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OCT Angiography in Young Children with a History of Retinopathy of Prematurity

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Purpose: To describe the size and appearance of the foveal avascular zone (FAZ) in the superficial and deep plexus in young children with treated or spontaneously regressed retinopathy of prematurity (ROP), in comparison with age-matched controls and young adults, as seen with OCT angiography (OCTA), and to compare these parameters with foveal classic OCT images and visual function.

Design: Prospective, cross-sectional study.

Participants: Twenty-five children with treated or spontaneously regressed ROP (mean 5.0±0.8 years) compared with 15 healthy term-born age-matched children and 20 healthy adults.

Methods: OCTA was performed using a DRI OCT Triton (Swept Source OCT, Topcon, Oakland, NJ). The best-quality images of 1 eye per patient were analyzed. Superficial FAZ and deep FAZ were analyzed separately. Single-scan OCTs were performed using a Spectralis SD-OCT (HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). The foveal pit characteristics and the degree of macular developmental arrest (MDA), defined as the ratio of the outer nuclear layer + external limiting membrane (ONL+) and the inner retinal layers in the fovea (ONL+/IRL-ratio), were analyzed with a custom-made automated layer segmentation tool (DiOCTA, copyright by Justus-Liebig-University, Giessen, Germany). Visual acuity (VA) was tested with Early Treatment of Diabetic Retinopathy Study letter charts.

Main Outcome Measures: The ONL+/IRL-ratio, superficial FAZ area, deep FAZ area, foveal parameters, and VA.

Results: Foveal pit depth and area were significantly reduced in both treated and spontaneously regressed ROP, whereas the foveal diameter was comparable in all groups. OCTA showed a significantly narrowed superficial FAZ in eyes with treated and spontaneously regressed ROP. In contrast, the deep FAZ was of comparable size in all groups. A reduced superficial FAZ significantly correlated with reduced ONL+/IRL-ratio, and thus the degree of MDA. In treated and spontaneously regressed ROP, reduced superficial FAZ and MDA correlated significantly with diminished VA.

Conclusions: OCTA is feasible in young children with a history of ROP and without neurodevelopmental delay. It allows detecting a decreased superficial FAZ size noninvasively. A small superficial FAZ, reduced ONL+/IRL-ratio as a measure of MDA, and reduced VA are concurrent factors in preterm children who are otherwise neurologically normal. *Ophthalmology Retina 2018;■:1–7 © 2018 by the American Academy of Ophthalmology*

The adult human fovea is a specialized region of the central posterior pole of the human retina and confers higher visual acuity (VA) than do other areas of the retina. This effect is attributed to an optimal configuration of retinal components that minimize light scatter, in particular vertically arranged elongated cones separated from each other by the processes of the radial fibers of Müller cells.[1,2] Inner retinal layers are displaced eccentrically from the fovea, resulting in a characteristic morphologic pit, which is accompanied by the absence of blood vessels overlying the outer nuclear layer (ONL). This avascular region is known as the foveal avascular zone (FAZ). The human retina contains 2 plexus, the superficial plexus located within the retinal nerve fiber layer (RNFL) and the deep plexus localized within the inner plexiform layer (IPL). These plexus are connected via a set of transverse capillaries. At the fovea, both plexus are physiologically absent, thus forming the FAZ, with the superficial plexal hiatus being approximately 600 μm in diameter, whereas the deep plexal hiatus is approximately 900 μm in diameter in healthy young individuals.[3]

The retina is one of the last tissues of the developing fetus to undergo vascularization, a process that begins at 14 to 16 weeks postconception.[4–6] While blood vessels proliferate across the retina, antiproliferative and anti-angiogenic factors expressed within the foveal region prevent the extension of capillaries into the incipient fovea, resulting in the FAZ.[7,8] The formation of the foveal pit involves centrifugal migration of inner retinal neurons away from the center and a centripetal migration of cone cell nuclei,[9] with the absence of foveal blood vessels as part of this development.[10] Data suggest that 24 to 27 weeks postconception is a critical period for the development of the fovea, including development of the perifoveal vascular plexus and formation of the foveal pit,[6] whereas

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Table 1. Demographic and Clinical Description of Preterm-Born Children and Full-Term Born Controls

Group	Patients = Eyes [n]	Age (yrs); Mean ± SD	Gender (M/F)	Stage (1/2/3)	Zone (I/II/III)	Treatment (Laser/Anti-VEGF)	GA (wks); Mean ± SD	GW (g); Mean ± SD	BCVA (logMAR); Mean ± SD	SER (D); Mean ± SD
Treated ROP	10	5.0±0.8	10/0	0/1/9	2/8/9	6/4	24.0±1.3	668.5±168.2	0.22±0.11	0.4±1.0
Spontaneously regressed ROP	15	4.9±1.5	11/4	4/11/0	0/10/5	—	26.3±2.0	790.5±260.7	0.08±0.14	1.1±2.2
Term-born children	15	5.1±1.4	6/9	—		—	—	3588±684.2	−0.02±0.04	1.3±1.7
Adults	20	29.4±10.7	6/14	—		—	—	—	−0.03±0.04	−1.1±1.3

Anti−VEGF = Anti−vascular endothelial growth factor therapy; BCVA = best-corrected visual acuity; D = diopter; GA = gestational age; GW = birth weight; logMAR = logarithm of the minimum angle of resolution; ROP = retinopathy of prematurity; SD = standard deviation; SER = spherical equivalent.

foveal cone packing proceeds throughout this critical period.[11] Any disturbance of the development during this critical period may affect VA.

Spectral-domain OCT (SD-OCT) studies in preterm children with or without a history of retinopathy of prematurity (ROP) described shallowed or absent foveal depressions and increased retinal thickness due to additional inner retinal layers overlying the ONL with a small or absent FAZ in a considerable number of former preterm subjects.[12–17] To describe this process, we suggested the term "macular developmental arrest" (MDA).[17] In the present study, we used the recently introduced OCT angiography (OCTA) to noninvasively assess FAZ architecture of the superficial and deep capillary plexus (superficial FAZ and deep FAZ). Furthermore, we investigated whether FAZ parameters correlate with other morphologic or functional foveal abnormalities in preterm children with a history of treated ROP or spontaneously regressed ROP. The data were compared with data from healthy age-matched term-born children and healthy adults.

Methods

Participants

This was an observational, prospective study. Research followed the tenets of the Declaration of Helsinki. Ethical approval was obtained from the local institutional ethics committee (Az 150/1). The study comprised 10 young children with treated ROP (6 with laser; 4 treated with intravitreal bevacizumab, 0.312 mg in 0.025 ml), 15 children with spontaneously regressed ROP, 15 healthy term-born age-matched children, and 20 term-born healthy adults. None of the healthy subjects reported a history of ocular or systemic disease, and results of a comprehensive eye examination were normal in all. The table-mounted OCTA technique requires a certain degree of collaboration from all children participating in the study. Therefore, only premature children without neurologic or mental/psychologic deficits or impairments, tested on a regular basis in pediatric screenings, were chosen to participate in the study. Demographics, gestational age at birth, birth weight, and ROP-related parameters are displayed in Table 1. Best-corrected VA was assessed using Early Treatment of Diabetic Retinopathy Study letter charts. Experienced orthoptists assessed VA in our clinic.

In all children, only best-quality OCTA images of 1 eye were used for analysis. In healthy adults and in children with equal-quality images in both eyes, the analyzed eye was randomly selected.

Foveal Pit Metrics

The Spectralis SD-OCT (HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) was used to obtain all standard scans. Spectralis uses an 870-nm wavelength imaging laser to obtain 40 kHz A-Scans and 1.536 A-Scans per B-Scan. The B-Scan was averaged at least 80 times to obtain high-quality single scans. The central SD-OCT single-line scan was used to determine the foveal metrics presented in Figure 1A. Layer segmentation was performed using the custom-developed segmentation tool DiOCTA (copyright by Justus-Liebig-University, Giessen, Germany)[18] and exported into a customized MatLab (MathWorks, Natick, MA) program. The highest peaks at the nasal and temporal aspects of the fovea were determined in an automated fashion. Foveal diameter was defined as the rim-to-rim distance in micrometers (shortest linear distance between the highest temporal and nasal peaks). The depth of the foveal pit (foveal depression) was defined as the difference in micrometers between the rim-to-rim vector and the lowest foveal pit position in micrometers. The foveal depression surface area (area under the curve) was calculated as the area within foveal circumferential margins and the foveal surface curve in square millimeters, defined by the surface of the nerve fiber layer (NFL).

ONL+/IRL-Ratio

The thicknesses of 6 retinal layers were quantified automatically from SD-OCT images in the central single scan. Measured were RNFL, ganglion cell layer plus inner plexiform layer (GCL+IPL), inner nuclear layer plus outer plexiform layer (INL+OPL), outer nuclear layer plus external limiting membrane (ONL+ELM, in short ONL+), inner segment plus inner ellipsoid segment of the photoreceptor layer plus outer segment of the photoreceptor layer (ellipsoid + OS), and retinal pigment epithelium (RPE). The ratio of ONL+ to the sum of the inner retinal layers (NFL+GCL+IPL+INL+OPL = IRL) at the foveal center was calculated as described in our recent publication (Fig 1B).[17] Central foveal thickness was defined at the central OCT A-Scan as the thickness of the entire retina from the inner aspect of the internal limiting membrane to the inner aspect of the RPE.

FAZ Measurement

The DRI OCT Triton (Swept Source OCT = SS-OCTA, Topcon, Oakland, NJ) was used for OCTA image acquisition. The Triton uses a 1.050-nm wavelength laser beam with 100 kHz A-Scans. A 6.0 × 6.0-mm angiography scan was centered on the fovea. Both the superficial and deep vasculature network were imaged simultaneously. The superficial vasculature network was assumed to be between the layer boundaries of the internal limiting membrane (+2.6 μm) and IPL (+15.6 μm), and the deep vasculature network between the layer boundary of IPL (+15.6 μm) and a parallel layer in a distance of 70.2 μm toward the RPE. All angiography images