The visual prognosis in Behcet's disease is reserved by the evolution and recurrence of the disease, by complications and sequelae. (19)

Treatment:

- inflammation control, through topical, systemic anti-inflammatory therapy
- topical steroids associated with mydriatics and cycloplegics
- systemic corticosteroids, sometimes combined with immunosuppression therapy
- immunosuppressants - Azathioprine, 2-2.5 mg/kg/day, Cyclosporine 3-5 mg/kg/day (contraindicated in Behcet's neurological determinations) - Cyclophosphamide, Methotrexate
- biological agents, antiTNF alpha: Infliximab 5m/kg/body, controls symptoms, minimizes recurrences, decreases corticosteroids, Adalimumab 40mg/2 weeks, in Infliximab intolerance
- Ophthalmological treatment of cataracts, ocular hypertension, vitrectomy if needed, laser photocoagulation, in ischemic areas
- Treatment of joint injuries: Colchicine, Azathioprine, Steroids (Methyl, Prednisone)
- Treatment of neurological lesions: Corticosteroids, Azathioprine, Cyclophosphamide

Vogt Koyanagi Harada syndrome (VKH) – multi-systemic, idiopathic, rare condition in children, where neurological manifestations are absent.

The ocular form presents anterior, granulomatous, recurrent, bilateral uveitis, with "mutton fat" precipitates, posterior synechiae, iris nodules, associated with posterior uveitis, papillary edema, Dalen-Fuchs nodules. Posterior uveitis is bilateral, suddenly associated with exudative retinal detachment, with a high decrease in vision. Exudative retinal detachment can be resorbed spontaneously or by systemic steroids. (2.3)

Long evolution, with complications: cataract 42%, secondary glaucoma 37%.

Treatment: intravenous Methylprednisolone 3 days, followed by oral Prednisone 1mg/kg/day.

Azatioprine, Mycophenolate mofetil, Methotrexate

Sympathetic ophthalmia is a granulomatous, bilateral panuveitis, rare in the child, in the second eye, when the first eye suffered a trauma in the region of the ciliary body; probably an autoimmune disease against the melanocytes of choroida, as a result of genetic predisposition. (1)

The clinical signs are serious, with anterior granulomatous uveitis, "mutton fat" corneal precipitates, posterior synechiae, iris nodules, associated with the posterior uveitis, hialitis, Dalen-Fuchs nodules, severe retinal detachment, papillary edema.

Treatment: corticosteroids, immunosuppressants, Azatioprin, Chlorambucil in recalcitrant forms; the recommended enucleation in the first weeks of trauma is currently controversial.

Toxoplasmosis is a parasitic disease produced by infestation with the toxoplasma gondii protozoan. Primary disease affects CNS and retina, having a predilection for nerve fibres.

Toxoplasmosis is the most common cause of pediatric posterior uveitis in the acquired form in 25% of cases. (1)

Acquired toxoplasmosis has multiple ocular manifestations, with anterior and posterior uveitis. The functional signs are related to the location of the outbreak.

Anterior uveitis is granulomatous, with "mutton fat" precipitates and the irido-crystalline synechiae.

Anterior uveitis in the acquired toxoplasmosis is associated with posterior uveitis, neuroretinitis, papillitis, possibly complicated by choroidal neovascularisation.

Treatment: Pyrimetamine, and Mycophenolate mofetil, (folic acid supplements), Clindamycin, Azithromycin, Trimotropin and Sulfamethoxazole to prevent recurrences.

Discussions

Uveites in children are rare: 3%, with a variable prevalence up to 10

Conclusions

Anterior, intermediate, posterior uveitis, panuveitis, are rare in children and have infectious etiology (bacterial, viral, parasitic), non-infectious etiology, strictly ocular, which is idiopathic uveitis (Fuchs', Coats' disease), or associated in system diseases (AIJ, spondyloarthropathy, sarcoidosis, Behcet's disease).

Pediatric uveitis is chronic, recurrent, with prolonged evolution and is accompanied by serious

complications: cataract, glaucoma, band *keratopathy,* decreased, loss of vision.

JIA is the most common cause of uveitis in the child, with an incidence of up to 30%, before the age of 16, asymptomatic, with white eyes, associated with chronic, oligoarticular arthritis, ANA+, RF-. The patient with uveitis should be diagnosed early and treated according to the stage of the disease, by regular check-ups (scheduled at 3.6,12 months) to limit and avoid the unfavourable evolution leading to vision loss.

Uveitis in JIA is anterior, unilateral, non-granulomatous, with chronic and complicated evolution, requiring judiciary, corticosteroid therapy, controlled for side effects, locally and systemically.

The second-line therapy in JIA consists of immunosuppressants - Methotrexate, *Azathioprine*, Cyclophosphamide, *Mycophenolate* mofetil and AntiTNF alfa, Infliximab, Adalimumab.

The treatment of complications requires the surgical treatment of cataracts with phacoemulsification with/without IOL, medical, surgical treatment of glaucoma, retinal detachment.

Anterior uveitis in children is also present in ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease.

Intermediate uveitis is rare in children and is present in the idiopathic uveitis in children under 7 years old, having a prolonged evolution and a reserved visual prognosis.

Posterior uveitis in children is complicated by the decrease of vision and have multiple and varied etiopathogenesis. The etiology is infectious, bacterial, viral, parasitic, or non-infectious associated with systemic diseases in sarcoidosis, Behcet's disease, VKH. It occurs sporadically, rarely in the child, with long evolution and complications.

Toxoplasmosis is the main cause of posterior uveitis in the child.

Pediatric uveitis has a chronic evolution, with complications and decrease/loss of vision, requiring aggressive, complex diagnosis and treatment with anti-inflammatory drugs, corticosteroids, immunosuppressants.

Prolonged monitoring of uveitis in the child is mandatory for improving the visual prognosis.

Conflicts of interests

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