• Letter to the Editor •

A practical imaging marker to determine the posterior zone II location in premature infants

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Dear Editor,

We identified a hypopigmented area located approximately at the boundary between zone I and zone II during routine examination and imaging for retinopathy of prematurity (ROP), and in this study we aimed to evaluate the potential of this finding as a practical anatomical marker for defining ROP zones.

ROP is a retinal vasoproliferative disorder affecting preterm infants, commonly leading to childhood visual impairment globally[1-2]. The location of retinal vascularization in infants is a critical indicator for assessing the risk of ROP development. In order to facilitate the documentation of vascularization progression and foster a standardized terminology among ophthalmologists, thus enabling consensus on the course and severity of the disease, the retina has been divided into three zones centered around the optic disc. Basically, zone I defines a circular area with radius twice the estimated distance from the optic disc center to the foveal center and zone II indicates a ring-like area extending nasally from the outer limit of zone I to the nasal ora serrata along with a similar distance temporally, superiorly, and inferiorly. Zone III is the crescent-shaped area extending from zone II periphery to the temporal ora serrata. In the last edition of International Classification of Retinopathy of Prematurity, Third Edition (ICROP 3), the area that includes two-disc diameters away from the zone I border has been defined as posterior zone II. This definition is clinically significant because ROP located posterior zone II may behave more aggressively than disease in the more peripheral zone II location[3].

In practice, a 28 D lens is utilized to identify the boundary between zones I and II during indirect ophthalmoscopy. Aligning the edge of the lens to visualize the nasal border of the optic disc, the boundary of the retinal area observed temporally corresponds to the boundary between zones I and II[3]. Despite the redefinition of the zone II posterior boundary in ICROP 3, individuals with limited expertise in ROP may face challenges in delineating the posterior zone II location during indirect ophthalmoscopy. Therefore, the aim of this study is to evaluate the potential use of a previously undescribed “hypopigmented area”, localized at the beginning of posterior zone II, as a practical anatomical marker for identifying the zone I-II boundary during ROP examinations.

Retrospective analysis of premature infants who underwent fundus examination and ultra-widefield fundus photography (UWF) at the Department of Ophthalmology, Faculty of Medicine, between December 2022 and December 2023. Ethics approval was not required for this retrospective study based on anonymized imaging data, and all procedures adhered to the tenets of the Declaration of Helsinki. The gestational age and postnatal age at the time of UWF imaging were obtained.

All examinations and UWF imaging were performed by two experienced ophthalmologists specialized in ROP management (Kola M and Günay M). For this purpose, after pupil dilation, a topical anesthetic drop was applied and an eyelid speculum was placed. Subsequently, fundus examination was performed using indirect ophthalmoscopy with 20 D and 28 D condensing lenses. Then, the Optos device (Optos plc, Dunfermline, UK), which operates on the principle of confocal scanning laser ophthalmoscopy, was employed for UWF imaging, enabling visualization of up to 200 degrees of the retina in a single capture[4]. Devices such as RetCam, 3nethra neo, Pictor, and Optos are widely used for the documentation of ROP. Although Optos has certain limitations—such as being a nonportable system, the potential for artifacts from the eyelid, eyelashes, or speculum if not properly positioned, and the need to hold the infant upright in a specific posture—Optos imaging was employed in this study due to its accessibility and its ability to provide wide-field, high-contrast, non-contact retinal images[4].

During imaging, all infants were positioned in a special posture known as the flying baby position[5], with the chin resting on the palm of the hand and the baby being supported on the forearm. No deterioration in the vital signs of any infant was observed during imaging.

All fundus photographs were reviewed by the same two independent retinal specialists, and zone markings were made. A localized hypopigmented area was identified at the temporal fovea. The relationship between this area and the boundary of posterior zone II was assessed. The distance between the localized hypopigmented area at the temporal fovea and the optic disc head was also calculated.

A total of 64 premature infants with ROP were included in the study, with a mean gestational age of 31±3.3 (23-36)wk. Each eye of the infants underwent an average of 4.7±4.4 (1-24) consecutive UWF imaging sessions. Totally, 554 of 600 UWF images (92.3%) from both eyes revealed the presence of a hypopigmented area localized at the temporal fovea. Analysis of the images identified that the beginning of this hypopigmented area (border near the fovea) approximately corresponds to the beginning of posterior zone II (Figure 1).

The first UWF imaging session was obtained at an average postnatal age of 58.3±32.1 (15-185)d. Measurements of the distance between the onset of the hypopigmented area and the temporal border of the optic disc were made using the initial imaging. This distance was found to be an average of 9.9±0.66 mm (8.1-11.4 mm) for the right eye and 9.7±0.77 mm (8.0-11.3 mm) for the left eye.

Among the 64 infants, 4 did not exhibit the described hypopigmented area in either eye from the initial visit, while in 6 infants, this area disappeared in both eyes after a mean postnatal period of 171.7±66.97 (78-260)d. Additionally, it was observed in subsequent visits that there was an increase in pigmentation in the area and/or a reduction in its size (Figure 2).

In this study, we identified a hypopigmented area at the temporal fovea as a novel anatomical marker in premature infants. This region could serve as an alternative landmarker for determining the beginning of the boundary between zones I and II during indirect ophthalmoscopy using a 28 D lens[3]. Furthermore, during examinations conducted with a 20 D lens, scleral depression performed to evaluate the temporal peripheral region and/or when the optic disc is not within the visualized area, may provide an anatomical indicator facilitating the identification of retinal vessels.

The increasing utilization of artificial intelligence (AI), machine learning (ML), and deep learning (DL) in ophthalmology has also found its place in ROP diagnosis and monitoring. With the growing success rates in the evaluating ROP-related parameters such as location, stage, pre-plus, and plus disease, AI applications is increasingly being integrated into ROP management[6-8]. We believe that the hypopigmented area described in premature infants could serve as an anatomical marker for future-ML based applications in ROP imaging and zone classification.

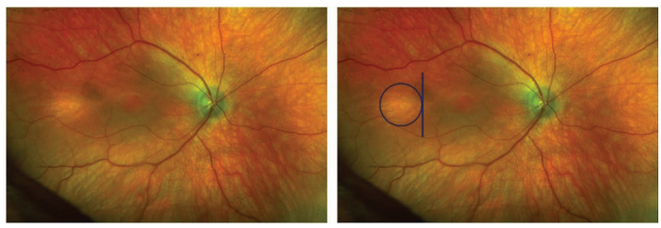

Figure 1 The ultra-widefield fundus photograph (UWF) was obtained at the 34th postnasal week of a preterm infant born at 30wk gestational age with retinopathy of prematurity (ROP) In the temporal region, hypopigmented areas are observed at the boundary of zone I and zone II.

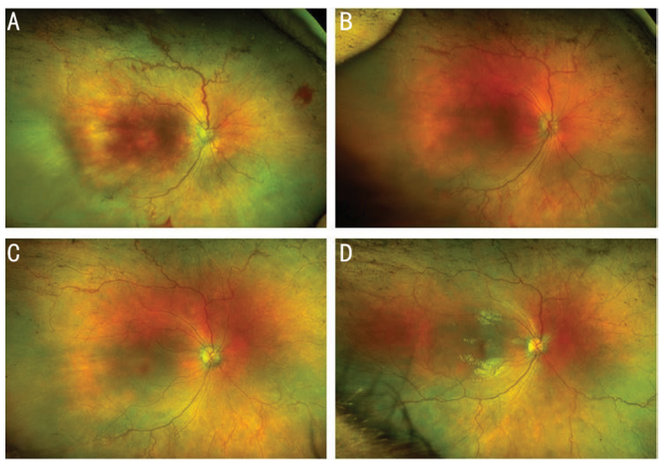

Figure 2 The ultra-widefield fundus photographs (UWF) of an infant with retinopathy of prematurity (ROP) born at 29wk gestational age, obtained during sequential follow-up sessions A: 33wk; B: 37wk; C: 49wk; D: 57wk. All examinations revealed hypopigmented areas at the border of zone I-II; however, it was observed that as the patient's age progressed, the size of the area decreased, and pigmentation increased.

The exact origin of this hypopigmented area remains uncertain; however, it may reflect relative immaturity or delayed pigmentation of the retinal pigment epithelium (RPE) in the developing temporal macula. The gradual disappearance or darkening of this region with increasing postnatal age may correspond to the maturation of the RPE and macular structure. In our study, we observed that with advancing age, pigment accumulation within this hypopigmented area increased, while the size of the area decreased or it disappeared completely. These findings suggest that the hypopigmented area may represent a histological stage in retinal development and indicate the need for larger and longer-term follow-up studies to further investigate this hypothesis. Furthermore, we believe that this hypopigmented area may be associated with the temporal bulge during macular development[9].

In future studies, it will be important to determine the anatomical characteristics of this hypopigmented area we have identified. For this purpose, there is a need for studies that include a larger series of infants with similar gestational ages, conduct imaging sessions more frequently, and also incorporate measurements of axial length and corneal diameter.

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