Multimodal imaging in pediatric uveitis

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***Abstract*:** Pediatric uveitis accounts for up to 10% of all uveitis cases, so special attention must be paid to ensure early diagnosis as well as treatment and follow-up of these young patients in order to decrease the risk of possible ocular complications and consequently vision loss. Multimodal imaging has been an effective and important adjunct in the diagnoses and management of uveitis, especially in children. Reviewed here are the currently utilized modalities, advances, as well as their applications in juvenile idiopathic arthritis–associated uveitis, pars planitis, retinal vasculitis, tubulointerstitial nephritis and uveitis syndrome, Behçet disease, Blau syndrome, and Vogt–Koyanagi–Harada syndrome.

Keywords: fluorescein angiography, fundus photography, indocyanine green angiography, optical coherence tomography, uveitis

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Introduction

Pediatric uveitis accounts for approximately 5–10% of all uveitis cases.[1] Cases are often idiopathic, but can occur in association with systemic diseases such as juvenile idiopathic arthritis (JIA), tubulointerstitial nephritis and uveitis (TINU) syndrome, and Behçet's disease (BD).[2] Classification is made based on time course (acute, subacute, or chronic), etiology (infectious or noninfectious), and location within the eye (anterior, intermediate, posterior, or panuveitis).[1] Up to 90% of pediatric uveitis cases present as chronic anterior uveitis[3] with ocular complications, although the prevalence of uveitis subtype varies based on geography and ethnicity.[4]

Unlike adults, children with uveitis can be asymptomatic with chronic, persistent, recurrent, and treatment refractory disease and could present at a later stage with severe inflammation.[4] Studies suggest that approximately 25–40% of pediatric uveitis patients may develop vision loss, and up to 25% may progress to legal blindness.[5–7] Recent studies have linked retinal vasculitis, a complication of uveitis involving the posterior segment, with worse visual outcomes and poorer therapeutic control of anterior uveitis.[2,8,9]

Children with uveitis are a unique population given the obstacles they face with diagnosis and management.[4] Prolonged cooperation with clinical examination may be challenging, and delayed presentation complicates diagnosis and treatment outcomes. Therefore, multimodal imaging techniques, which offer a critical help to clinical examination to diagnose and monitor disease, are crucial in pediatric uveitis. Such imaging technology includes optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), fundus autofluorescence (FAF), fluorescein angiography (FA), and indocyanine green angiography (ICGA), particularly in the context of ultra-widefield (UWF) imaging.

In this review, we will discuss the benefits and challenges of each modality in pediatric uveitis. We will also highlight imaging findings in several pediatric uveitic diseases, including JIA uveitis, pars planitis, retinal vasculitis, TINU, BD, Blau syndrome, and Vogt–Koyanagi–Harada (VKH) syndrome.

Overview of imaging modalities

OCT

OCT is a non-invasive method for delineating the structure of tissues using light.[10] As light travels through different structures, it interacts with the structures, scattering based on the inherent

properties of the tissue. Schematically, a source of light is split into two, a reference beam and a sample beam; reflections of the sampling beam off the tissues and the reference beam off the reference mirror at various depths are captured, and the topography is created from the reflections.[11,12] The three major modalities of OCT, including time-domain OCT (TD-OCT), spectral-domain OCT (SD-OCT), and swept-source OCT (SS-OCT), represent evolution of the technology.[11]

Shortly after the first *in vivo* OCT of the human retina in 1993 using TD-OCT,[13] Fourier-domain or frequency-domain OCT was proposed in 1995 introducing a different light source and detector.[11] The two systems developed on this principle, SD-OCT and SS-OCT, are both faster than TD-OCT.[11] In TD-OCT, the reference mirror off which the reference beam reflects is moved sequentially at each depth, in contrast to SD- and SS-OCT wherein the reference mirrors are stationary.[12] TD-OCT scans are also performed sequentially at different depths and then laterally, resulting in slower scanning speeds.[11] In SD- and SS-OCT, simultaneous reflection of multiple wavelengths of light results in faster and more dynamic evaluation of tissue, which has made OCT an indispensable tool in ophthalmology.[12]

Given its speed and non-invasive yet impactful yield of information, OCT has been widely used for evaluation of the posterior segment, especially in uveitis.[12,14] Importantly, OCT is tolerated well by children and is now a mainstay in diagnosis and management of uveitis and its complications.[15] Moreover, the advent of higher resolution OCT has paved the way for quantitative evaluation and monitoring of uveitis.[14,16] The objective quantification of uveitis by OCT enables reliable assessment of progression or regression of disease, with less reliance on child cooperation at the slit lamp.

OCTA

Building on OCT technology, OCTA allows for visualization of various vascular networks found in the retina. The possibility of OCTA grew from the advent of SD-OCT, as imaging speeds were able to detect the subtle movement of erythrocytes coursing through vasculature.[17] Through obtaining up to hundreds of thousands of scans in any cross-section per second, OCTA visualizes not only the superficial vascular plexus (as does FA), but all vasculature within the retina, including the radial peripapillary capillary plexus, superficial vascular plexus, intermediate capillary plexus, and deep capillary plexus.[17,18] OCTA demonstrates different pathologies including vascular occlusions and neovascularization, among others, via a topographic layout of the vascular network of the retina,[17,19] providing more detail and higher resolution of vascular pathologies in the posterior segment.[19] Importantly, OCTA, like OCT, is tolerated by children,[20] allowing for use of this imaging modality in the diagnosis and monitoring of pediatric disease.

FAF

Unlike fundus FA and ICGA, which require venipuncture and exogenous administration of dyes, FAF relies on the inherent fluorescent property of lipofuscin. Lipofuscin refers to a heterogeneous population of intracellular granules that classically accumulate in cells of different tissues and organs in the body, with retinal pigment epithelium (RPE) lipofuscin being thought to originate from incomplete breakdown of photoreceptor outer segments.[21] As RPE cells play a major role in metabolism of lipofuscin, pathologic processes altering the natural flux of synthesis, breakdown, and removal of lipofuscin lead to aberrations on FAF imaging with focal hypo- or hyperintensity.[22]

Fundus FA

The addition of FA to the clinical examination allows for enhanced appreciation of clinical markers of disease activity in uveitis, such as cystoid macular edema (CME), retinal vascular leakage, nonperfusion, and neovascularization.[23] In children, clinical utility and tolerance of imaging modality are important considerations. While fundus photography may be better tolerated in pediatric patients than clinical examinations,[24] it is often challenging to obtain in younger children without sedation in the outpatient setting[25] as imaging often involves dilation of the eyes and intravenous injection of fluorescein followed by photography of the retina. Venipuncture in children is more technically challenging and may be psychologically traumatizing. Fortunately, angiography with orally administered fluorescein has been demonstrated to be sufficient for evaluation of retinal vascular leakage.[26–28] A notable drawback with oral FA is the increased time between ingestion of dye and imaging; however, increasing the amount of oral fluorescein can decrease this time.[29] In a proof of concept study evaluating

sublingual and transoral FA,[30] significant benefits of sublingual administration included relatively smaller dose of fluorescein needed in comparison with oral administration, due to a decrease in first pass hepatic metabolism, as well as decreased time between ingestion and imaging.

ICGA

In the 1990s, ICGA was recognized as a standard for imaging the choroid as a result of technological advancements that allowed for better signal capture.[31] ICGA is best for identifying choroidal pathology,[32] as may occur in posterior uveitis. ICG, which fluoresces in the infrared spectrum, is injected, becomes largely bound by proteins (~98%), and extrudes into the choroid through vascular fenestrations.[33] With inflammation or damage of the choroidal vasculature, greater than expected fluorescence is seen, whereas inflammatory foci within the choroidal stroma result in hypofluorescence as ICG diffuses around these lesions.[34] These features make ICGA invaluable for evaluating choroidal involvement in uveitis. However, ICGA in children is subject to the same challenges as FA, and orally administered ICG could similarly make this imaging modality more tolerable for pediatric patients. While no oral formulation or protocol is available yet for humans, an animal model has been used to demonstrate the feasibility of ICGA with sublingual administration of dye.[35]

UWF imaging

In recent years, the development of UWF imaging has accelerated understanding of peripheral retinal diseases.[23,24] While multiple options for confocal scanning laser ophthalmoscopy (cSLO) instruments exist, the Optos cSLO UWF (Optos, Dunfermline, Scotland, UK) imaging platform is commonly used because it has the widest field of view, 200°.[36] Another UWF system, the Clarus 500 (Carl Zeiss Meditec AG, Jena, Germany) produces true color imaging of the retina to better match what is observed on fundoscopy[23] and at higher resolution than the Optos, but captures a smaller field of 133°.[37] Appreciable use of the Clarus 500 in uveitis studies, especially in pediatrics, remains to be seen.

The Optos cSLO permits the imaging of vitreoretinal pathology without the use of contact lens or dilation, and is capable of performing FA, ICGA, FAF, and OCT.[23] In a study of 243 patients comparing UWF-FA with simulated 50° FA images, UWF-FA was able to better demonstrate peripheral vascular leakage, peripheral nonperfusion, and neovascularization.[38] Importantly, in a study of 107 eyes of 55 pediatric patients aged 3–18, Kothari *et al.*[39] demonstrated that UWF-FAF and UWF-FA could be performed in children without the need for sedation in an outpatient clinical setting.

Imaging in pediatric uveitis

JIA-associated uveitis

JIA is a group of pediatric-onset arthritides of unknown etiology which affect children under the age of 16. The diagnosis is made if arthritis persists for at least 6 weeks.[40,41] It is estimated that 30–80% of pediatric uveitis is attributable to JIA,[3] with incidence ranging from 2 to 23 per 100,000 children and prevalence ranging from 4 to 400 per 100,000 children.[42] Frequency of uveitis varies across the seven subtypes of JIA, with oligoarticular JIA being associated with the highest rate of uveitis.[3,40] In one cohort study following JIA patients over a mean of 6.9 years, 13.1% of patients developed uveitis.[40] Given that uveitis is the most common extra-articular complication of JIA and may be asymptomatic, routine ophthalmologic screening is recommended for children diagnosed with articular disease.[42] Prompt diagnosis and treatment of ocular inflammation is crucial for optimizing visual outcomes in these children, as uncontrolled disease can lead to blindness.[43]

JIA uveitis most commonly presents as a bilateral chronic anterior uveitis.[3,42] Slit lamp examination has traditionally been the mainstay for evaluation of disease, and may identify the presence of anterior chamber cell and flare, posterior synechiae, band keratopathy, and cataracts.[3,15,43] In addition, patients may present with hypotony, defined as intraocular pressure (IOP) < 5 mm Hg or IOP ≥ 5, but < 8 mm Hg, which adversely affects visual potential.[44]

Ultrasound biomicroscopy (UBM) is a non-invasive method of evaluating the ciliary body, pars plana, and retro-iridal vitreous areas. UBM may be used in children with hypotony to further elucidate the etiology of hypotony.[44] UBM can help differentiate mechanically induced hypotony with cyclitic membranes causing traction and subsequent detachment of the ciliary body or hypotony

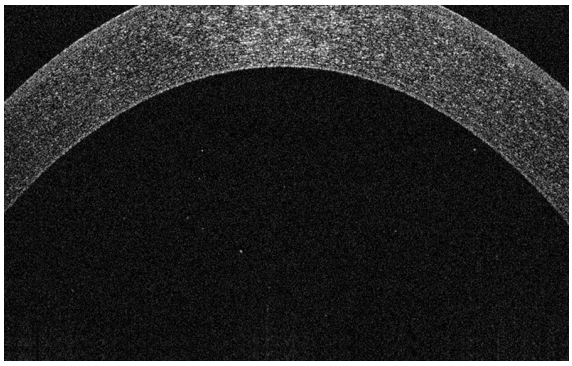

Figure 1. Anterior-segment optical coherence tomography (AS-OCT) demonstrating hyperreflective foci in the anterior chamber (AC) which represents cells in the AC in a 7-year-old female with juvenile idiopathic arthritis–associated uveitis with a Standardization of Uveitis Nomenclature (SUN) Working Group grading criteria of 1+ AC cell.

from a dysfunctional cause due to ciliary body atrophy from chronic inflammation leading to decreased production of aqueous humor.[44,45] Of note, the use of UBM in pediatric populations may be limited by patient cooperation due to need for supine positioning and discomfort caused by either the immersion or contact methods.[46]

Indirect ophthalmoscopy may also demonstrate optic disk edema and epiretinal membrane,[43] and macular edema and foveal detachment have been described on OCT.[15,43] Major limitations of slit lamp examination in the pediatric population include its dependence on patient cooperation and its subjective nature, which can complicate management due to intra- and inter-user grading variability. The ubiquity and reliability of OCT make this tool an emerging adjunct for screening and monitoring uveitis. Cells in the anterior chamber can be successfully imaged with anterior-segment OCT (AS-OCT), appearing as hyperreflective foci (Figure 1). In a feasibility study, AS-OCT was found to be reliable and well-tolerated for quantitative evaluation of JIA-associated uveitis.[47] Using a cohort of children with uveitis and normal controls, Akbarali *et al.*[47] evaluated the correlation of AS-OCT cell with slit lamp exam, and AS-OCT was found to have a sensitivity of 91.7% and specificity of 85.7% for detecting anterior chamber cell in this population.

Pars planitis

Pars planitis is a form of idiopathic intermediate uveitis that primarily affects children. The incidence of pars planitis has been reported to be 1.5–2 cases per 100,000 persons,[48,49] accounting for 5.6–24.0% of pediatric uveitis diagnoses.[7,50,51] The majority of cases present bilaterally with symptoms of floaters and decreased vision. Diagnosis is made by identifying the characteristic formation of snowbanks, which represent inflammatory debris overlying the pars plana, or snowballs (Figure 2(a)), which comprise aggregates of inflammatory cells in the anterior vitreous, in the absence of an infection or systemic disease. Common complications of pars planitis include CME, cataract, epiretinal membrane, and posterior synechiae.[52]

Fundus photography allows for documentation of baseline appearance of retinal lesions and is useful in monitoring for changes over time. Fundus photographs can identify snowbanking and reveal complications of pars planitis, including retinoschisis, peripheral tractional membranes, and macular

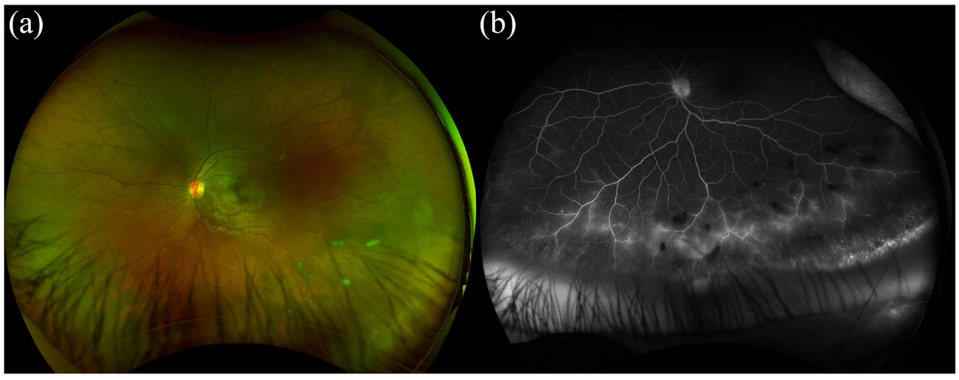

Figure 2. Ultra-widefield (UWF) imaging in a 17-year-old female with pars planitis at initial presentation with snowballs of the left eye (a). UWF fluorescein angiography (b) demonstrates mild peripheral vascular leakage associated with snowballs inferiorly.

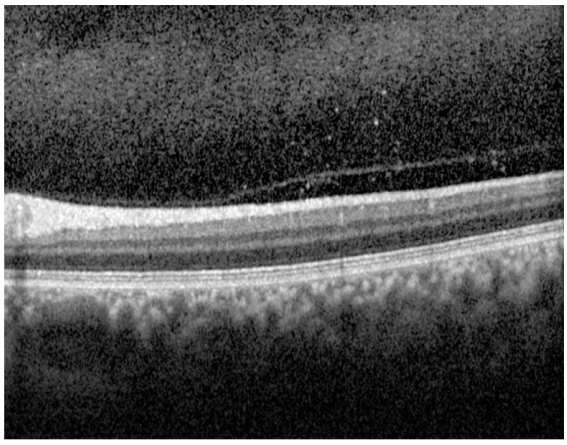

Figure 3. Spectral-domain optical coherence tomography (SD-OCT) image in a 12-year-old male with idiopathic panuveitis demonstrating vitreous hyperreflective foci which are representative of vitreous cells.

pathology. A primary limitation of this technique is poor visualization due to vitreous haze or cataract formation.

The use of OCT as a screening tool has been proposed for the initial work-up of children with pars planitis to identify possible CME and inform disease management and visual prognosis.[53] In a recent study of patients with pars planitis presenting at mean age of 14.3 ± 10.5 years, using SD-OCT, Yalçındağ *et al.*[54] found that the presence of diffuse CME and loss of normal foveal contour were predictive of poor visual acuity. In monitoring treatment response, SD-OCT may show decreased vitreous punctate spots, indicative of vitreous cells (Figure 3) and CME.[53,55,56]

Reports of OCTA imaging in pediatric intermediate uveitis are scarce. Interestingly, in adult patients with intermediate uveitis, OCTA imaging shows reduced vascular density in the superficial and deep retinal layers as well as greater heterogeneity of choriocapillaris perfusion, indicating impairment of the macular microvasculature.[57] As OCTA undergoes further study in the pediatric population, it would be important to determine how well the findings in pediatric intermediate uveitis compare with disease in adults. In a study by Soberón *et al.*[58] that included five pediatric and four adult subjects with idiopathic intermediate uveitis, OCTA was able to identify neovascularization and structural blood vessel changes, but was not able to quantify the foveal avascular zone or identify inflammatory changes, such as vascular leakage. In a recently published review by Khochtali *et al.*,[59] the OCTA findings of a pediatric patient with pars planitis with macular edema revealed enlargement of the foveal avascular zone, dilated capillaries, and disorganization of the normal architecture of the capillary network at the deep capillary plexus.

FA can be used to identify peripheral retinal vasculitis (Figure 2(b)), neovascularization, CME, and optic disk edema. As CME is the major cause of visual loss or impairment in children with pars planitis, early detection of CME using FA is crucial for the prevention of visual loss. Low-grade edema may only be detected by FA, which can serve as a basis for disease monitoring and indication for treatment.[60] In a retrospective study of 54 eyes among patients with mean age of 12.84 ± 8.26 years at diagnosis, the common FA findings during the inflammatory episodes were staining of the optic disk, hyperfluorescence due to dye leakage in the macular area, and staining and leakage of peripheral retinal vessels.[61] UWF-FA has been used in pediatric pars planitis and increases identification of pathology and vessel leakage compared with conventional FA.[38,62]

UBM was first described for use in pars planitis by Garcia-Feijoo *et al.*,[63] and it provides fine resolution within the anterior and intermediate segments. Doro *et al.*[64] concluded that the 50-MHz probe was ideal for visualization of angle structures and exudation involving the pars plana and peripheral retina; the 20-MHz probe was superior for evaluating anterior vitreous involvement and cyclitic bands. In a retrospective study of 118 eyes ($n=66$) among pediatric patients (10.85 ± 6.03 years) in Mexico City, UBM identified cyclitic membranes in 68% of the study population over the study period,[65] reporting a much higher rate compared with a prior study (15%) which had used clinical examination via slit lamp and indirect ophthalmoscopy.[66] Given the utility of visualizing the anterior chamber, ciliary body, and peripheral retina, UBM can be used for guiding management (e.g. identifying site for intravitreal injections, determining entry-port location for vitreo-retinal surgery) and monitoring response to treatment.[65–68] As discussed above, wider use of UBM in children may also be limited due to patient cooperation.[46,69]

Retinal vasculitis

Among pediatric patients with idiopathic uveitis, retinal vasculitis may be present in up to 80% of

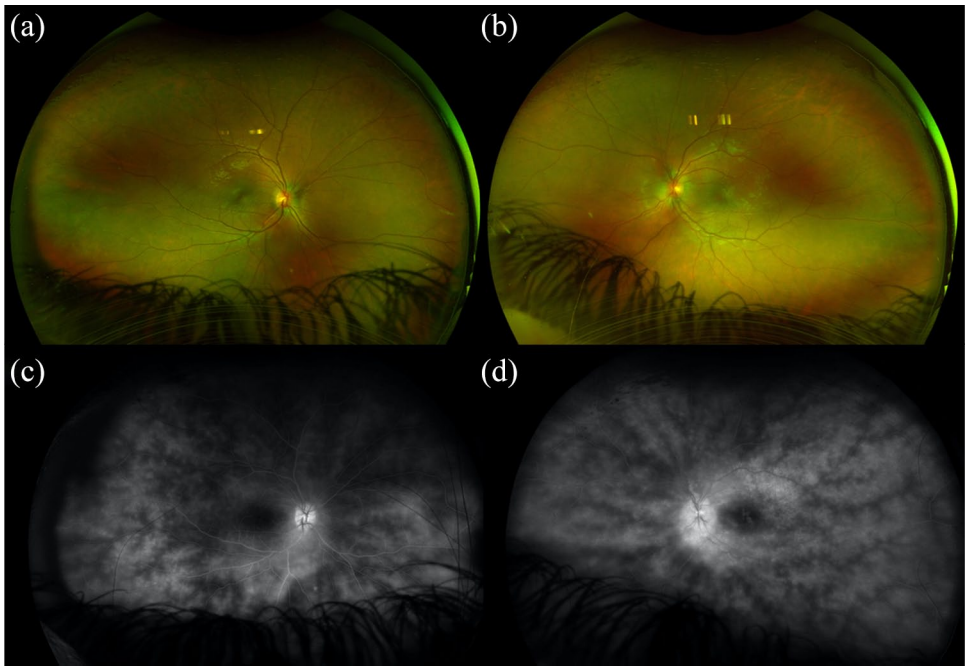

Figure 4. Ultra-widefield (UWF) imaging at presentation of an 11-year-old female with bilateral panuveitis demonstrating an unremarkable fundus photograph without any vascular sheathing in the right (a) or left (b) eyes; however, use of UWF fluorescein angiography reveals diffuse (fern-like) vascular leakage in both eyes (c, right eye, d, left eye).

eyes.[2] Retinal vasculitis in children often presents insidiously and may occur as an isolated condition or in association with a systemic inflammatory or infectious disease. In children, retinal vasculitis mainly manifests as a retinal capillaritis or microvasculitis with vascular leakage at the posterior pole or peripheral retina on FA.[2]

FA is the diagnostic gold standard for identifying a disruption in the blood-retinal barrier.[70] In a large retrospective study of pediatric patients ($n = 1867$) with uveitis, Yang *et al.*[2] found that retinal vasculitis was present in at least one eye in 79.6% of patients using FA examination. Those with retinal vasculitis were significantly more likely to have band keratopathy, posterior or anterior synechia, and macular edema. Given the high prevalence of retinal vasculitis and its implications as a predictor of treatment failure, Yang *et al.*[2] recommended routine screening by FA examination for pediatric patients with uveitis. In a retrospective study of pediatric patients ($n = 14$), FA identified a significant percentage of patients (79%) with posterior segment-involving uveitis deemed quiescent on clinical examination[71] (Figure 4), again highlighting the usefulness of FA in monitoring disease control.

A prospective study by Leder *et al.* comparing UWF-FA and FA in pediatric and adult patients found that active retinal vasculitis was detected in 68% of UWF-FA images in contrast to 45% using conventional FA. With the additional information acquired from UWF-FA in these patients, a decision to alter management was made in 51% of patient visits.[72] UWF-FA has therefore become the standard method of assessment and monitoring in various uveitis centers.[73,74] UWF-FA has been obtained in children as young as 3 years old without sedation in an outpatient clinic setting.[39]

Given that OCTA allows for non-invasive study of the posterior segment of the eye and have been used in children, their use in evaluating retinal vasculitis in children could be revealing. Unfortunately, compared with adult literature, there is a dearth of studies using this tool in the study of pediatric retinal vasculitis. Qu *et al.*[20] recently published a retrospective study of 32 pediatric uveitis patients (mean age 11.1 ± 2.2 years) and 30 matched normal controls (mean age 10.7 ± 2.4 years) wherein they tested the utility of OCTA in pediatric uveitis and found the vascular densities of the superficial capillary plexus and deep capillary plexus to be reduced in uveitis patients compared with normal

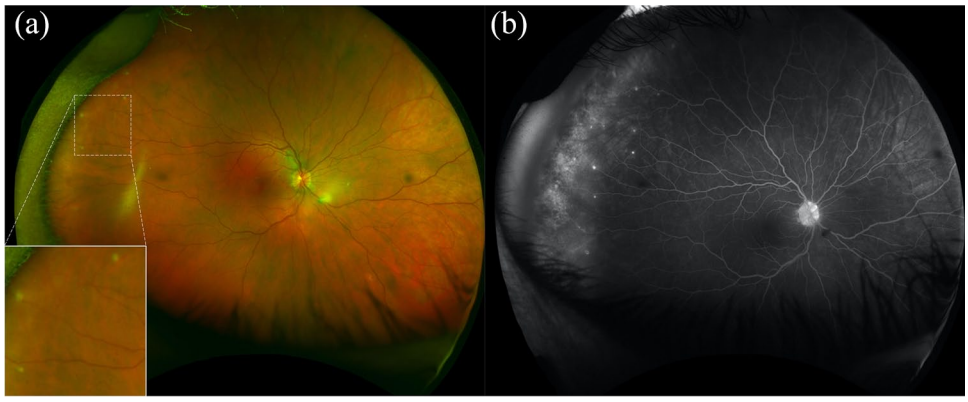

Figure 5. Ultra-widefield (UWF) imaging in a 16-year-old female with tubulointerstitial nephritis and uveitis (TINU) syndrome demonstrating peripheral circular chororetinal lesions (inset) which have associated hyperfluorescence (staining) on UWF fluorescein angiography.

controls. Notably, 29 of the 32 uveitis patients in the study had idiopathic uveitis.[20] Thus, more studies with OCTA are needed to better characterize features of pediatric retinal vasculitis to aid management and prognostication, as exists for adults.[75]

TINU syndrome

First described in 1975 in two case reports of adolescents presenting with eosinophilic interstitial nephritis, bone marrow granuloma, and anterior uveitis,[76] TINU has been recognized as an uncommon syndrome of pediatric uveitis that typically presents with acute bilateral nongranulomatous anterior uveitis associated with acute interstitial nephritis in the absence of any systemic inflammatory disease.[77] TINU has also been reported in older individuals.[78,79] Pediatric TINU patients present at a median age of 15 years, with earlier reports suggesting a 3:1 female: male ratio, though this is currently in dispute.[77] Notably, renal and ocular pathologies may not present at the same time; acute tubulointerstitial nephritis often precedes uveitis,[77–79] reinforcing the importance of robust history and interdisciplinary coordination of care.

Eye pain, redness, blurred vision, and photophobia are the most common presenting symptoms,[78,79] with findings on exam including anterior chamber cell, conjunctival injection, keratic precipitates, vitreous humor cells, chorioretinitis, intraretinal hemorrhages, and retinal vascular sheathing.[77–79] While most present with mild anterior uveitis, panuveitis, intermediate,[79] and posterior uveitis[77] have also been reported, and are typically responsive to corticosteroids.[77,79,80] Diagnosis and prompt treatment with corticosteroids is necessary to prevent complications, which may include posterior synechiae, chorioretinal lesions (Figure 5), rhegmatogenous retinal detachment, and choroidal neovascularization.[77–79] If corticosteroid treatment is ineffective or unable to be tapered to a safe level, immunomodulators can be considered.[80]

In a retrospective, consecutive case series ($n = 10$ patients including three children) of TINU using UWF-FA and OCT, abnormalities on UWF-FA included retinal vascular leakage (72.2%), macular leakage (33.3%), optic disk leakage (27.8%), and peripheral nonperfusion (11.1%), with macular edema (35%) and epiretinal membrane (20%) and optic nerve edema (5.6%) observed on OCT.[81] O the 20 eyes in the study, 19 demonstrated posterior segment abnormality on dilated exam including vitreous cell (55%), optic disk edema (15%), snowballs or snowbanks (25%), and vascular sheathing (10%).[81] The one eye that did not have posterior segment findings on exam was found to have optic disk leakage on UWF-FA.[81] Interestingly, UWF-FA was more sensitive in identifying one or multiple findings such as vascular leakage, optic disk leakage, leakage within the macula, and peripheral nonperfusion, in 16 eyes compared with OCT, which demonstrated findings in only 8 eyes, including intraretinal fluid/cystoid macula edema, epiretinal membrane, and optic nerve edema.[81] While this Cao *et al.* study of 10 patients with age range of 10–83 years featured only 3 pediatric patients, Koreishi *et al.*[82] in their retrospective chart review of 17 patients had 12 pediatric patients aged

7–15 years and made similar observations that posterior findings are more common than previously believed. Interestingly, Scifo *et al.*,[83] in their report of a case series of three patients, two of whom were children aged 9 and 10 years, showed the value of ICGA in detecting subclinical choroidal inflammation in TINU. Together, these studies further underscore the importance of multimodal imaging in thorough evaluation of patients and monitoring of disease course. As OCT, UWF-FA, and ICGA serve to better delineate pathological features of TINU that are not appreciated on dilated exam,[81,83] UWF-FA and OCT can be complementary in diagnosis and management of the disease.

BD

More prevalent among individuals who originate from regions along the Silk Road, BD is a rare condition that results in multi-systemic inflammatory disease and vasculitis.[84] The pathogenesis of BD is unclear, but reported immunopathology of involved tissues has suggested a predominantly T-cell driven inflammatory process; eye specimens in particular have demonstrated perivascular infiltrates of CD4+ T-lymphocytes, as well as plasma cells and B-lymphocytes in some cases, suggesting involvement of both humoral and cell-mediated immunity.[85] To address limitations of traditional BD diagnostic criteria for the pediatric population, the Pediatric Behçet's Disease Study Group (PEDBD) reported consensus classification criteria based on an international, multicenter prospectively enrolled series of 156 pediatric patients with confirmed BD.[86] These criteria comprised recurrent oral ulcers (at least three attacks/year), genital ulcers, cutaneous involvement (erythema nodosum, acneiform lesions, necrotic folliculitis), neurologic signs (with the exception of isolated headaches), vascular signs (vessel thrombosis or aneurysm), and ocular involvement (anterior uveitis, posterior uveitis, retinal vasculitis); pediatric BD is diagnosed if a patient meets three or more separate criteria. In the PEDBD cohort, oral ulcers were the presenting sign in 81% of children, with males more often experiencing additional skin, eye, and vascular symptoms, and females more often having genital ulceration.[86] Ocular symptoms were overall observed less frequently than in adults, and ocular and vascular involvement generally appeared later than other symptoms.[86] Of note, ocular involvement was also associated with poorer prognosis, with 12.3% of children ultimately meeting the criteria for legal blindness.[86]

Classic ocular findings in BD include shifting hypopyon, vitritis, retinal vasculitis, and retinitis, but based on existing multimodal imaging studies of adults and children with BD, particular attention should be paid to changes in choroidal thickness and morphology. Balbaba *et al.*[87] reported SD-OCT and FA findings in a series of 23 pediatric patients with BD and ocular involvement, and found subfoveal choroidal thickness to be significantly increased, which is corroborated by several reports in adults and felt to be related to choroidal effusion from the influx of inflammatory mediators during acute episodes. Ishikawa *et al.*[88] illustrated similar findings in 23 eyes of 13 patients with BD using EDI-OCT; choroidal thickness correlated significantly with anterior, posterior, and total inflammation scores, and decreased following treatment of their patients with infliximab. In contrast, other studies have observed a decrease in choroidal thickness, particularly in patients with longer average duration of disease and recurrent posterior uveitis, and this finding is suspected to be related to fibrosis within the choroid.[89] Long-term studies will need to be performed to confirm the presence of analogous findings in pediatric BD patients with chronic disease.

Findings of ICGA have not been commonly reported in pediatric BD, but may potentially demonstrate abnormalities of the choroidal vasculature as described in adult BD patients. Bouchenaki *et al.*[90] reported findings of choriocapillaris perfusion delay and indistinct choroidal vessels without diffuse late choroidal hyperfluorescence in patients with acute ocular inflammation. Similarly, Ishikawa *et al.*[88] described staining and irregular filling of choroidal vessels on ICGA, as well as decrease in observed dye leakage from choroidal and retinal vessels following infliximab treatment.

In terms of retinal findings, BD patients appear to demonstrate either equivalent or increased macular thickness due to edema during acute inflammation, and decreased macular thickness following resolution of inflammation. Balbaba *et al.*[87] found no significant overall difference in retinal thickness between pediatric BD patients with or without ocular involvement, but did report two patients who presented with atrophic

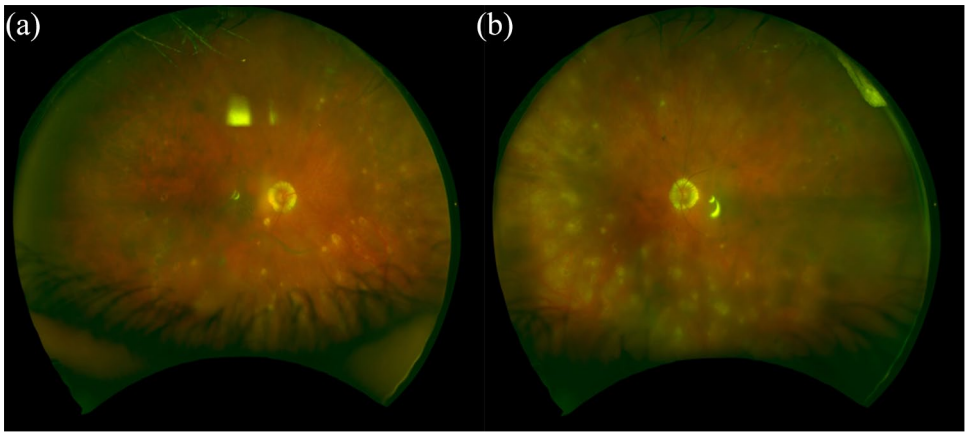

Figure 6. Ultra-widefield fundus photography in a 12-year-old male with Blau syndrome demonstrating multifocal chorioretinal scars in both eyes (a, right eye, b, left eye).

maculae and associated decrease in central retinal thickness. After excluding patients with macular edema, Coskun *et al.*[89] reported decreased mean central macular thickness as well, again in patients with known macular atrophy on exam. These changes have been attributed to retinal ischemia from recurrent refractory ocular inflammation, as well as potential contribution from subfoveal choroidal atrophy.

Blau syndrome

Blau syndrome is a rare granulomatous autoinflammatory disease caused by an autosomal dominant mutation in the nucleotide-binding oligomerization domain-containing protein two (*NOD2*) gene.[91] The clinical phenotype is essentially identical to early onset sarcoidosis; children often present at less than 5 years of age with one or more symptoms of the classic triad of arthritis, dermatitis, and/or uveitis, though some patients never manifest all three components during their disease course. Arthritis typically affects patients' wrists, knees, ankles, and fingers, and patients may also experience concurrent tenosynovitis and contracture of interphalangeal joints. Cutaneous involvement may take the form of an erythematous or tan-colored papular rash that fades early in life, followed by a generalized rash involving the trunk and extremities.[92] Uveitis is the least common of the triad, with the majority of those affected presenting with bilateral chronic relapsing panuveitis associated with multifocal choroidal scars throughout the posterior pole (Figure 6).[93] Diagnosis is made definitively by genetic testing confirming a disease-causing mutation of *NOD2*, and is supported by the presence of noncaseating granulomas on biopsy of skin lesions or affected synovia.[94]

As panuveitis of Blau syndrome can evolve from anterior uveitis, AS-OCT stands as a valuable objective non-invasive tool for diagnosis and management. As demonstrated in a recent case report of two siblings, an 8-year-old female and a 5-year-old male, with Blau syndrome, diagnosed with genetic testing, with one having uveitis and the other asymptomatic, AS-OCT allowed for non-invasive imaging of both patients.[95] Findings in the 8-year-old patient included hyperreflective dots in the aqueous humor and hyperreflective dots on the posterior corneal surface, thought to correspond to anterior chamber cells and keratic precipitates, respectively, as visualized on biomicroscopy; these anterior-segment findings, as well as any others, were absent in the 5-year-old male.[95]

Several reports have depicted posterior segment findings of Blau syndrome via multimodal imaging. Friesen *et al.*[96] described large perivascular, presumably granulomatous lesions within the middle retina without detectable flow on en face structural OCT and OCTA imaging in a 12-year-old patient with Blau syndrome. In addition, widefield imaging and angiography in this patient demonstrated multiple aneurysmal-like hypopigmented lesions, multifocal pigmented chorioretinal scars, optic disk leakage, and diffuse peripheral retinal vascular leakage.[96] In another case report of an affected 5-year-old girl, DeSouza and Shah characterized findings of midperipheral and peripheral retinal vascular and peripapillary leakage, vessel attenuation, and peripheral snowballs

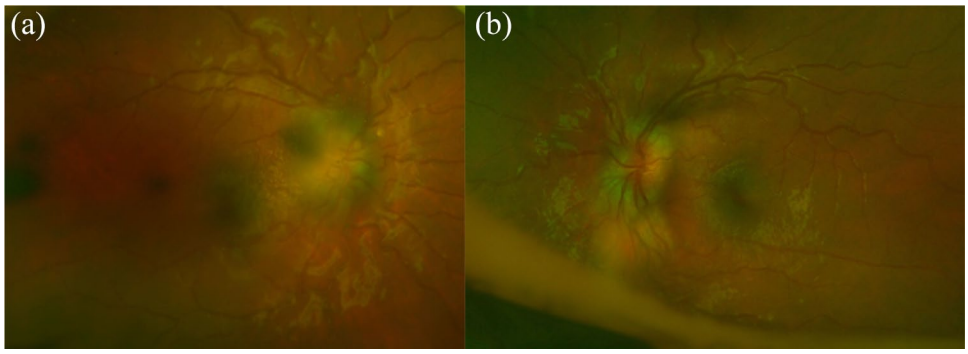

Figure 7. Optic disk photographs in a 5-year-old female with Blau syndrome demonstrating optic disk edema in the right (a) and left (b) eyes.

using the portable Retcam and Optos widefield systems.[97] Of note, they remarked that a standard 50° fluorescein angiogram would not have captured the peripheral findings, and that Retcam widefield angiography was a sufficient alternative for detection of subclinical retinal vasculitis during exams under anesthesia for children less cooperative with sitting upright for tabletop platforms.[97] Finally, an ICGA performed in an 8-year-old girl with Blau syndrome demonstrated multiple hypocyanescent choroidal stromal granulomas throughout the posterior pole that improved after 6 months of adalimumab therapy.[98]

In addition to chorioretinal changes, patients with Blau syndrome have been reported to have characteristic optic nerve features, even in the apparent absence of posterior pole involvement. These include mixed peripapillary hypo- and hyperpigmentation with nodular excrescences, optic nerve head pallor, blurred disk margins (Figure 7), and disk vessel sheathing.[93,99]

VKH syndrome

VKH syndrome is characterized by a constellation of clinical signs, including chronic progressive bilateral granulomatous panuveitis and choroiditis, exudative retinal detachments (Figure 8), and signs of meningeal irritation with or without auditory disturbances and skin changes (vitiligo, alopecia, poliosis).[100] As with many autoimmune conditions, the pathogenesis of VKH is unclear, but is suspected to stem from a T-cell-mediated autoimmune reaction against antigens of melanin-containing cells in the eye, ear, skin, and meninges.[101] The syndrome is more prevalent in Asia, the Middle East, and Latin America, and overall, the entity is rare in children, with an estimated 3% of those affected being 16 years of age or younger.[102] Clinical presentation is similar between adults and children, but the latter tend to suffer vision-threatening complications at a higher rate, possibly due to delayed presentation.[103] A retrospective review out of Saudi Arabia of 97 consecutive patients diagnosed with VKH syndrome, out of whom 13 were children, also highlighted that children may experience a more aggressive disease course that responds less to treatment.[101] Eight of the 13 pediatric patients presented with panuveitis (61%), 4 with exudative retinal detachment (31%), and all 13 with disk hyperemia (100%).[101] Complications developed at a higher rate in children compared with adults, including cataracts (61% *versus* 14% in adult group) and glaucoma (46% *versus* 14% in adult group); the latter evolved due to formation of synechiae and chronic angle-closure.[101] More children ended up with a final visual acuity in their better eye of 20/200 or less (61% *versus* 26% in adult group), and pediatric patients were more often observed long term to develop depigmentation of (RPE), multifocal nummular chorioretinal scars, and subretinal neovascularization as a result of their disease.[101]

Multimodal imaging of pediatric VKH has been described in the literature in patients as young as 3 years of age, and demonstrates the utility of serial imaging for following the often aggressive disease course in children. Katsuyama *et al.*[104] reported imaging findings of a 3-year-old girl with VKH using OCT, which demonstrated bilateral serous retinal detachments and choroidal thickening on presentation, persistence of subretinal fluid (SRF) despite two courses of high-dose intravenous corticosteroid therapy, and ultimate resolution of SRF and restoration of the ellipsoid

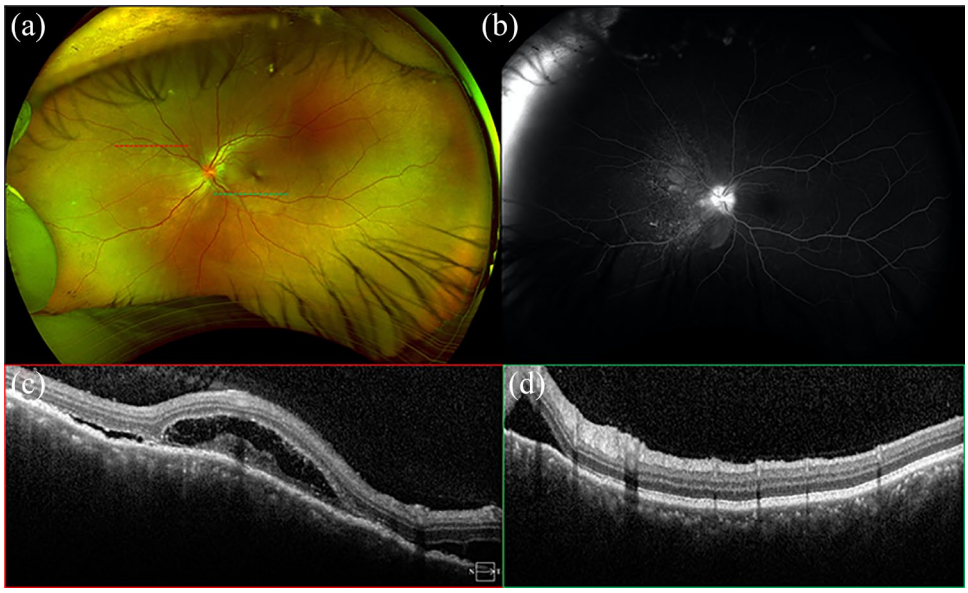

Figure 8. Multimodal imaging at presentation in a 15-year-old male with Vogt–Koyanagi–Harada disease. Ultra-widefield (UWF) fundus photography shows scattered areas of serous retinal detachments and disk hyperemia (a). UWF fluorescein angiography shows pinpoint leakage and pooling associated with areas of serous retinal detachment (b). Optical coherence tomography (OCT) demonstrates subretinal and intraretinal fluid nasal to the optic nerve and choroidal undulations (c) and subretinal fluid within the macula (d). Green and red dashed lines in A correspond to areas of the OCT B-scans (c, d, respectively).

zone after her third course of corticosteroid therapy. Khalifa *et al.*[103] described a 12-year-old female patient who experienced improvement in serous detachments following treatment with infliximab and methotrexate treatment, but was found to have persistent submacular fluid on OCT and eventually required cyclophosphamide to achieve quiescence of inflammation. Another report of an affected 12-year-old girl demonstrated a scalloped pattern of SRF on OCT, multiple areas of early pinpoint leakage and late pooling with disk hyperfluorescence on widefield FA, and multiple hypofluorescent choroidal spots in all phases and areas of hyperfluorescence in intermediate to late phases on ICGA.[105] Serial widefield fundus photographs and OCT visualized re-accumulation of SRF after the patient was switched from intravenous to oral corticosteroids, as well as sunset-glow fundus changes following resolution of acute inflammation. Follow-up FA demonstrated resolution of pinpoint leakage on steroid therapy.[105] The ICGA findings in this patient appeared consistent with those described in adult patients; Bouchenaki *et al.*[90] and Bouchenaki and Herbort[106] described a pattern of stromal inflammatory vasculopathy (fuzzy indistinct vessel appearance in intermediate phase, diffuse hyperfluorescence in late phase) in VKH, and that this pattern always responded to anti-inflammatory therapy when ICGA was repeated in follow-up.

Subsequent complications of VKH syndrome in children can also be readily followed with multimodal imaging, namely, subretinal and choroidal neovascularization. Soheilian *et al.*[107] reported the development of bilateral macular choroidal neovascular membranes (CNVMs) in 7 of 10 consecutive pediatric patients with VKH panuveitis, and FA confirmed the presence of these CNVMs.

Conclusion

Available modalities for imaging children with uveitis include OCT, OCTA, ICG, FA, and FAF. UWF capabilities have allowed for enhanced visualization of the periphery in ICG, FA, and FAF studies, though the clinical utility of peripheral imaging remains to be fully established.[108] While there may be abnormalities seen in the peripheral retina, it is unclear whether intervention prevents future disease or if these findings represent physiological variation, as healthy subjects have also been found to demonstrate some peripheral aberrancies. However, having UWF undoubtedly allows for better delineation

of clinically relevant pathology, and facilitates objective monitoring of changes over time. In addition, use of multimodal imaging provides the potential of developing quantitative biomarkers that can be used to objectively detect and monitor intraocular inflammation over time.

Author contributions

FGID, KM, and JLC conducted the literature review and wrote and revised the manuscript. ET conceived the review, provided supervision, and edited the manuscript. All authors proofed the manuscript.

Conflict of interest statement

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