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Review

OCT Angiography: A Technique for the Assessment of Retinal and Optic Nerve Diseases in the Pediatric Population

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Featured Application: To provide the first review article regarding the use of optical coherence tomography angiography (OCT-A) in pediatric population. The knowledge of its application in the daily clinical practice and research, can help to define future utilities of this complementary technique.

Abstract: Optical coherence tomography angiography (OCT-A) is a novel, rapidly evolving, non-invasive imaging technique that allows images of the retinal vasculature to be obtained in a few seconds. Blood vessels of different retinal vascular plexuses and the foveal avascular zone (FAZ) can be examined without the administration of any contrast or dye. Due to these characteristics, OCT-A could be an excellent complementary test to study retinal vascularization in children. Until now, most of the studies with OCT-A have been conducted in adults and only a few have been carried out in children. In this review, we describe the principles and advantages of OCT-A over traditional imaging methods and provide a summary of the OCT-A findings in retinopathy of prematurity and other retinal and optic disc pathologies in children. In view of the promising results from studies, the advantages of a relatively rapid and non-invasive method to assess the retinal vasculature makes OCT-A a tool of which applications in the field of pediatric ophthalmology will be expanded in the near future for patient diagnosis and follow-up in every day clinical practice.

Keywords: OCT-A; pediatric; retina; optic nerve

1. Introduction

Optical coherence tomography angiography (OCT-A) is a technique that arose in 2013 as a non-invasive diagnostic imaging technique, which can provide data from microvascular retinal flow in a few seconds [1]. To date, there are two gold-standard procedures that are used to study retinal and choroidal circulation: Fundus fluorescein angiography (FFA) [2,3] and indocyanine green angiography (ICGA) [2]. Both procedures require the administration of an intravenous dye with the consequent risk of allergic reactions [2,3]. They are time-consuming [3], and discrimination of the different layers of the retinal and choroidal microvasculature is limited due to the generation of two-dimensional images [4]. On the contrary, OCT-A provides images of the retinal vasculature in a few seconds without the need to use a dye, eliminating the risk of allergic reactions and patient discomfort [2]. In light of the foregoing,

OCT-A could be an excellent ancillary test for the diagnosis and follow-up of several pediatric retinal and optic nerve head pathologies.

OCT-A obtains images of the retinal vessels by comparing the signals of a series of consecutive B-scans performed at the same location [5]. The temporal evolution of the optical coherence tomography (OCT) signal, caused by the motion of scattering particles such as erythrocytes within vessels, allows the visualization of functional blood vessels [2,5–7]. Furthermore, OCT-A allows a separate visualization of different capillary networks (inner retina, outer retina, and choriocapillaris) [4], which are allocated to the superficial or deep retinal slabs depending on the segmentation method and retinal layer designation used by each device [2]. Moreover, in the inner retinal vascular plexus two different plexuses can be recognized: A superficial and a deep vascular plexus [2]. The former would supply the retinal nerve fiber and ganglion cell layers and the latter would supply the inner plexiform, inner nuclear, and outer plexiform layers [2,8,9]. Furthermore, OCT-A is able to examine the size and the contour of the foveal avascular zone (FAZ) [10,11]. The FAZ is an avascular area that results from the absence of terminal capillaries of both superficial and deep plexuses [8]. The FAZ is considered to be of special relevance for the appropriate development of the fovea and it is thought to remain avascular throughout ocular development [12], being already visible at the 25th week of gestational age. In fact, the process of foveal formation begins at the 12th week and continues its development until the individual is 13–16 years old [4]. Such development of the fovea is a sequential process in which several stages can be distinguished. Some of the most relevant stages are: Centrifugal displacement of the inner retinal layers, centripetal displacement of the photoreceptors, and specialization of the cones [8,12–16]. The aim of these changes in the foveal area, in which the FAZ is involved, is to facilitate light transmission to the photoreceptors and avoid as much as possible any potential interference [17,18]. In this regard, some studies have shown that the size and morphology of the FAZ correlates with the visual acuity in some vascular retinal pathologies [19–21].

Another advantage of OCT-A is its ability to provide quantitative information [22,23]. Therefore, it can be very useful to describe the status of the retinal vasculature and help during the follow-up of retinal and optic nerve disorders in which microcirculation is affected. Several quantitative OCT-A parameters have been reported in previous studies such as: FAZ size, vessel density, area of non-perfusion, blood flow index, skeletonized vessel density or vessel length density, and fractal dimension [22,23]. OCT-A has also been shown to have good reproducibility between different operators, as well as good reliability and sensitivity both in the study of healthy subjects and in the study of individuals who have different retinal and/or optic nerve pathologies [1,24].

To date, this complementary technique has been used in the evaluation of common and also infrequent ophthalmologic diseases such as diabetic retinopathy [25–35]; congenital and acquired retinopathies [36]; preretinal, intraretinal, and subretinal neovascularization [37–47]; retinal venous occlusions [48–51]; retinal artery occlusions [52]; macular teleangiectasia [53–57]; senile macular degenerations [58–60]; glaucoma [60–67]; uveitis [68–71]; and optic neuropathies [72–77], among other ocular conditions. Until now, most of these studies describing the use of OCT-A have been conducted in adults with very few studies carried out in pediatric patients [10,12,78–84].

2. OCT-A Applications in Pediatric Population

2.1. OCT-A in Retinopathy of Prematurity

Retinopathy of prematurity (ROP), a vasoproliferative retinal disorder that occurs in preterm children, is one of the leading causes of childhood blindness in the world [85]. This vasoproliferative eye condition is a consequence of abnormal retinal blood vessel growth due to a complex physiopathology that merges vascular endothelial growth factor (VEGF) and insulin-like growth factor I (IGF-I) overexpression, secondary to an incomplete development of the retinal vasculature [86]. Therefore, knowledge about the process of normal retinal vascularization and FAZ development are important to understand the changes that occur in ROP. In healthy subjects, retinal vascularization

arises from mesenchymal cells that are near the hyaloid artery at the 16th week of gestational age. Once the blood vessels have been formed, they grow centrifugally from the optic nerve reaching the nasal ora serrata at the 32nd week and the temporal ora serrata at the 40th week [87]. The development of the FAZ has already been described in the previous section.

Historically, the standard procedure for diagnosing ROP has been indirect ophthalmoscopy performed by an experienced examiner. However, inter-observer agreement has been shown to be variable and subjective by some authors [88]. In this regard, complementary diagnostic tools could be helpful to diminish this variable inter-observer agreement, as spectral domain OCT has allowed the description of several anatomical aspects of ROP and OCT-A is able to provide important information about the retinal vasculature in these infants. Some of these anatomical aspects described with OCT are: Persistence of the inner retinal layers in the foveal center, decreased foveal depression, decreased thickness of the retinal layers, attenuation or alterations of the photoreceptor layer, absence of the outer limiting membrane layer, and absence of the layer that represents the interdigitations between the OS of the photoreceptors and the retinal pigment epithelium [13,89].

Moreover, absence of FAZ has been described by FFA in some patients with ROP [90]. In fact, several studies have reported the absence of FAZ in all patients who suffered from threshold or pre-threshold disease [91,92]. Falavarjani et al. [10] conducted a study in 43 subjects to quantify the FAZ in preterm patients using OCT-A and compared the measurements with age-matched term subjects. These authors found that both gestational age and birth weight influenced the dimensions of the FAZ. In this regard, a lower birth weight and lower gestational age were related to a smaller FAZ and a denser superficial capillary plexus (SCP). On the other hand, they also studied the existing differences between preterm patients who required retinal laser treatment and preterm patients who did not require retinal laser treatment. They found that laser-treated patients had smaller FAZ and greater vascular density in the foveal area. furthermore, among patients with ROP who required laser treatment, there was a higher percentage in which FAZ was not distinguishable. Against all expectations, the vision found in these patients was in some cases as good as 20/20. This finding was in accordance with other previous studies that suggest that the decrease in visual acuity is attributable to a failure in the specialization of the cones that are located in the fovea rather than alterations in the FAZ [12,93].

The following figure provides an example of OCT-A images from a patient with ROP who required laser treatment and a healthy child of the same age. A smaller FAZ and a disruption of the deep capillary plexus (DCP) can be seen in the ROP patient compared with a normal OCT-A of the healthy child in Figure 1.

Imaging children is sometimes challenging due to lack of cooperation, patient motion, poor fixation, and positioning, among other issues. In an effort to overcome these difficulties, new handheld OCT (HH-OCT) and OCT-A (HH-OCTA) devices are undergoing development and validation to determine the role they will play in the clinical management of patients with ROP and children with other ophthalmic pathologies [89,94–97]. In 2010, Maldonado et al. evaluated the specific problems that arose from performing hand-held spectral domain OCT (HH-SD OCT) in children. They tested some technical corrections in the OCT device, which led to an improved image acquisition [94]. Later, Campbell et al. presented a prototype of a portable OCT-A and a portable ultra-wide field OCT [89]. When this device was used with a noncontact lens, only a 40° field of view was obtained, but when a pediatric wide-angle lens and a contact lens were used, almost a 100° × 100° OCT and 20° × 20° OCT-A scans could be obtained in two seconds [89]. The development of these OCT-A portable devices could improve the understanding of choroidal and retinal vasculature development. In addition, portable ultra-wide field OCTs could depict the changes that occur in the peripheral vitreoretinal interface of ROP patients [89,94–97].

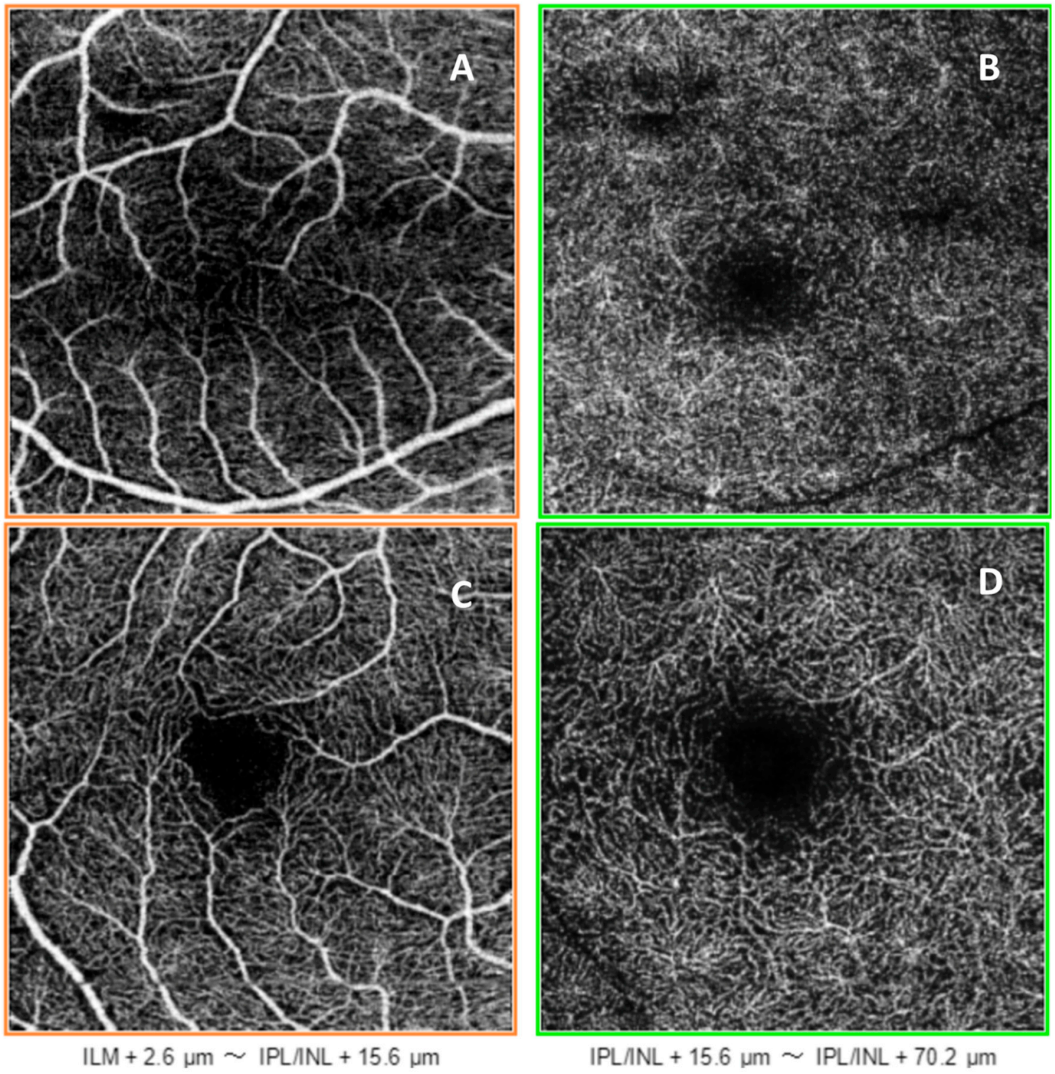

Figure 1. (**A**,**B**) Optical coherence tomography angiography (OCT-A) of 4.5 × 4.5 mm (DRI OCT Triton (plus), TOPCON Co., Japan) corresponding to the right eye of a patient with ROP that required laser treatment. In the superficial capillary plexus (SCP) segmentation (**A**), a decreased foveal avascular zone (FAZ) (43.97 µm^2) and disorganization of the capillaries in the deep capillary plexus (DCP) (**B**) were observed. (**C**,**D**) OCT-A of 4.5 × 4.5 mm (DRI OCT Triton system, Topcon) corresponding to a patient born at term of the same age as the first patient. We can appreciate a bigger FAZ (265,694 µm^2) in this case and a normal capillary architecture in the DCP (**D**).

2.2. Applications of OCT-A in Other Pediatric Retinopathies

OCT-A has been used in the study of other pediatric retinal pathologies including X-linked retinoschisis (XLRS) [78,98,99], an X-linked recessive disorder that occurs almost exclusively in young males and that entails an early-onset bilateral visual loss due to foveal schisis. In these studies, a reduced macular deep vessel density was seen. This finding was attributed to a displacement and disruption of the vessels due to schitic cysts [98,99].

OCT-A has also been used to study epiretinal membranes in children, which are a rare condition and usually secondary to other pathologies or personal past ophthalmic histories [78]. However, an erroneous segmentation due to an important anatomic disruption made it difficult to interpret the images provided by OCT-A [78].

OCT-A use has also been reported in the study of Best vitelliform macular dystrophy (BVMD) [78], the most frequent macular dystrophy characterized by yellowish vitelliform or egg yolk-like lesions

that are usually localized in the macular area [100,101]. In these patients, OCT-A was found to be useful to detect choroidal neovascularization (CNV) associated with BVMD.

Furthermore, OCT-A has been used to investigate retinal vascular networks in patients with Coats' disease [78,102], of which etiology and pathophysiology remain to be studied in greater depth. In this ocular disease, OCT-A demonstrated saccular aneurysmal dilatations [78] and suggested that a distortion of the inner blood–retinal barrier takes place in this entity, probably due to a bilateral defect in midcapillary angiogenesis [102].

Furthermore, OCT-A has been used to study children with idiopathic and secondary-to-laser-pointer-exposure CNV. Thus, children with idiopathic CNV showed type 1 CNV on OCT-A, while patients with secondary-to-laser-pointer-exposure CNV had type 2 CNV on OCT-A [79]. Regarding CNV in the pediatric population, it is interesting to remember that, unlike what happens in the adult population, CNV in children is more often a classic type 2 membrane affliction and they do not have thickening or calcification of Bruch's membrane, nor diffuse disruption of the retinal pigment epithelium [103]. Moreover, CNV in the pediatric population usually has a solitary vascular in-growth site, as opposed to what happens in age-related macular degeneration-associated CNV [103].

Some patients with foveal hypoplasia, a condition that can be present in aniridia, albinism, nanoftalmos, incontinentia pigmenti, retinopathy of prematurity, and achromatopsia, have been studied with OCT-A [12]. The findings in these cases commonly include the presence of SCP and the absence of DCP [12].

OCT-A may be particularly useful in the study of patients with paracentral acute middle maculopathy (PAMM) as it has been proposed that an ischemia of the capillaries in the DCP is the possible cause and FFA is limited in visualizing vascular lesions located in this vascular plexus [103]. Thus, OCT-A of patients with PAMM show images corresponding to perfusion of the acute focal lesions followed by a reduction of blood flow in the deep vascular plexuses in long term cases. On the other hand, this entity may also be idiopathic or secondary to vascular diseases of the retina or systemic vascular diseases. When the disease is secondary to an occlusion of the central retinal artery, a marked hypoperfusion of the deep capillary plexus is observed [103].

2.3. Applications of OCT-A in Children in Other Conditions

With regard to the use of OCT-A in congenital alterations of the optic nerve, a dense peripapillar microvascular network has been shown in Morning Glory syndrome, a network that is absent both in colobomas and in optic disc pits [81]. With respect to papillary edema and papillitis, greater vascular tortuosity and dilatation have been described in the prelaminar capillary network [74], a fact which can be seen in Figure 2.

Recently, OCT-A has also been used to assess the vascular density of the retinal capillary and radial peripapillary plexuses and FAZ in children with amblyopia. [104,105]. A reduced macular vessel density in both the SCP and the DCP was found in amblyopic patients when compared to control eyes. The decreased vessel density that was found in amblyopic eyes has been hypothesized to be secondary to alterations in the retinal or choroid microvasculature due to underuse or to congenital or acquired retinal vascular capillary disorders associated with amblyopia [104,105]. In addition, the absence of abnormalities in the papillary and peripapillary vessel density in amblyopic eyes found in the study of Lonngi et al. [104] supported the findings of the Pediatric Eye Disease Investigator Group, in which amblyopia did not seem to be related with a pathologic condition of the optic nerve [106]. Finally, amblyopic eyes did not show differences in the dimensions of the FAZ in the SCP and DCP when compared to healthy controls in any of the studies [104,105].

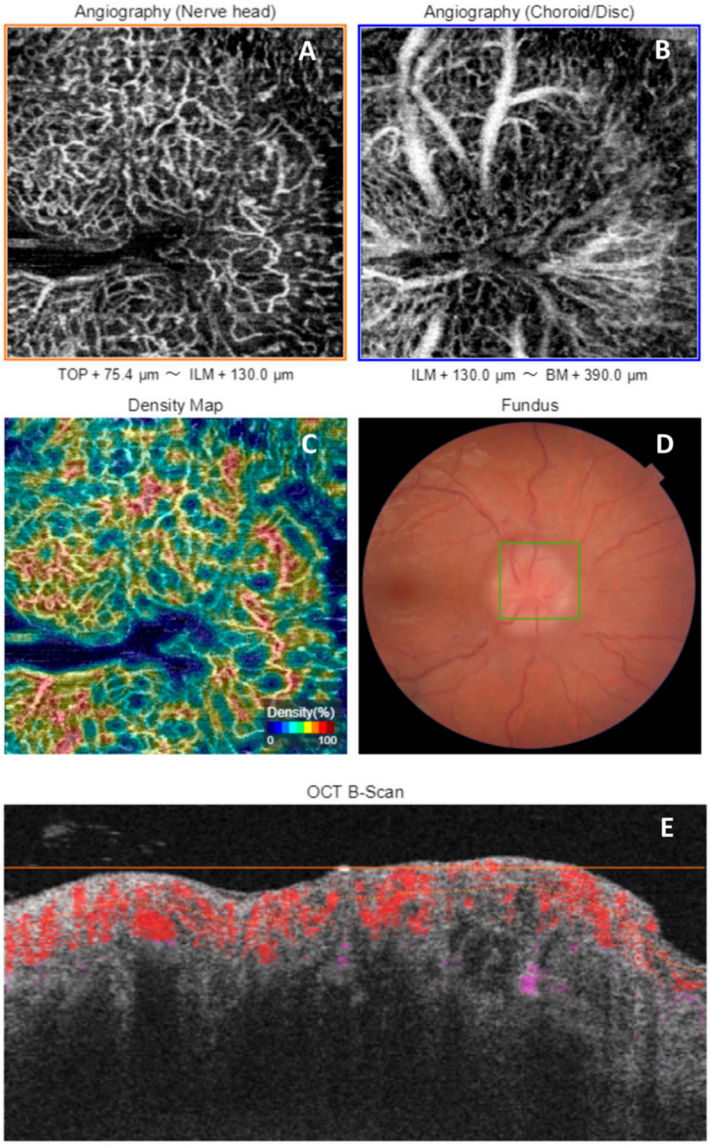

Figure 2. Optic nerve OCT (DRI OCT Triton system, Topcon) corresponding to the right eye of a patient with chronic bilateral papilledema secondary to intracranial hypertension (**A**–**E**). (**A**,**B**) Vascular tortuosity in different segmentations and enlargement of the vessels and capillaries can be seen. (**C**–**E**) The corresponding vessel density map, fundus photograph and B scan are provided in (**C**–**E**) respectively.

3. Future Perspectives

Despite the mentioned advantages, OCT-A is still infrequently used in children. Only few ophthalmic pediatric conditions have been studied by OCT-A and normal values for patients younger than 18 years are not available yet. Although there have been some initial reports for Chinese children [84], normative databases for OCT-A parameters in healthy pediatric populations for other ethnicities is still not accessible. Moreover, in all likelihood a specific database should be built for each of the commercially available OCT-A devices since they use different segmentation algorithms.

A non-invasive technique such as OCT-A would be ideal for pediatric disease screening purposes in patients at risk or as an aid in assessing the stage of a disease. For example, studies by OCT-A in diabetic adults have found a correlation between microvascular abnormalities and different stages of the retinopathy. Even in diabetic patients, with the absence of diabetic retinopathy, some alterations have been found [39]. Until now, OCT-A measurements between healthy and diabetic children without

retinopathy have not shown differences and longitudinal studies will be needed to stablish if these measurements have any predictive value [107].

OCT-A could also be useful in a different spectrum of pediatric conditions in which anatomic ocular changes are not a hallmark of the disease. In this regard, a recent study has found that OCT-A reveals diminished superficial and deep retinal capillary density in the macula of patients with amblyopia [104]. In the future, pediatric neurologic diseases could also be analyzed by OCT-A in search for new biomarkers.

4. Conclusions

Since the introduction of conventional OCT in 1991 [108] and the emergence of OCT-A around 2013, we have witnessed from our experience [109–114] and the experience of the scientific community that this technology is constantly evolving [115,116]. OCT-A is a novel, relatively rapid, and non-invasive imaging technique that can be useful in distinguishing the blood vessels of the different retinal vascular plexuses and the FAZ. It can provide qualitative and quantitative information. To date, few OCT-A studies have been published in pediatric subjects to assess children with retinopathy of prematurity, choroidal neovascularization, foveal hypoplasia, PAMM, congenital alterations of the optic nerve, and other pediatric macular diseases. The advantages of this technique in assessing the retinal vasculature makes OCT-A a tool of which applications in the field of pediatric ophthalmology will be expanded in the future for the diagnosis and follow-up of patients in clinical practice.

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