



## Uveitis or not? Diagnostic doubts in the pediatric age group

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### ABSTRACT

Many localized and systemic diseases in children may occur with symptoms observed during uveitis, or symptoms that may imitate uveitis. These include neoplastic diseases, such as: leukemia, lymphomas, Langerhans cell histiocytosis, retinoblastoma, medulloepithelioma, uveal melanoma and non-cancerous illnesses: juvenile xanthogranuloma, retinal detachment, persistent hyperplastic primary vitreous, Coats' disease and pigment dispersion

syndrome. It is often difficult or even impossible to cooperate with young children during an ophthalmological examination, which makes the detection of subtle changes inside the eyeball even more challenging. The proper diagnosis may decide upon the right treatment at the early stage and thus improve the prognosis not only in terms of visual acuity, but also as far as the child's life is concerned.

**KEY WORDS:** pediatric, uveitis, masquerade syndrome.

### INTRODUCTION

Pediatric uveitis may involve single structures of the choroid, or the whole interior of the eyeball. The course of the disease may be acute, recurrent or chronic [1, 2]. Juvenile idiopathic arthritis is the most common etiological factor of anterior uveitis in children. Inflammation of the intermediate part is often idiopathic, while inflammation of the posterior segment is usually caused by toxoplasmosis [3].

The affected eye often remains pale and painless. Children rarely report their ailments, and even if they do, they happen to be ignored by adults [3]. They develop complications much earlier and they are usually more difficult to treat than in adults. The risk of amblyopia in the eye affected by the disease has to be considered. The lack of cooperation on the part of the child may significantly impede the examination and may be the reason for overlooking of, for example, a delicate exudate in the vitreous fluid [3]. In justified cases, ophthalmological examination is performed under short-term general anesthesia.

Some eye diseases in children may mimic uveitis, e.g., in retinoblastoma cancer cells imitating exudate, pseudohypopyon, are sometimes observed in the vitreous fluid, along with delicate gray deposits on the corneal endothelium, and nodules and congestion within the iris. Uveitis may also be secondary [4], e.g. to retinal detachment [1].

Due to the diversity of uveitis etiology and existence of diseases that should be differentiated from this disease, careful history of accompanying and past conditions, medications used by

the patient, as well as selected appropriate diagnostic tests and consultations play an extremely important role. The correct diagnosis may decide about the early introduction of appropriate treatment, and thus improve the prognosis not only regarding visual acuity, but sometimes also the child's life [1].

### SYMPTOMS OF UVEITIS

#### Anterior uveitis

Acute anterior uveitis lasts less than 6 weeks, and manifests with eye pain, photophobia, lacrimation, ciliary irritation of the eyeball, corneal deposits, miosis and posterior synechiae. Inflammatory cells and exudate may be present in the anterior chamber, that may take the form of purulent hypopyon. Visual acuity is usually moderately reduced [1].

Chronic anterior uveitis is often characterized by an insidious, asymptomatic course. Persistent corneal deposits may become saturated with dye. Symptoms of chronic inflammation are nodules of the iris, its neovascularization, heterochromia and atrophy [1]. Intraocular pressure may be lowered as a consequence of ciliary body failure, or elevated because of various mechanisms, including steroid treatment. Visual acuity may be significantly reduced as a result of complications: band keratopathy, cataract or cystoid macular edema [5].

#### Intermediate uveitis

Intermediate uveitis is a chronic disease manifested by insidious blur of vision with accompanying movable "floaters" [1, 5]. The affected eye often remains pale and painless.

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Small, diffuse deposits may occur in lower parts of the cornea. Posterior synechiae are rare. Characteristic symptoms of the disease include: presence of inflammatory cells in the anterior part of the vitreous body, “snowballs” (whitish, focal clusters of numerous inflammatory cells and exudate, most commonly found in the lower part of the vitreous body) and “snowdrifts” (gray-white, fibrous-vascular and/or exudative plaques, also most commonly seen in lower quadrants) [1]. Peripheral periphlebitis is quite common, especially in patients with multiple sclerosis. Occasionally, neovascularization occurs in the retina periphery, within “snowdrifts” or on the optic disc, which can lead to formation of an inflammatory membrane behind the lens, vitreous hemorrhage and retinal detachment. Other complications of intermediate uveitis include: cystoid macular edema – the main cause of decreased visual acuity, as well as cataract, edema of the optic disc, glaucoma and epiretinal membrane [1, 5].

### Posterior uveitis

Symptoms of posterior uveitis are: photophobia, floaters in the field of vision, decreased visual acuity, and metamorphopsias [1, 5]. In the course of acute inflammation, inflammatory cells are most abundant around the focus of inflammation, with no aggregates formed within the vitreous body.

During chronic inflammation clusters of inflammatory cells are observed, forming “snowballs”, spindles, “strings of pearls” or bands of connective tissue [1]. Fresh foci of retinitis and uveitis are white, convex, “fluffy” and blurred. Old post-inflammatory foci are flat or recessed, sharply limited, chalk-white or stained [5]. Inflammation may also involve venous and arterial vessels [1]. Complications include: macular edema, optic nerve involvement, vascular obstruction and retinal detachment resulting from serous, tear or traction mechanism, and late secondary choroidal neovascularization [1].

In children, many local and systemic disorders may involve or imitate symptoms seen during uveitis. Examples of neoplastic and non-neoplastic diseases are given below.

## NEOPLASTIC DISEASES

### Retinoblastoma

Retinoblastoma is the most common intraocular malignancy in childhood. The malignancy in approximately 1 : 18,000 live births [6]. RB1 tumor-suppressor gene mutations predispose to its development. The genetically determined type of retinoblastoma occurs in about 40% of cases – the majority

of tumors are bilateral and multifocal. Mutations in the RB1 gene are also responsible for other cancers: osteosarcoma, soft tissue sarcoma, melanoma and pineocytoma [1]. Non-genetically determined retinoblastoma usually develops unilaterally. It does not predispose to secondary malignant proliferation outside the eye [1, 6] (Table I).

Retinoblastoma often develops with symptoms reminiscent of those seen in uveitis. These are: presence of tumor cells in the ventricular fluid imitating exudate, pseudohypopyon, anterior chamber hemorrhage, delicate gray deposits on the corneal endothelium, and nodules and hyperemia within the iris.

The most common symptom of retinoblastoma is leukocoria, followed by strabismus. Insight into the fundus may be hindered by tumor cells diffused throughout the vitreous body. Retinal detachment, pre- and intraretinal infiltrates, and panuveitis have also been reported [5]. Visual acuity is reduced to varying degrees. There may be also accompanying secondary glaucoma and eye pain reported [5, 7]. A simple leukocoria screening test is to check for the absence of red glare from the fundus in direct ophthalmoscopy. Examination performed under general anesthesia should include: tonometry, corneal diameter measurement, anterior segment assessment, ophthalmoscopy with documented imaging of the fundus, and refraction after evoked paralysis of accommodation [1]. A general examination for birth defects of the face and upper limbs is also advisable [1].

Ultrasonographic examination of the eyeball allows you to assess the size of the tumor and the presence of characteristic calcifications within. Computed tomography (CT) also reveals calcifications, but its disadvantage is an exposure to a high dose of radiation [1].

Retinoblastoma growing in the form of diffuse retinal infiltration are characterized by a low incidence of calcifications, which hinders ultrasound and tomographic diagnostics [7]. Optical coherent tomography (OCT) shows the involvement of neurosensory retina, especially of photoreceptors and the external retina. These changes are clearly visible on early stages of tumor growth or on its front edge. In large and advanced tumors, the entire photoreceptor layer may become involved, but the underlying retinal pigment epithelial layer remains intact [8]. Fluorescein angiography is helpful in differentiating retinoblastoma from Coats disease, astrocytoma and toxocariasis. Transdural biopsy and biopsy through the pars plana are contraindicated because of the risk of dissemination of cancer cells [8]. Magnetic resonance imaging (MRI) is useful in tumor differentiation, and the assessment of the degree of infiltration of structures adjacent to the eyeball. The examination also allows the detection of pineocytoma.

In case of confirmed presence of metastatic disease, bone marrow aspiration and lumbar puncture should be performed [1]. A genetic test should also be performed of the tumor tissue and blood of the patient and his/her relatives. Patient siblings who are at risk of developing retinoblastoma should be subject to prenatal ultrasound screening. Ophthalmoscopic examination is performed soon after birth, then regularly repeated up to the age of 5 years [1].

**Table I.** Non-hereditary and hereditary form of retinoblastoma – differentiation

Non-hereditary form	Hereditary form
Early symptoms in 1-5 year of life	Early symptoms under the age of one year old
Usually unifocal	Usually multifocal
Usually unilateral	Usually bilateral
About 60% of patients	About 40% of patients
Secondary cancers do not occur	Risk of developing secondary cancers

## Leukemia

Malignancies of the hematopoietic system, mainly leukemia, are the most common pediatric cancers [9]. 95% of leukemia cases in this age group are acute forms, while 5% are chronic. A slightly higher prevalence of cancer is found in males [10].

Acute lymphoblastic leukemia (ALL) is diagnosed in the US twice as often in Caucasians than in non-Caucasians, and is the most common form of leukemia in children. In Poland, ALL is diagnosed annually in 30 out of 1 million children. It usually develops between 2 and 7 years of age [10]. A much greater predisposition to this form of leukemia is observed in children with chromosomal disorders and, primarily with chromosome 21 trisomy [11], as well as Fanconi aplastic anemia and ataxia-telangiectasia syndrome [10].

Early symptoms of the disease may be underestimated. They usually consist of: decrease in appetite, general weakness, fever, inflammatory changes in the throat and the nasal cavity, and skin pallor. Symptoms of hemorrhagic diathesis in the form of ecchymosis on the skin and mucous membranes are often observed, as a result of thrombocytopenia. They may also be accompanied by enlargement of peripheral and mediastinal lymph nodes, bone pain and hepatosplenomegaly [10].

Ocular changes are more common in acute than in chronic leukemia [1, 12]. They may affect all structures of the eye. Their occurrence is rarely caused by primary leukemia infiltration [1]. It can affect the choroid, orbital tissues, or spread from the central nervous system by infiltration of the optic nerve, cranial nerve palsy, giving symptoms of neuroocular disorders and causing edema of the optic disc [13]. Secondary lesions are more common, accompanied by anemia, thrombocytopenia, increased blood viscosity and opportunistic infections. They are manifested as ecchymosis and subconjunctival hemorrhages, bleeding into the anterior chamber, the vitreous chamber, as well as the pre- and intraretinal hemorrhages, with presence of bundles of "cotton wool" and venous thrombi [1]. Ocular changes may also be caused by side effects of drugs used and the graft-anti-host reaction in patients after allogeneic transplantation of hematopoietic bone marrow stem cells [14]. Some common leukemia symptoms resembling uveitis are also: presence of leukocytes in the ventricular fluid and the vitreous body, pseudohypopyon, and serous retinal detachment. Infiltrations of the iris and in the filtration angle can cause secondary glaucoma [5]. The presence of ocular symptoms in the course of leukemia is associated with less favorable prognosis, caused by myeloid recurrence or central nervous system involvement [15].

Blood cell count with leukocyte differentiation and determination of reticulocyte count are necessary diagnostic tests for confirmation of suspected hematopoietic neoplasm (usually anemia, thrombocytopenia and granulocytopenia are found). The total leukocyte count may be normal, decreased or elevated. The diagnosis of acute lymphoblastic leukemia is established solely on the basis of a bone marrow smear result [10]. Anterior ventricular and vitreous puncture or biopsy is rarely required to determine the presence of pleomorphic cells [5], e.g. in conjunctival infiltration [16].

## Hodgkin lymphoma

Hodgkin lymphoma, formerly called malignant granuloma, accounts for 30-50% of lymphomas in the pediatric population. The peak of incidence is observed for the age of 15-35 years and around 50 years of age.

The cancer is manifested by enlarged lymph nodes in the neck, less often in the mediastinum. Then, other groups of lymph nodes are involved, as well as the spleen, liver, bone marrow and lungs. In advanced disease, systemic symptoms may appear in the form of periodic fever, night sweats and itchy skin. Impaired cellular immunity occurring in the course of disease promotes frequent viral and fungal infections [10].

Symptoms of the disease may mimic granulomatous inflammation of the iritis and ciliary body with the presence of hypopyon. Hodgkin's lymphoma may be associated with retinopathy secondary to the accompanying infection [5].

## Non-Hodgkin lymphoma

Non-Hodgkin lymphoma accounts for 5-7% of all pediatric cancers. The peak of incidence is observed for patients between the age of 5 and 15 years. Boys are affected more commonly than girls (2.5 : 1). Only highly malignant and very rapidly progressing non-Hodgkin lymphomas are found in children.

Clinical symptoms depend on the location of foci of the disease [10]. In patients with central nervous system lymphoma, ocular symptoms may be the first notable symptoms of the disease. Usually they are unilateral at first, but with time they can become bilateral and include: large, irregular deposits on the corneal endothelium, cell bundles in the vitreous body, and perivascular retinal infiltrates. Extensive infiltrations of the choroid and iris, and secondary glaucoma have been reported in patients with systemic non-Hodgkin's lymphoma [5]. Massive necrosis associated with rapid tumor growth may be the cause of acute tumor lysis syndrome. Therefore, the suspicion of non-Hodgkin's lymphoma should prompt for urgent referral of a patient to a comprehensive oncological center [10].

## Medulloepithelioma

Medulloepithelioma is the second most common intraocular cancer in children [17]. It originates from epithelial cells of the ciliary body [18] and in rare cases also from the retina [19] and the optic nerve [19, 20]. The first symptoms are usually observed before the age of 10 [5]. The occurrence of this cancer is usually non-hereditary; however, a case related to mutations in the DICER1 gene and coexistence with pulmonary-pleural blastoma have been reported in the available literature [21].

This tumor is most often seen as a white, pink, brown or yellow mass within the ciliary body, behind the lens or in the anterior chamber [1]. The occurrence of cysts within the tumor tissue is characteristic. Those cysts can be seen in ultrasound images [22]. The most common symptoms of the cancer include: deterioration and loss of vision, pain, leucocoria, secondary glaucoma (as a result of iris neovascularization) and lens abnormalities [22], such as notch defect, lens subluxation, cataract and retrolenticular membrane [18, 22]. Spontaneous bleeding into the anterior chamber has also been reported [5].

Medulloepithelioma may occur in the benign or malignant form [1], but is usually characterized by slow, locally invasive growth [22]. Histopathological examination is necessary to make the diagnosis [12]. Cases of orbital infiltration and intracranial dissemination are associated with the worst prognosis for a patient's survival [22].

### Langerhans cell histiocytosis

Langerhans cell histiocytosis occurs very rarely, the morbidity is 2 : 1,000,000 per year [10] and is more common in boys than girls [23]. It is caused by excessive proliferation of histiocytes and Langerhans cells. In the generalized form, the first clinical symptoms occur most often before the age of 2 years, and in the localized form in older children [10].

Although it is a disease mainly occurring in childhood, it can develop in people of all ages. Its symptoms may include, among others: soft bulging of the skull (corresponding to bone loss), cradle cap difficult to remove, chronic oozing from ears, papular rash on the skin of the trunk, infiltration and soreness of gums, diabetes insipidus and feverish conditions [10].

Ophthalmic manifestation is reported in 10% of cases and most often affects the orbit [24]. The intraocular form of the disease may mimic anterior and intermediate uveitis [12]. Infiltration involving the conjunctiva, lacrimal caruncle, orbital tip, cavernous sinus, choroid, optic chiasm [23] and eyelids [23, 25] have also been reported.

Diagnostic methods helpful in the diagnosis of Langerhans cell histiocytosis include: imaging (X-Ray, CT, MRI) of flat and long bones, spine and lungs, blood cell count, albumin and bilirubin blood levels, ESR, as well as urinalysis and pathomorphological assessment of material collected from the lesion [10]. Depending on the age at which the first clinical symptoms appear and the number of tissues and systems involved, the disease may be very mild or fatal as a result of organ failure, especially liver and lung [10, 26].

### Uveal melanomas

Choroidal melanoma accounts for 80% of all uveal melanomas in adults and is the most common primary malignant intraocular tumor in this age group [1]. The cancer occurs rarely in children – only 1% of cases are found in patients under 20 years of age [27].

It may be the cause of bleeding into the vitreous body and of edema of the optic disc [28]. Sometimes, the tumor in the form of a focal, unstained choroid lesion imitates granuloma, e.g. in the course of sarcoidosis or tuberculosis. In turn, ciliary body melanoma with presence of sentinel vessels requires differentiation with scleritis and episcleritis. Secondary glaucoma has been reported as a result of dye dispersion and tumor invasion to the filtration angle [12]. Iris melanoma may mimic anterior uveitis (in the case of diffuse infiltration – heterochromic Fuchs uveitis) [12].

Regardless a patient's age, early diagnosis of cancer is associated with a lower risk of metastasis. For reasons not currently fully understood, the prognosis is slightly better in the pediatric population than in adults [29].

## NON-CANCER CONDITIONS

### Old hemorrhage to the vitreous body

Old hemorrhage to the vitreous body may require differentiation with uveitis [30]. The study published in 2006 (by Spirn *et al.*) presents the results of studies of 168 patients under 18 years of age (186 eyes), with hemorrhage to the vitreous body that was not a consequence of the active phase of retinopathy of prematurity [31].

The most common symptom observed in older children was a decrease in visual acuity, while in the younger – nystagmus and strabismus. In 73% of cases, hemorrhage was a consequence of trauma, most often blunt (29.6%) and penetrating (24.7%); 27% of hemorrhage cases occurred spontaneously (often as a result of retinopathy of prematurity in the regression phase), of which 90.5% were unilateral and 9.5% bilateral. Shaken baby syndrome was the cause of 50% of bilateral hemorrhages [31].

### Retinal detachment

Pediatric retinal detachment (PRD) accounts for 3.2-6.6% of all cases of detachment [32] and it differs in terms of etiology, characteristics and anatomical features, therapeutic management and prognosis from cases occurring in the adult population. Tear PRD is the most common type, and PRD occurring as a consequence of traction or exudate is less common [33].

The symptoms of retinal detachment similar to uveitis are: cells, hemorrhage, and pigment clusters scattered throughout the vitreous body, the so-called "tobacco dust" (Shafer's symptom), as well as low intraocular pressure. It should be borne in mind, however, that PRD is a possible complication of retinitis and uveitis, as well of inflammation of the flat part of the ciliary body [5]. Retinal detachment can also cause secondary anterior uveitis [1].

### Juvenile xanthogranuloma

Juvenile xanthogranuloma is a rare disease, most often affecting the skin and resulting from proliferation of histiocytes (non-Langerhans cells). It usually affects infants and children, although there are also cases reported in adults.

A relationship between juvenile myelocytic leukemia, neurofibromatosis type 1 and juvenile xanthogranuloma has been reported in the literature [34]. An increased risk of organ complications correlates with the presence of multiple skin lesions and age below 2 years of age, and most often is associated with the eye [34, 35]. Other non-dermal locations of changes include: the brain, lungs, spleen and liver. The incidence of ophthalmic symptoms of the disease varies considerably from less than 1% to even 10% of cases, depending on the report [36, 37].

The intraocular pathological process may affect the choroid, retina, optic nerve, orbit, and other structures of the eye, but most often affects the iris [37]. In a limited form, it appears as a small, yellowish nodule (or nodules). In the diffuse form, the nodule infiltrates the iris over a large area, causing heterochromia. Other symptoms resembling uveitis in juvenile xanthogranuloma include: pseudohypopyon and tumor cells in vitreous fluid. Spontaneous bleeding into the anterior chamber

is very characteristic of this disease. It is extremely important to differentiate the disease with bleeding in the course of trauma or other conditions (including blood cell count, determination of coagulation parameters, assessment of liver and kidney function). Secondary glaucoma, being a complication of bleeding into the anterior chamber, may cause a decrease in visual acuity because of corneal edema, accompanied by acute eye pain and photophobia [5].

Diagnosis of juvenile xanthogranuloma may be based on a biopsy of a skin lesion. Nonetheless, absence of skin changes is not sufficient to exclude the disease, as those lesions often undergo spontaneous regression [37]. Moreover, in 50% of patients, the skin is not affected at all, and eye problems are the first symptoms of juvenile xanthogranuloma [38]. In rare cases, a diagnostic biopsy of ocular lesions may be required [5]. The diagnostics should also be extended with orbital and ocular ultrasound examination and possibly also MRI of the head and orbit [37].

#### Persistent hyperplastic primary vitreous

Persistent hyperplastic primary vitreous (PHPV) is a congenital defect with no genetic background. Both the anterior and posterior types may cause the symptom of a white pupil. The anterior type is usually unilateral and is accompanied by microphthalmia of varying degree. The presence of fibrous membranes and persistent blood vessels within the vitreous body is characteristic [5]. Lesions observed in the posterior form of PHPV include: a fibro-vascular membrane extending from the optic disc towards the ora serrata, accompanying retinal detachment, presence of persistent vitreous artery, and of extracellular masses of various shapes. Both in the anterior and posterior types of PHPV, as well as in the course of uveitis, cataract, glaucoma and retinal detachment may occur [39].

#### Coats disease

Coats disease usually occurs in boys and young men (75% of cases) in the first and second decade of life. It is an idiopathic disease, in 90% of cases occurring unilaterally [40].

A characteristic feature of this disease is the presence of aneurysmal bloated foci, winding retinal vessels and extensive intra- and subretinal areas of yellowish exudate. Possible com-

plications of both Coats disease and uveitis include: exudative retinal detachment, lens opacity, iris neovascularization, and secondary glaucoma [5].

#### Pigment dispersion syndrome

Pigment dispersion syndrome (PDS) is most common in young Caucasian men with myopia.

The release of the pigment from the pigmented iris layer is accompanied by its accumulation on the surface of intraocular structures, such as the cornea, trabecular mesh as well as the lens and iris. Pigment molecules within the anterior chamber of the eye may mimic inflammatory cells [41], while coexisting iris atrophy can be mistakenly associated with uveitis in the course of Herpes simplex or Herpes zoster infection. In differentiation, it is important that atrophy is sectoral during viral infection, while in PDS pigment is released from the mid-peripheral part of the iris and is accompanied by formation of radial, fissure-like defects [1, 13, 41]. Pigment dispersion syndrome predisposes to ocular hypertension and pigmentary glaucoma [1].

#### CONCLUSIONS

Uveitis in children can cause severe visual impairment and even blindness. Cooperation with young patients during ophthalmological examination is often difficult or even impossible, which makes making the correct diagnosis a real challenge. In justified cases, ophthalmological examination is performed under short-term general anesthesia.

In children, many local and systemic disorders may involve or imitate symptoms seen during uveitis. These include cancer, such as leukemia, lymphoma and, Langerhans cell histiocytosis, retinoblastoma, medulloepithelioma and choroidal melanoma, as well as non-cancerous conditions, such as juvenile xanthogranuloma, retinal detachment, persistent hyperplastic primary vitreous, Coats disease and pigment dispersion syndrome.

The correct diagnosis can decide on early introduction of appropriate treatment and thus ensure maintenance of good vision, and sometimes save a child's life.

#### DISCLOSURE

The authors declare no conflict of interest.

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