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Current diagnostic options in uveitis – a review of the literature

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ABSTRACT

Most cases of uveitis in the pediatric population with an identifiable etiology are non-infectious (67.2–93.8%) and occur in the setting of severe systemic disease. Collaboration among physicians of different specialties and a wide range of specialized diagnostic tests are essential in determining the correct diagnosis of the disease entity. Children are at greater risk of developing serious ophthalmic complications that can threaten vision, interfere with normal childhood development, and lead to severe disability. Therefore, it is important to diagnose the disease at an early stage. A reliable diagnosis allows the implementation of appropriate therapy, which can prevent the occurrence of further complications. The authors of this study reviewed the current literature (2018–2023) in PubMed and Google Scholar, outlining the current diagnostic options for uveitis.

Keywords: uveitis in children; etiology of uveitis; diagnostics of uveitis in children.

INTRODUCTION

Most cases of uveitis in the pediatric population are idiopathic (40%) and non-infectious (67.2–93.8%) [1]. The most common identifiable cause is juvenile idiopathic arthritis (JIA). In addition, uveitis develops in approx. 10–45% of patients with this condition [2]. It should be emphasized that in the pediatric group, a holistic approach to the etiology of the condition, requiring multidisciplinary cooperation, is particularly important because uveitis in children is more often associated with diseases of other organs than in the adult population [3]. Recognition of concomitant systemic disease is often a crucial process for the application of appropriate therapy. Uveitis in the course of many diseases precedes the onset of symptoms from other organs, and therefore its early diagnosis, correct classification, and inclusion in treatment are predictive indicators of the further development of the disease and the appearance of organ complications. Establishing the correct diagnosis of the causative disease entity for uveitis is often delayed due to difficult cooperation with the pediatric patient, often in the absence of other organ manifestations. If warranted, an extensive ophthalmologic examination can be performed in infants and young children under short-acting general anesthesia.

MATERIALS AND METHODS

The authors of this study reviewed the current literature (2018–2023) in PubMed and Google Scholar search engines, outlining the current diagnostic options for uveitis. Search terms included: uveitis in children, etiology and diagnosis of uveitis in children, indocyanine and fluorescein angiography, optical coherence tomography (OCT), fundus autofluorescence (FAF), ultra-widefield imaging (UWF), optical coherence tomography angiography (OCT-A). In addition, the references cited in the identified articles were reviewed to identify additional reports. From the group of available articles, we selected only those that contained the most recent data on the use of the diagnostic and laboratory methods described below in the diseases listed below, which comprised 58 articles used to write this article. Because of the wide etiologic spectrum of uveitis pathogens, current diagnostic methods for selected diseases most commonly seen in pediatric patients are described below.

Toxoplasmosis

Diagnosis of toxoplasmic uveitis is based on characteristic symptoms on ophthalmoscopic examination of the fundus (creamy white, exudative focal retinitis and choroiditis, retinal and choroidal scarring), which are confirmed by the following laboratory tests [4]: polymerase chain reaction (PCR) method, serological methods, immunohistochemical identification of the parasite (i.e. immunoperoxidase staining), *in vitro* culture and, rarely, detection of the protozoan parasite antigen in serum and body fluids, as well as the skin test for toxoplasmin and antigen-specific lymphocyte transformation. Several serologic techniques are used, including: Sabin–Feldman dye test (DT), indirect fluorescence assay (IFA), direct agglutination test (DAT), differential agglutination test (HS/AC test), latex agglutination and indirect agglutination test (LAT test), immunosorbent agglutination test (ISAGA), immunochromatographic tests (ICT), enzyme-linked immunosorbent assay (ELISA), IgG avidity test, and Western blot analysis (WB). The most appropriate method for detecting antibodies to *Toxoplasma* spp. classes IgA, IgG, and IgM is ELISA, which can discriminate between recent and past infection [5]. When non-invasive methods fail

to make a definitive diagnosis, invasive diagnostics are used, which involve sampling for the detection of *T. gondii* by PCR. This is the main method used in congenital infections, ocular inflammation, and in immunocompromised patients, including organ transplant recipients and human immunodeficiency virus (HIV)-infected patients.

Recently, a study on dual-target PCR (B1, Rep529) has been published. The clinical use of this test for intraocular fluid testing increases the sensitivity of the method without losing specificity [6]. The most appropriate sample for detection of *T. gondii* DNA is the vitreous body, since it is in contact with the posterior chamber where infection occurs. However, the most commonly used sample is aqueous humor because it is easier, cheaper, and safer to obtain than vitreous fluid [7].

Herpes simplex virus

Diagnostic criteria for herpes simplex virus (HSV)-induced uveitis developed by the Standardization of Uveitis Nomenclature (SUN) Working Group include unilateral anterior segment uveitis with: (i) a positive aqueous PCR test for HSV, (ii) sectoral iris atrophy in a patient ≤50 years of age, or (iii) HSV-induced keratitis. Exclusion criteria include varicella and hemiparetic virus infections, cytomegalovirus, syphilis, and sarcoidosis. Serologic testing has a low positive predictive value due to its widespread presence in the general population [8]. Polymerase chain reaction test detects the virus in the active phase of replication. A disadvantage of the method may be the need for repeated anterior chamber punctures due to numerous false-positive results, especially with concurrent antiviral treatment. Polymerase chain reaction is more effective than viral culture due to faster results, higher sensitivity, and Goldmann–Witmer ratio analysis (helps determine intraocular production of pathogen-specific antibodies). A favorable response to empiric treatment may also be diagnostically helpful. Metagenomics next generation sequencing (mNGS) is emerging as a promising technology. It compares DNA or RNA extracted from small intraocular samples with large sequenced databases to identify e.g. HSV [9].

Cat-scratch disease

Uveitis develops in 36% of cat-scratch disease (CSD) cases in all age groups [10]. Because of the wide range of symptoms associated with CSD, laboratory tests play a key role in making a definitive diagnosis. Diagnostic methods include serologic testing (anti-*Bartonella henselae* IgM and/or IgG antibodies detected by enzyme immunoassay) and PCR testing for *B. henselae* [11]. These methods have limited specificity and sensitivity because of the difficult growth conditions of the host strain and the difficulty of isolating *B. henselae* from serum. Establishing the child's exposure to animals may be helpful in making the diagnosis. Metagenomics next generation sequencing is currently considered the most sensitive method, providing valuable sequence information in a single run with minimal sample input. The use of this method is relatively infrequent due to excessive cost and insufficient availability of the test [12].

Ocular tuberculosis

Positive immunological tests, together with the characteristic ocular phenotype, allow the diagnosis of ocular tuberculosis (OTB). Immunological tests used in tuberculosis diagnosis include the purified protein derivative (PPD) skin test (detects skin hypersensitivity to mycobacterial antigens) and interferon gamma release assay (IGRA) – tests interferon-γ (IFN-γ) release after stimulation of patient's lymphocytes with *Mycobacterium* tuberculosis (MTB) specific antigens: ESAT-6 and CFP-10; the QuantiFERON-TB Gold In-Tube test also has the TB7.7 protein. Positive test results are unreliable in the absence of clinical symptoms. The gold standard is the direct detection of OTB in tissues or fluids. Unfortunately, results from ocular specimens (culture or smear) are difficult to interpret due to the insufficient amount of specimens collected for testing and the low mycobacterial content. A 2013 study by Sharma et al. describes the use of multidirectional PCR for OTB diagnosis, which allows simultaneous amplification of 3 OTB-specific targets: IS6110, MPB64, and protein B [13]. However, most current studies are based on novel nucleic acid amplification techniques: the GeneXpert MTB/RIF assay, the line probe assay (LPA) and the GenoType MTBDRplus. These methods provide extremely useful information on drug resistance [14]. Techniques used to detect a phenotype suggestive of OTB and to monitor disease progression include indocyanine angiography (ICGA), OCT, fundus fluorescein angiography (AF), FAF, UWF, and OCT-A. Indocyanine angiography imaging (used with the highest efficiency) covers both the choroid and the choroidal stroma. Full thickness tuberculosis involving the uveitis in late stages remains hypofluorescent. Partial thickness tuberculosis (not involving the capillaries) shows hypofluorescence in the early and intermediate stages, but becomes isofluorescent in the late stage. This test is also used to identify choroidal neovascular membranes, which may complicate choroidal scarring or retinal vascular proliferation [15].

Uveitis associated with juvenile idiopathic arthritis

The diagnosis of uveitis developing in the course of JIA is based on the detection of characteristic signs (inflammatory cells in the anterior chamber, protein leakage into the anterior chamber due to damage to the blood-aqueous humor barrier, and saddle-shaped corneal deposits and iris nodules) under the slit lamp. The standardization criteria of the SUN [16] allow us to determine the location, course, and severity of uveitis. The differential diagnosis should include arthropathy associated with inflammatory bowel disease, infections (Reiter's syndrome, CSD, HSV, Epstein–Barr virus, HIV), rheumatic diseases (systemic lupus erythematosus – SLE, nodular arteritis), vasculitis (Kawasaki disease, Behçet's disease – BD, Henoch–Schönlein purpura, granulomatosis with vasculitis), and other diseases: tubulointerstitial nephritis and uveitis (TINU) syndrome, sarcoidosis, Blau's syndrome, chronic infantile neurological, cutaneous and articular syndrome. Screening for uveitis in patients with JIA is recommended. The American College of Rheumatology guidelines [17] provide the following recommendations – screening should be performed every 3 months for those at high risk of

developing uveitis and every 6–12 months for those at intermediate or low risk [18, 19] – Table 1.

TABLE 1. American College of Rheumatology guidelines for screening for uveitis in the course of JIA [17]

High risk of developing uveitis	Medium or low risk of developing uveitis
children with positive ANA test results	children with negative ANA test results
age of onset less than 7 years	age of onset greater than 7 years
arthritis evolution treatment for the first 4 years	after the first 4 years of developing arthritis
polyarthritis/ RF-negative polyarthritis/ psoriatic arthritis/ undifferentiated arthritis	non-articular inflammation/ RF--negative polyarthritis/ psoriatic arthritis/ undifferentiated arthritis
	systemic, multi-joint JIA with positive RF
	arthritis associated with tendonitis
	any form of JIA associated with the HLA-B27-positive genotype

ANA – antinuclear antibody; RF – rheumatoid factor; JIA – juvenile idiopathic arthritis; HLA-B27 – human leukocyte antigen B27

Ocular sarcoidosis

The gold standard for the diagnosis of sarcoidosis is histologic evidence of non-serous epithelioid giant cell granuloma. Intraocular biopsy is associated with a high risk of complications and its diagnostic value is still controversial [20]. Diagnostic criteria for sarcoidosis-associated uveitis were proposed by the International Workshop on Ocular Sarcoidosis (IWOS) in 2017. In addition to histologically confirmed sarcoidosis, the group defined presumptive ocular sarcoidosis (SO) in the presence of bilateral hilar adenopathies and probable SO in the absence of these adenopathies. Diagnostic criteria for sarcoidosis-induced uveitis, combining the characteristic ophthalmic picture with sarcoidosis symptoms, were developed by the SUN group in 2021 [21] – Table 2.

TABLE 2. Classification criteria for sarcoidosis-induced uveitis according to Standardization of Uveitis Nomenclature (SUN) Working Group [21]

No.	SUN classification criteria for sarcoidosis-induced uveitis
1	clinical picture characteristic of sarcoidosis-associated uveitis: • frontal segment uveitis, or • intermediate or front/intermediate uveitis, or • posterior segment NPS with associated choroiditis, or • uveitis with choroiditis or retinal vasculitis or retinal vascular obstruction
2	evidence supporting sarcoidosis: • presence of non-serous granulomas found in tissue biopsy, or • bilateral hilar adenopathy on chest imaging
3	exclusion criteria: • positive serology for syphilis using a spirochete test, • confirmed *Mycobacterium tuberculosis* infection

When uveitis is suspected in SO, diagnostic workup including complete blood count (CBC), C-reactive protein, serologic tests for syphilis and tuberculin skin tests (or IFN-γ release tests, IGRA), and chest imaging with computed tomography (CT) scans are recommended as an option [22]. Considerations for the use of 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) for this purpose are also described, particularly in cases of suspected extrapulmonary involvement in this disease [23]. Reports on the presence of SO-specific biomarkers in serum can be found in the literature. However, they are not sufficient to establish a definitive diagnosis. Lymphopenia appears in the IWOS criteria (sensitivity and specificity against sarcoidosis are 75% and 77%) [24]. Angiotensin converting enzyme (ACE) is the best-known and most widely used marker: sensitivity 38.2–84%, specificity 83–97.8% [25, 26]. The co-occurrence of elevated serum ACE and lymphopenia in patients with granulomatous uveitis strongly suggests the diagnosis of sarcoidosis. At the same time, the absence of these markers has a high negative predictive value (89.5%) [27, 28].

Blau syndrome

Ocular symptoms affect 60–80% of patients with Blau syndrome (BS) and may precede skin and joint involvement. The most common symptom is anterior segment BS, which is bilateral. Fundus imaging can reveal the presence of vascular leakage due to retinal vasculitis and macular edema. Perivascular nodular growths have been observed in more than 75% of eyes [29, 30]. The differential diagnosis should include sarcoidosis, JIA, BD, and tuberculosis [31, 32]. Other tests used in the differential diagnosis include AF, ICGA and OCT. Lesions to exclude BS in patients with OTB and sarcoidosis include retinal vasculitis and optic neuritis with hyperfluorescence in AF and active inflammation and granulomas of the choroid manifested by hypofluorescence in AF and ICGA [33]. In 2021, the importance of anterior segment OCT (AS-OCT) in patients with BS was described [34]. Anterior segment optical coherence tomography showed highly reflective layers in the anterior cornea and hyperreflective changes in both the aqueous humor and the posterior corneal surface; AS-OCT is a valuable non-invasive tool that may improve the diagnosis of retinal and corneal lesions in children with BS. The diagnosis of BS is confirmed by genetic testing for mutations in nucleotide-binding oligomerization domain 2 (NOD2). The most common mutation is the R334W mutation in the *NOD2* gene. Other reported mutations include E600K, Y563S, and M513T [30]. If a child is diagnosed with BS, genetic counseling should be offered to the family [33].

Tubulointerstitial nephritis and uveitis syndrome

The SUN Working Group has proposed criteria for the classification of TINU syndrome. They recommend that the presence of anterior segment non-small cell lung cancer (NSCLC) and tubulointerstitial nephritis – TIN (confirmed by renal biopsy or abnormal renal function tests) should be classified

as TINU syndrome if syphilis and sarcoidosis have already been excluded [35]. The correct diagnosis can only be made on the basis of a positive renal biopsy. Laboratory findings include normochromia, normocytic anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and elevated C-reactive protein levels [36]. Other findings include unexplained acute kidney injury and progressive decline in glomerular filtration rate [37]. Urinalysis often shows sugaruria, aminoaciduria, acidosis, and biomarkers of tubular damage such as N-acetylglucosaminidase and β2-microglobulin (B2M). A positive correlation has been found between urinary B2M levels and histological grade of TIN in children, and it has been proposed to use this diagnosis in screening for TINU syndrome [33]. At present, no diagnostic option using genetic techniques has been described. However, it has been noted that human leukocyte antigen-DR isotype (HLA-DR) DQ class II DNA typing may be useful for diagnosis in cases of recurrent or atypical uveitis where renal impairment has not been investigated or identified. There are reports of the use of diffusion-weighted magnetic resonance imaging (DW-MRI) in the early stages of renal involvement. This method is safe in children, which may have implications for future diagnostic development in this direction [38]. The differential diagnosis should include sarcoidosis, Sjögren's syndrome, SLE, Wegener's granulomatosis, Behçet's syndrome, infectious diseases (syphilis, tuberculosis, brucellosis, toxoplasmosis, and histoplasmosis) [37].

Behçet's disease, Behçet's uveitis

The SUN group has proposed classification criteria for Behçet's uveitis (BU) that include a diagnosis of BD based on the International Study Group for BD criteria. Behçet's disease (oral aphthae recurring at least 3 times per year and at least 2 of the following criteria fulfilled: skin lesions, BU, recurrent genital ulcers or a positive pathergy test) and the characteristic type of BU (anterior segment BU, intermediate segment BU, posterior segment BU or panuveitis with retinal vasculitis and/or focal retinal infiltrates) with exclusion of syphilis and sarcoidosis [39]. Ocular involvement has been reported in 14.1–66.2% of pediatric BD cases [40]. Behçet's disease of the posterior segment is the most common and severe form of BD. It can manifest as hemorrhagic retinitis (mainly venous and probably occlusive in nature). Color fundus photography is the method used to visualize BD lesions. Particularly characteristic is the demonstration of vitreous opacities and infiltrates in the peripheral retina [41]. The gold standard for the diagnosis of BU is AF. Detected lesions include dilation and increased tortuosity of retinal veins, choroidal exudation and exudative changes of the optic disc, macular area and retinal capillaries. The most characteristic symptom is fernlike capillary leakage even in inactive uveitis. Fundus fluorescein angiography can be used to determine the need for laser photocoagulation. Fundus fluorescein angiography findings may have prognostic value; excessive retinal vascular leakage, optic disc hyperfluorescence, optic disc neovascularization, anemic macular area, exudative macular lesions, posterior and diffuse retinal vasculitis, lack of peripheral capillary perfusion, cystic macular edema and arteriolar stenosis have been associated with poor prognosis in BD [42, 43]. The ultra-widefield technology, together with the Optos autofluorescence module, allows imaging of the retina over a previously unattainable angular range of up to 200°. A 2017 UK study demonstrated that 43.4% of lesions detected with wide-field imaging could not be visualized with standard AF [42]. Optical coherence tomography is used to monitor macular complications such as macular edema, epiretinal membrane, vitreoretinal traction, macular degeneration, retinal detachment, and macular hole. Dilatation of the fovea and irregularity of the ellipsoid zone seen on OCT reflect irreversible macular damage in branch retinal vein occlusion and indicate a poor visual prognosis. In chronic cases, OCT alone is inadequate because permanent vascular damage may result in macular thickening regardless of disease activity. Optical coherence tomography does not image the current state of the retinal vasculature. Optical coherence tomography angiography is an imaging modality that detects blood vessel movement without the need for contrast and provides visualization of the retinal and choroidal vasculature [44]; OCT-A better visualizes microvascular changes in the macular area (capillary atrophy, enlargement of the foveal non-vascular zone, telangiectasias, fistulas and the neovascularization zone) compared to AF with active BU [41].

Juvenile spondyloarthropathies

The SUN 2021 criteria for classification of human leukocyte antigen B27 (HLA-B27)-associated spondyloarthritis and anterior segment uveitis include: evidence of anterior segment uveitis (anterior chamber cells or vitreous) and 2 of 3 of the following parameters: (i) a characteristic course of acute, recurrent acute, chronic with recurrent acute unilateral or unilateral alternating inflammation; (ii) spondyloarthropathy as defined by the Assessment of SpondyloArthritis International Society (ASAS) – axial or peripheral – and/or an HLA-B27 positive result; (iii) chronic uveitis with ASAS-defined spondyloarthropathy – axial or peripheral – and an HLA-B27 positive result. The exclusion factors are evidence of syphilis, sarcoidosis, presence of cytomegalovirus, HSV or varicella and hemiplegia virus [45]. Slit lamp examination allows anatomical classification of uveitis, differentiation of inflammatory subtype (granulomatous and non-granulomatous), and quantification of the severity of inflammation, which can be quantified by the number of intraocular cells and the presence of protein in the anterior chamber and aqueous humor. Damage to the blood-tissue barrier may result in direct leukocyte precipitation into the anterior chamber ("hypopyon"). Fibrin exudation may lead to the formation of posterior adhesions. A distinguishing feature of juvenile spondyloarthropathies (JSpA)-associated uveitis is reduced intraocular pressure (IOP) in the affected eye compared to the fellow eye (presumably due to prostaglandin release). This may help to distinguish JSpA from viral uveitis, which

is often associated with significantly elevated IOP. Optical coherence tomography is used to monitor a threatening complication, macular edema caused by posterior involvement with extracellular fluid accumulation. In particular, BD, Vogt–Koyanagi–Harada disease (VKHD), TINU syndrome, sarcoidosis, syphilis, Lyme disease, tuberculosis, and herpes virus-induced uveitis should be considered in the differential diagnosis [46].

Childhood-onset systemic lupus erythematosus

The presence of uveitis in the course of SLE usually indicates an active inflammatory process and may herald the onset of nephropathy. The lesions of uveitis are usually localized in the posterior segment. Clinical diagnosis combined with ophthalmic imaging (FAF, ICGA, OCT) is crucial in the diagnosis of choroidal and retinal pathology [47]. Uveitis manifestations of SLE include inflammation of the iris, ciliary body, and vessels, and non-inflammatory choroidal degeneration (choroidopathy). Indocyanine angiography shows transient foci of uveitis hypofluorescence in the early phase and hyperfluorescence in the intermediate to late phase. Deposition of immune complexes may occur in the deeper layers of the choroidal stroma [48]. Other causes of multifocal central serous retinopathy should be considered in the differential diagnosis: sympathetic inflammation, ankylosing spondylitis, reactive arthritis, BD, VKHD, sarcoidosis, toxoplasmosis, toxocariasis, and choroidal metastases and JIA due to the similarity of vascular manifestations [49].

Multiple sclerosis

Key criteria for multiple sclerosis (MS)-associated uveitis developed by the SUN group include: unilateral or bilateral intermediate segment uveitis as indicated by cells in the vitreous or vitreous opacity, anterior chamber cells may also be present, no evidence of retinitis pigmentosa or choroiditis, a diagnosis of MS using the 2017 revised McDonald diagnostic criteria, and no exclusion criteria including suspected syphilis, sarcoidosis, and Lyme disease [50]. On examination, peripheral retinal inflammation, optic disc swelling, and scattered vitreous cells, aggregates, and inflammatory exudates (snowballs and drifts) may be observed, usually requiring indirect ophthalmoscopy to visualize. Because of the association between uveitis in MS and peripheral retinal vasculitis, it is particularly important to evaluate the retina with wide-field OCT (for signs of poor perfusion, perivascular inflammation, and neovascularization). Optical coherence tomography allows visualization of the optic nerve and macula for cystic macular edema, preretinal membrane, and macular hole. Differential diagnoses include idiopathic pars planitis, ocular toxocariasis, syphilis, Lyme disease, sarcoidosis, CSD, tuberculosis, human T-lymphotropic virus type 1 (HTLV-1), intraocular lymphoma, and inflammatory bowel disease. Routine tests performed to determine the etiology include CBC, ACE assay, IGRA, tuberculin skin test, and chest X-ray [51, 52] – Table 3.

TABLE 3. McDonald's 2017 criteria for the diagnosis of multiple sclerosis [52]

The spread of CNS lesions in space and time		
number of attacks	**clinical presentation**	**additional diagnostic criteria**
≥2	clinical signs indicating ≥2 foci of CNS damage or clinical evidence of 1 lesion with historical evidence of a previous attack involving a lesion in another location	–
spreading through space		
≥2	clinical evidence of 1 focus of CNS damage	with an additional clinical attack involving another location
		≥1 hyperintense lesion characteristic of MS on T2-weighted MR images in ≥2 CNS areas: periventricular, cortical, periventricular, subthalamic, or spinal cord
spread over time, confirmed		
1 attack	≥2 foci of CNS damage	with an additional clinical attack
		with MRI examination[1]
		oligoclonal striations in the cerebrospinal fluid
spread over time, confirmed		
1 attack	1 focus of CNS damage	additional clinical attack in another CNS location confirmed by MRI scan
		with an additional clinical attack
		with MRI examination[1]
		oligoclonal striations in the cerebrospinal fluid

CNS – central nervous system; MS – multiple sclerosis; MR – magnetic resonance; MRI – magnetic resonance imaging
[1] Simultaneous presence of enhancing and non-enhancing lesions after gadolinium administration at any time or by a new hyperintense lesion on T2 or with gadolinium enhancement on follow-up MRI, with respect to the baseline study, regardless of the timing of the baseline MRI study.

Vogt–Koyanagi–Harada disease

The SUN group criteria for early stage VKHD are: (i) exudative retinal detachment with a characteristic appearance on AF or OCT, or (ii) uveitis with ≥2 of 5 neurological symptoms (headache, tinnitus, hearing loss, meningeal symptoms, cerebrospinal fluid pleocytosis). Key criteria for late-stage VKHD include a history of early-stage VKHD and: (i) sunset glare on the fundus, or (ii) uveitis and ≥1 of 3 skin manifestations (acquired vitiligo, alopecia, graying hair-poliosis) [53]. The most common methods used to diagnose VKHD are slit-lamp biomicroscopy, AF, ICGA, OCT and ultraviolet biomicroscopy (UBM). Early symptoms

include focal areas of subretinal fluid, serous retinal detachment, punctate leakage, multifocal hyperfluorescence, and choroidal thickening. Late symptoms include choroidal depigmentation known as "sunset glow fundus" and choroidal-retinal scarring. Cerebrospinal fluid and hearing testing are also important because of the most common extraocular manifestations of VKHD (meningitis and hearing loss). Because of the role of HLA-DR4 in the pathogenesis of the disease, genetic testing is also used in diagnosis. Due to its cost and difficult availability, it is recommended only for patients with autoimmune diseases [54].

Eales disease

The primary diagnostic tool in Eales disease (ED) is FAF. The early venous phase shows staining of the walls of inflamed capillaries, neovascularization in the arteriovenous phase is manifested by hyperfluorescence. In the late phase, there is extravasation of dye. Sclerosed vessels may show a lack of capillary perfusion-hypofluorescent areas [55]. Conventional fundus angiography visualizes only 30–50° of the retina and misses the peripheral area where most disease activity occurs. Ultra-widefield imaging allows evaluation of peripheral ischemic areas with greater efficiency than AF. Ultra-widefield imaging system can image up to 82% of the retina in a single examination. B-scan (ultrasound) imaging is useful for detecting retinal detachment, posterior vitreous detachment, vitreoretinal adhesion, vitreous hemorrhage, and membranes in the vitreous cavity [56]. Macular involvement is a common manifestation of ED. Optical coherence tomography imaging allows assessment of macular edema, intraretinal fluid, subretinal fluid, vitreoretinal detachment, and vitreoretinal and epithelial membranes of the macular area [57] – Table 4.

TABLE 4. Eales disease – differential diagnosis [58]

A disease entity with which ED should be differentiated	Laboratory tests
Leukemia, other hematological disorders	CBC, ESR, blood sugar and coagulation profile
Tuberculosis	HRCT of the chest, chest X-ray and Mantoux test
Sickle cell retinopathy	hemoglobin electrophoresis
Sarcoidosis	angiotensin-converting enzyme, HRCT of the chest
SLE	determination of antinuclear antibodies in serum
Syphilis	VDRL microscopic flocculation test, TPHA

ED – Eales disease; SLE – systemic lupus erythematosus; CBC – complete blood count; ESR – erythrocyte sedimentation rate; HRCT – high-resolution computed tomography; VDRL – veneral disease research laboratory; TPHA – Treponema pallidum hemagglutination assay

CONCLUSION

Uveitis in children may have an infectious etiology, but chronic non-infectious uveitis in the setting of systemic disease is much more common. Their clinical presentation includes a wide spectrum of symptoms resulting from the involvement of multiple organs and requires multidisciplinary diagnosis. The correct pathogenetic diagnosis of the disease entity requires the cooperation of specialists in various fields. A thorough ophthalmologic examination in the diagnosis of uveitis can contribute a lot of important information to the diagnostic process, since the onset of ophthalmologic symptoms often precedes the development of pathology in other organs, thus allowing early diagnosis and implementation of treatment not only of uveitis, but also of the underlying disease. Various imaging methods are used in ophthalmological diagnostics. Among the most commonly used are slit-lamp biomicroscopy, ICGA, OCT, OCT-A, AF, FAF, UWF, and UBM. Genetic testing is also increasingly being used, creating new diagnostic possibilities, and rapid medical development can be observed in this field.

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