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Optical Coherence Tomography Angiography in Pediatric Retinal Disorders

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Abstract

Purpose: The rapid and noninvasive nature of optical coherence tomography angiography (OCTA) makes it a potentially valuable tool for imaging the retina in children. With the optimization of tabletop systems and the development of experimental handheld OCTA devices, there is expanded potential for OCTA in the clinic and the operating room. This article reviews the utility of OCTA in some of the most common pediatric retinal disorders. **Methods:** A thorough computerized PubMed search was performed to review relevant published journal articles to contextualize and identify the role of OCTA in common retinal disorders with vascular involvement affecting children. Pertinent results and findings from original investigations and case reports were summarized. **Results:** The ability to quickly collect both qualitative and quantitative information about retinal microvasculature, in both the clinic and operating room settings, with OCTA, has led to the uncovering of microvascular features and morphologic changes in many pediatric retinal disorders such as Coats Disease, familial exudative vitreoretinopathy, incontinentia pigmenti, sickle cell retinopathy, Stargardt Disease, X-linked juvenile retinoschisis, retinopathy of prematurity, diabetic retinopathy in type 1 diabetes, pediatric retinal tumors, and choroidal neovascularization. **Conclusions:** OCTA is a relevant tool to aid early detection, guide intervention, monitor treatment response, and understand pathogenesis in a number of pediatric retinal disorders.

Keywords

Coats disease, familial exudative vitreoretinopathy, incontinentia pigmenti, OCTA, OCT angiography, retinopathy of prematurity, sickle cell retinopathy, Stargardt disease, X-linked juvenile retinoschisis

Introduction

Optical coherence tomography angiography (OCTA) is a relatively recent noninvasive imaging modality that maps flow in retinal and choroidal vasculature.[1] It has been used to characterize various ophthalmologic disorders such as age-related macular degeneration, diabetic retinopathy (DR), and glaucoma; however, its role in pediatric retinal disorders is less well established.[2] Through signal decorrelation between consecutive cross-sectional OCT scans at the same retinal location, OCTA software detects differences from moving erythrocytes. Note the allowing mapping of flow through microvasculature at various vascular layers.[1] With this methodology, OCTA can show flow deficits, abnormal vascular distribution, and pathologic vascular layer features.

Unlike fluorescein angiography (FA), which is typically the gold standard for retinal vascular visualization, OCTA is entirely noninvasive and does not require dye, making OCTA imaging faster without the risk of allergic reaction.[3,4] In addition, FA images allow for clear visualization of superficial vascular plexus vessel margins only, can become obscured by dye leakage, and have lower image resolution, whereas OCTA provides depth-resolved, segmented retinal and choroidal flow images. Although current OCTA imaging does not demonstrate dynamic real-time leakage and has limited ability to capture far peripheral images, it does provide a fast, safe, noninvasive method to track and monitor the progression of retinal disorders that might be particularly advantageous in pediatric patients.

Visual outcomes in many pediatric retinal diseases rely on early detection, close monitoring for progression, and evaluation of treatment response; thus, sensitive measures to aid in these aims are invaluable. Because OCTA provides both qualitative and quantitative information about retinal microvasculature and anatomy, it allows for objective assessment of change over multiple visits. Quantitative measures of the foveal avascular zone (FAZ) and vessel density are calculable from OCTA scans, providing repeatable parameters that might relate to disease progression and treatment response.[5] Discernment of the different vascular plexuses is necessary to accurately detect retinal plexuses; different imaging systems often use not only different slab

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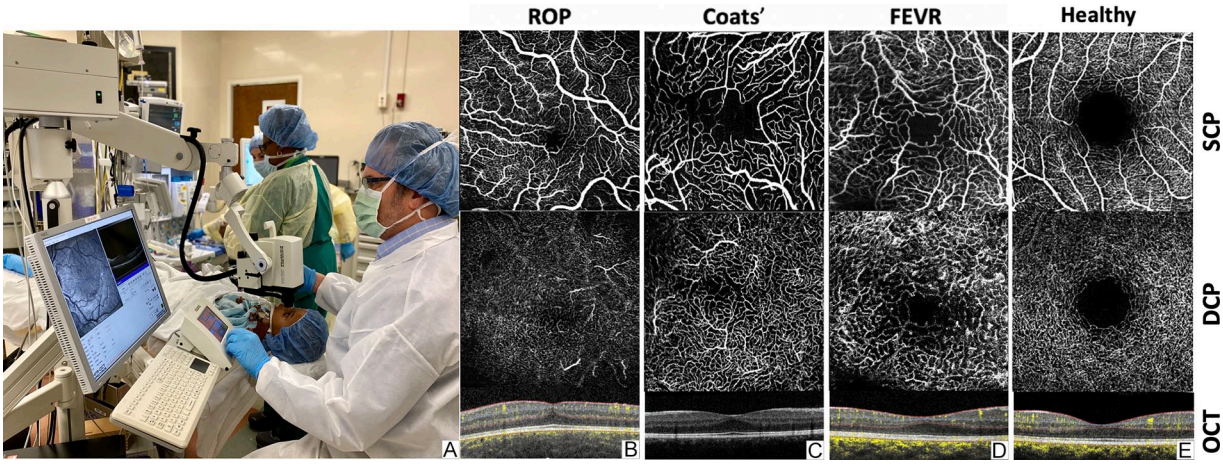

Figure 1. Macular findings in pediatric retinal diseases during examination under anesthesia. (A) Investigational handheld optical coherence tomography angiography (OCTA) unit in use in the operating room. (B) Superficial capillary plexus (SCP) and deep capillary plexus (DCP) with corresponding OCT B-scan in a retinopathy of prematurity patient. Note the decreased foveal avascular zone (FAZ), persistent spiderweb-like central capillary network, decreased vessel density, and superficial vessels diving into DCP. (C) SCP and DCP with corresponding OCT B-scan in a Coats patient. Note the irregular FAZ with crossing vessels. (D) SCP and DCP with corresponding OCT B-scan in a familial exudative vitreoretinopathy patient. Note the decreased FAZ, decreased density, and disorganized vessels with loops and end bulbs. (E) SCP and DCP with corresponding OCT B-scan in a healthy pediatric patient. Images courtesy of Michael P. Kelly.

definitions but also various plexus definitions to differentiate between superficial and deep retinal vasculature. In this paper, we use superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Methods

The current Food and Drug Administration–approved OCTA devices are mounted as tabletop systems for the clinical setting. Real-time tracking and motion-correction software in commercial tabletop OCTA systems might improve imaging in children, in whom motion artifacts, issues with cooperation, and fixation difficulties can produce substantial artifact in OCTA images as well as increased acquisition times.[6] The recent development of an investigational portable OCTA system (Spectralis HRA+OCT with Flex and OCTA module, Heidelberg Engineering) has made it possible to obtain clear OCTA images during examinations under anesthesia with reduced motion or fixation error–induced artifacts, allowing imaging of patients who previously could not be imaged because of a lack of cooperation (Figure 1).[7-9]

In this review, we explore the utility of OCTA in several of the most common pediatric retinal disorders with vascular involvement.

Results

Healthy Children

In pediatric patients without known intraocular disease or significant systemic findings (Figure 1E), it has been observed that there are considerable variations of the FAZ with race as captured by OCTA. Namely, African American patients have been found to have a significantly larger FAZ than White patients.[10] Increasing age in children has also been found to be linked to a larger FAZ, as has been seen in adults.[11] In both the SCP and DCP, vessel length density and vessel area density also vary with age.[10] It has also been demonstrated that decreased perfusion density in the choriocapillaris is associated with older age.[11] There is excellent agreement between eyes in pediatric patients and as such, unaffected contralateral eyes may be used as comparison controls in the assessment of eyes with unilateral disease.[10]

Coats Disease

The pathology in Coats disease is often located in the peripheral retina. Careful examination of the fovea in Coats with OCTA (Figure 1C) has demonstrated previously undescribed anomalous superficial retinal vessels traversing the FAZ in some affected eyes, as seen in Figure 2.[12,13] In addition, an indistinct FAZ with anomalous transverse vessels and vascular congestion in the parafovea has been observed in unaffected fellow eyes.[12,14-16] These findings are consistent with the hypothesis that more cases of Coats disease might be bilateral than previously thought, although they are highly asymmetric in nature. This asymmetry is clearest in marked decreased vascular density in the SCP and DCP in eyes with Coats disease compared with that in fellow eyes. These differences in density have been shown to precede clinical findings and staging.[17]

Initial OCTA devices were limited to imaging small areas of the retina, typically a 3×3-mm or 6×6-mm cube centered on

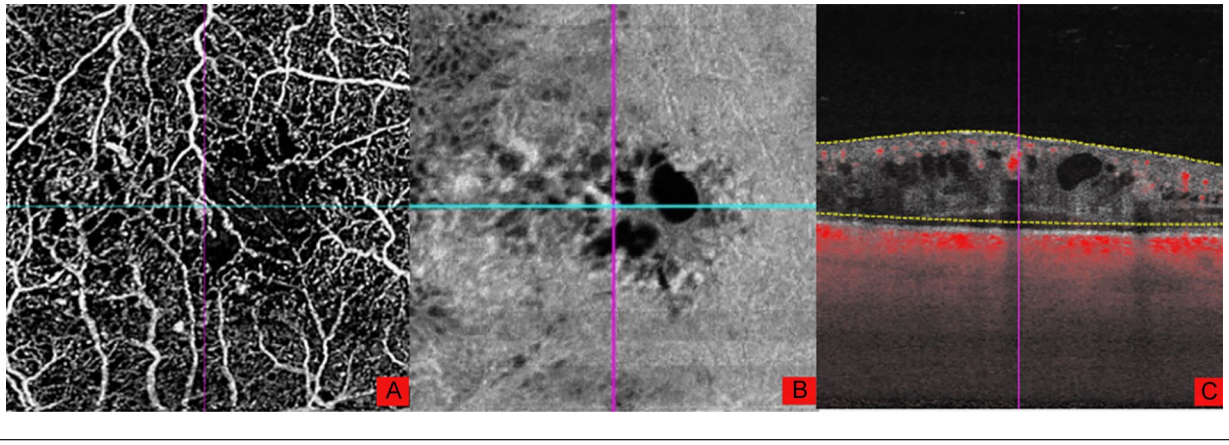

Figure 2. Male patient with unilateral Coats disease in the right eye. (A) Optical coherence tomography angiography (OCTA) 3 × 3-mm full retina slab (Optovue) of the right eye. (B) Enface OCT revealing perifoveal large cysts and smaller cysts peripherally in the right eye. (C) Coregistered structural OCT with flow overlay in the right eye.

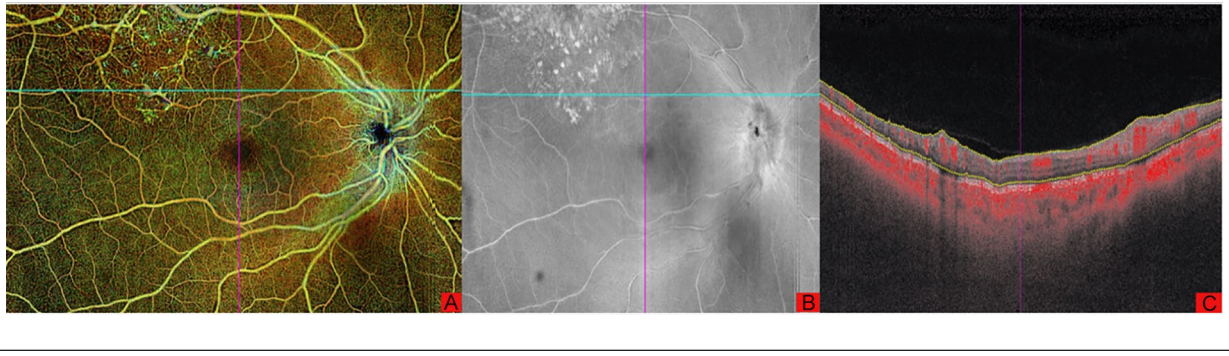

Figure 3. (A) A 15 × 9-mm optical coherence tomography angiography (OCTA; Zeiss Plex Elite SS-OCTA) showing the peripheral focal aneurysmal dilations in Coats disease OCTA. (B) En face OCT. (C) Structural OCT with flow overlay.

the fovea. To obtain images of peripheral vascular anomalies, such as those seen in Coats, small OCTA scans can be targeted eccentrically to the peripheral retina. Newer OCTA devices have larger scanning patterns such as that shown in Figure 3, which is a 15 × 9-mm depth-encoded OCTA showing a full retina slab. This can demonstrate inner retinal microaneurysms and telangiectatic vessels in the SCP extending into the DCP in Coats patients. Each OCTA image is accompanied by an en face OCT (Figure 3B) and structural OCT (Figure 3C), which are useful to localize retinal edema and exudate.

Exudates in Coats disease have been associated with formation of macular fibrosis in the context of aggregates of macular exudates.[18] This finding has been associated with FAZ obliteration by irregular coarse vessels, suggestive of vascularized fibrosis.[13] This macular fibrosis can lead to the development of subfoveal fibrotic nodules that portend poor visual outcomes at baseline and after treatment.[19-21] Type 3 neovascularization might be visualized with OCTA in eyes demonstrating macular fibrosis.[13] OCTA can be used repetitively to monitor retinal edema, neovascularization, and macular fibrosis in Coats; however, it might not completely replace FA, which can reveal dynamic leakage activity and better image far peripheral pathology.[22]

Familial Exudative Vitreoretinopathy

OCTA has revealed microvascular abnormalities in the macula and central foveal capillary network in eyes with familial exudative vitreoretinopathy (FEVR) (Figure 1D), providing evidence that FEVR involves more widespread aberrant angiogenesis than previously thought.[23] Eyes with FEVR have a smaller FAZ area and decreased parafoveal vessel density compared with control eyes as well as vessels crossing the FAZ in some cases.[24] Increased vessel dilation, vascular loops and curls, and macular vasculature straightening have been observed in the SCP, and disorganized vasculature and end bulb vessel terminations were seen in the DCP. These stub-like dilated vessel ends have not been previously described either in healthy patients or patients with pediatric retinal diseases and appear to be unique to FEVR.[23]

An association has been noted between abnormalities of the macular microvasculature and peripheral vascular pathologic

features in FEVR, where decreased macular vessel density on OCTA is correlated with increased peripheral capillary nonperfusion seen on FA.[25] It has also been found that decreased complexity of macular vessels measured from OCTA images is correlated with increased early capillary inflammatory changes, specifically late-phase angiographic posterior and peripheral vascular leakage, as visualized on FA.[25] These macular OCTA findings in FEVR might prove to be a useful way to noninvasively monitor for disease progression of the peripheral retina abnormalities that can portend poorer visual outcomes.[25]

Incontinentia Pigmenti

Retina findings in incontinentia pigmenti (IP) include an avascular retina with ischemia, neovascularization, and fibrovascular scarring that can lead to retinal detachment.[26,27] OCTA has been used to investigate macular vascular abnormalities in IP patients both in the clinic and operating room using an experimental handheld system; findings include decreased SCP and DCP density, decreased macular perfusion through vessels in the superficial and deep plexuses, and abnormal vascular loops.[28-30]

Sickle Cell Retinopathy

In contrast to adults with severe sickle cell disease, whose resulting sickle cell retinopathy can result in enlarged FAZs with irregular contours and avascular density in temporal regions, sickle cell disease in general does not lead to sickle cell retinopathy with visual symptoms in children; however, changes in retinal vasculature in this population are prevalent.[31,32] Decreased flow in the superficial and deep vascular complexes can be seen on OCTA images in sickle cell retinopathy patients. This flow deficit has been shown to be more pronounced in the deep vascular complex in adults on OCTA.[32] In the pediatric population specifically, it has been shown that patients with sickle cell disease have less-dense vasculature on OCTA than age-matched controls.[33] Most recently, a prospective assessment of OCTA images in pediatric patients with sickle cell disease showed flow voids in areas of retinal thinning in all included individuals.[34] It was observed that in all the patients older than 10 years with the genotype HbSS, the flow voids involved both plexuses with more prominent voids in the DCP.

Stargardt Disease

Eyes with Stargardt disease (STGD) show increased intercapillary space centrally in the macula overlying focal outer retinal changes. Regions of overlying retinal pigment epithelium (RPE) and photoreceptor alteration have been found to be larger than regions of choriocapillaris changes, suggesting that RPE and photoreceptor alterations precede choriocapillaris loss.[35,36] Further OCTA studies found that in addition to choriocapillaris loss, a reduction in the SCP and DCP vessel density occurs in STGD.[37] Classification based on OCTA quantification of such vascular network alterations has been shown to be able to detect different morphofunctional STGD phenotype groups in adults.[38]

X-Linked Juvenile Retinoschisis

OCTA findings children and young adults with X-linked juvenile retinoschisis (XLRS) reveal irregular FAZ with an increased FAZ area compared with that in control eyes.[39-41] Flow loss within the DCP that corresponds to the distribution of schisis and a petaloid pattern within the DCP have also been observed.[40] Alterations similar to telangiectasias with tortuous vessels that have abnormal protrusions in the perifovea have been described.[42] These abnormal perifovea vessels are much more notable in the DCP than in the SCP.[39,41] OCTA before and after treatment with acetazolamide and dorzolamide collyrium in XLRS patients showed that DCP density increased post treatment, demonstrating the immediate clinical utility of OCTA in evaluating response to treatment.[43]

Retinopathy of Prematurity

Use of handheld OCTA units in the operating room and neonatal intensive care nursery has shown significantly smaller FAZs with persistent spiderweb-like central capillary networks in children with a history of retinopathy of prematurity (ROP) (Figure 1B).[44-46] Vessel density at the parafovea is also significantly lower in these children than in healthy controls.[45,46] In addition, multiple vascular abnormalities have been found via OCTA in patients with type I ROP. These include irregular angular vascular pattern, large superficial vessels diving into the DCP, SCP vessels in the SCP located deeper than expected, and incomplete perifoveal DCP development.[47]

Interesting and immediate changes in retinal microvasculature following treatment have been described using OCTA before and after laser treatment.[48] Ten days after laser treatment in a neonate with aggressive posterior ROP, OCTA imaging revealed resolution of all plus disease and of previously observed flat neovascularization and its deeper extensions.[48] With a detailed knowledge of a patient's vascular anatomy, treatment modalities such as laser photocoagulation vs antivascular endothelial growth factor injection could be more directly used for each individual patient.

Diabetic Retinopathy in Type 1 Diabetes

DR is exceptionally rare before puberty but can develop in adolescents with type 1 diabetes mellitus (DM1) with similar risk factors as adults (disease duration, glycated hemoglobin A_{1c} [HbA_{1c}]).[49] In pediatric patients aged 12 to 19 years with DM1 without clinical signs of DR, OCTA revealed decreased vessel density in the SCP and DCP,[50] which has been noted as a first sign in diabetic adults who progress to develop DR.[51,52] The reduction in vessel density was noted in the temporal subfield of the macula of children with DM1, suggesting it might be the initial site of pathology.[50] Reduced vessel density in the

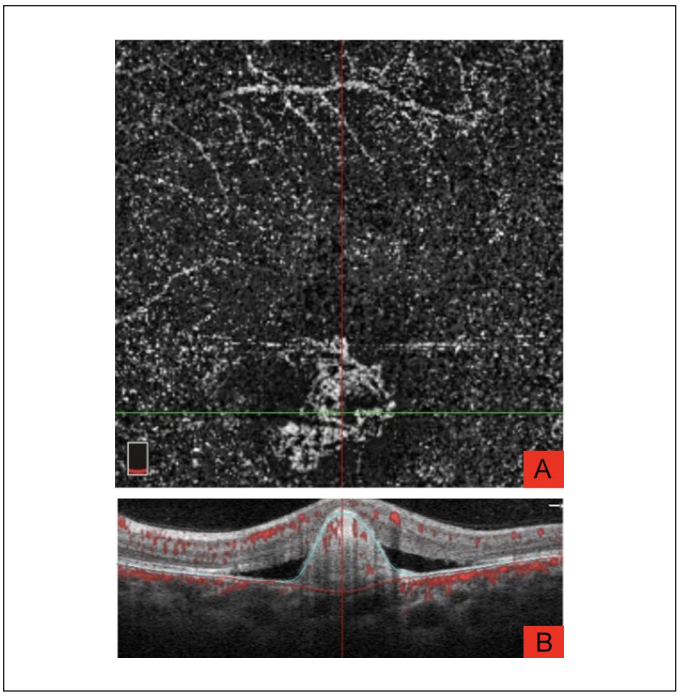

Figure 4. A 15 × 9-mm optical coherence tomography angiography (OCTA; Zeiss Plex Elite SS-OCTA) showing presence of a choroidal neovascular membrane between (A) the retinal pigment epithelium and Bruch membrane and (B) structural OCT with flow overlay.

perifoveal SCP was correlated with increased HbA_{1c} levels in children with DM1.[53] As early OCTA findings are discovered, it might be useful to screen children with DM1 at risk for retinopathy, in particular those with longer disease duration and higher HbA_{1c} levels.

Pediatric Retinal Tumors

OCTA might be useful to characterize pediatric ocular tumors and to evaluate microvascular response to treatment options. However, limited depth penetration with elevated lesions can preclude acquisition of clear images in elevated tumors.

In children with combined hamartoma of the retina and RPE (CHRRPE), marked alterations of the SCP, DCP, and choriocapillaris layers have been imaged with OCTA. These layers were found to have significantly reduced vessel densities in CHRRPE patients compared with the density in healthy controls. Increased tortuosity of superficial vessels and a reduced FAZ area were also observed.[54] At a follow-up 1 year after surgery for epiretinal membrane, OCTA demonstrated a marked reduction in SCP tortuosity and recovery of DCP and choriocapillaris vessel density.[54]

In treatment-naive patients with retinoblastoma, OCTA findings concur with those of FA and include complex branching patterns, irregular vessel caliber, and early termination of vessels.[55] After intravenous chemotherapy, it has been observed that these individuals have lower vessel density in the DCP without alterations in central macular thickness or visual compromise.[56]

Choroidal Neovascularization

The etiology of choroidal neovascularization (CNV) in children differs from that in adults. Type 2 CNV secondary to inflammation, trauma, and idiopathic retinal dystrophies is most common. Vascular flow and distinct patterns in CNV in children can be clearly visualized with OCTA (Figure 4).[57,58] CNV with active vascularity is characterized on OCTA by fine capillaries with frequent anastomoses and vessel loops as opposed to quiescent CNV with low vessel density and no anastomoses or vessel loops. Knowledge of these features combined with structural OCT and clinical examination might help to determine CNV activity and inform retreatment criteria for CNV. At present it can be difficult to determine active vs inactive CNV via OCTA alone in adult retinal disease.[59]

OCTA has also been useful for initial detection of CNV associated with Best vitelliform macular dystrophy. The CNV may be obscured by the vitelliform material and anatomic disruptions on FA; however, OCTA can more clearly image the CNV complex.[60]

Conclusions

The noninvasive and fast nature of OCTA allows for frequent depth-resolved evaluation of microvascular abnormalities in a number of pediatric retinal diseases. OCTA's limited field of view, potential for projection artifacts, inability to visualize low-flow lesions, and depth-resolution issues in elevated lesions are areas that could be enhanced; these issues are the focus of active and diligent research. With optimization, the relevance of OCTA is expanding. The identification of new microvascular features and morphologic changes in pediatric retinal disease provides increased opportunity to predict the presence of disease and monitor early progression, showing promise for OCTA as a useful screening tool. Frequent monitoring of pathological vascular features of pediatric retinal disease processes via OCTA will also allow evaluation of response to treatment during return visits and provide guidance for intervention.

Ethical Approval

This review paper did not involve any research subjects or direct surveillance of patient information. Ethical approval for images acquired from the Duke University Health System Institutional Review Board granted under Protocol00073505 and Protocol00065236.

Statement of Informed Consent

No informed consent needed because this was a review of the literature.

Declaration of Conflicting Interests

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