Peripapillary Choroidal Thickness in Former Preterm and Full-Term Infants Aged From 4 to 10 Years

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Purpose. The aim of the study was to investigate peripapillary choroidal thickness in former preterm and full-term infants with spectral-domain optical coherence tomography (SD-OCT).

Methods. Subanalysis of infants with successful peripapillary choroidal thickness measurements of a prospective, controlled, cross-sectional, hospital-based study in a tertiary center of maximum care. The study examined 503 infants aged 4 to 10 years at the time of examination. Infants were divided into different groups: group 1 born with gestational age (GA) ≥37 weeks, group 2 born with GA between 29 and 32 weeks without ROP (retinopathy of prematurity), group 3 born with GA ≤28 weeks without ROP, and group 4 born with GA ≤32 weeks and presence of ROP.

Results. Peripapillary choroidal measurements were available for 388 of 503 participants. No significant differences were found among the four groups for global peripapillary choroidal thickness. Multivariable analysis revealed no association with low GA, birth weight, ROP occurrence, perinatal adverse events, and logMAR visual acuity. Only infants born small for GA (SGA) revealed peripapillary choroidal thinning in the superior ($P = 0.033$) and nasal ($P = 0.024$) sectors compared with infants born appropriate for GA (AGA). Infants SGA had lower visual acuity than AGA infants (0.03 ± 0.07 logMAR SGA versus 0.01 ± 0.05 logMAR AGA; $P = 0.029$).

Conclusions. Our results indicate that prematurity itself does not affect choroidal thickness in the peripapillary region. Only infants born SGA revealed peripapillary choroidal thinning compared with AGA infants. Our data indicate that fetal growth restriction leads to choroidal long-term alterations in the peripapillary region.

Keywords: prematurity, peripapillary choroidal thickness, low gestational age, low birth weight, retinopathy of prematurity, visual acuity

Prematurity leads to an abrupt change of the fetal environment, with numerous effects on infant outcome as well as on the ocular and choroidal development. The choroid has important functions in providing oxygen, nutrition, and support for the outer retina as well as the regulation of eye growth.[1] In recent studies, an association of submacular choroidal thinning with low birth weight, low birth length, and regressed retinopathy of prematurity (ROP) was detected.[2,3] Possible alterations of the submacular choroid may also cause lower visual functionality in infants with ROP.[4]

Although submacular choroidal structures in prematurity have been analyzed, no data exist on whether the peripapillary choroidal development is also affected by prematurity. Only for adults has an association of peripapillary choroidal thickness and severe ocular pathologies been reported.[5–8] For infants, only limited data about peripapillary choroidal thickness are available. In one study, Read et al.[9] reported that thinning of the peripapillary choroid was associated with myopia in childhood.

Detailed measurement of the choroid is now possible with spectral-domain optical coherence tomography (SD-OCT) which has facilitated an increased understanding of the ocular anatomy of former preterm infants.[2,4,10,11]

Our present prospective investigation aimed to assess peripapillary choroidal thickness in a cohort of former preterm infants with ROP compared with preterm infants without ROP, and that of former full-term neonates, considering the associated influencing factors, such as gestational age (GA), pre- and postnatal history, the presence or absence of ROP, and ophthalmologic findings using SD-OCT.

Methods

This trial was conducted in accordance with the Declaration of Helsinki. Study approval was obtained from the local ethics committee (Physician Chamber, Hessen, Germany). Written informed consent was obtained from the parent or legal guardian of each child before study entry. The authors declare no financial or proprietary conflict of interest.

Participants

The Wiesbaden Prematurity Study (WPS) was performed at the Helios Dr. Horst Schmidt Klinik (tertiary center of maximum

care with level IV neonatology) in Wiesbaden, Germany. Between July 2014 and March 2015, we examined former preterm infants born in our hospital with a GA of ≤32 weeks and full-term newborns with a gestational age ≥37 weeks, currently aged from 4 to 10 years. Designated participants were contacted by phone and invited for ophthalmologic assessment and SD-OCT measurement. Data of infants with successful peripapillary choroidal SD-OCT measurement were analyzed in the present study.

Subjects with severe congenital anomalies were excluded from the study. Data from the WPS were included in the study if peripapillary SD-OCT scan implementation was achievable without significant movement or acquisition artefacts and choroidal thickness measurement with the Heidelberg analysis software tool was possible. The following were the exclusion criteria: execution of SD-OCT scan was not possible, SD-OCT scan quality was low because of unstable fixation, choroidal thickness measurement was not conceivable, spherical equivalent exceeded ± 5 diopters (D), or astigmatism exceeded 3 D. We excluded infants with refractive errors of more than 5 D and adjusted data analysis for axial length and refractive error to minimize statistical errors due to varying axial length and refractive errors between the different groups.

For statistical analysis, infants were grouped to former full-term neonates with GA ≥37 weeks (group 1), preterm infants of GA between 29 and 32 weeks without ROP (group 2), preterm infants of GA ≤28 weeks without ROP (group 3), and preterm infants with ROP occurrence after birth and GA ≤32 weeks (group 4). An additional evaluation with the inclusion of all participants (preterm infants and full-term neonates) was performed comparing all infants born with birth weight below the 10th percentile (small for GA [SGA]) and with infants born with birth weight ≥10th percentile (appropriate for GA [AGA]).[12–14] Ultrasound sonography was performed in the last trimester as described in the obstetric charts.

Assessment of Pre- and Postnatal History

The medical records of all participants were evaluated and parents completed a detailed questionnaire. Prematurity complications, according to international definitions, such as bronchopulmonary dysplasia, sepsis, periventricular leukomalacia, intraventricular hemorrhage, and necrotizing enterocolitis, were recorded as perinatal adverse events. According to German screening guidelines, postnatal ROP screening was initiated at 6 weeks after birth with regular follow-up until full retinal vascularization or until ROP activity regression after expected date of birth was achieved.[15] If therapy was necessary, diode laser photocoagulation was performed.

Ophthalmologic Examination

A detailed ophthalmologic assessment was performed for every subject. This included best-corrected visual acuity testing, cycloplegic refraction, keratometry analyzed with a Nikon Nidek ARK-1s keratometer (NIDEK CO., LTD., Gamagori, Japan), axial length measurement with the IOL Master 500 (Carl Zeiss Meditec, Jena, Germany), and a peripapillary SD-OCT scan with the Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany).

Choroidal Thickness Measurement

Peripapillary SD-OCT scans were obtained using SD-OCT with a peripapillary scan centered on the optic disc. During SD-OCT assessment, each infant was asked to fixate on a blue circle with the other eye covered if possible. Choroidal thickness was measured using Heidelberg Eye Explorer Software (Version 6.0.7.0; Heidelberg Engineering). As automated choroidal thickness measurement was not provided by the software, manual alignment of the choroidal interfaces was performed by a "masked" investigator in the peripapillary two-dimensional view. The inner choroidal interface delineation was placed on Bruch's membrane as the discriminator between the RPE and the choroid. The outer choroidal interface delineation was placed between the choroid and the sclera. Afterward, choroidal thickness was calculated by the Heidelberg Eye Explorer Software for each sector (temporal superior [TS], temporal [T], temporal inferior [TI], nasal superior [NS], nasal [N], nasal inferior [NI], and global [G]) (Fig.). The superior temporal and superior nasal sectors, as well as the inferior nasal and the inferior temporal sector, were summarized. For the first 40 eyes measured, standardized measurements by a second "masked" investigator were performed to test the repeatability of the measurements. Only data from the right eye were included in the data analysis. Data of the left eye were additionally analyzed to rule out interocular differences.

Statistical Analyses

Calculations were performed using IBM SPSS 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as means ± SD. Categorical variables were expressed as proportions. A χ^2 test was used to analyze the association between categorical variables. The distribution of the data was tested for normality using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare independent continuous parameters between two groups and the Kruskal-Wallis test, between several groups. The intraclass correlation coefficient was used to describe the reproducibility of the choroidal thickness measurements. Data of choroidal thickness were adjusted for sex, age at examination, spherical equivalent, and axial length, and groups were compared in multivariable analysis. Univariate and stepwise (combining forward and backward) multivariable linear regression analyses were used to explore influencing factors associated with peripapillary choroidal thickness. Multivariable analysis of the possible influencing factors included GA, birth weight, ROP occurrence, perinatal adverse events, and visual acuity (logMAR). The standardized coefficient beta was used to describe the influence, and 95% confidence intervals are given. For all analyses, a $P \leq 0.05$ was considered to indicate a statistically significant result.

Results

Patient Characteristics

A total of 503 infants, consisting of 239 former preterm infants and 264 full-term neonates, participated in this study. Peripapillary SD-OCT choroidal thickness measurement was available for 388 subjects: 220 of the 264 full-term neonates of GA ≥37 weeks (group 1), 100 of 125 preterm infants of GA between 29 and 32 weeks without ROP (group 2), 37 of 59 preterm infants of GA ≤28 weeks without ROP (group 3), and 31 of 55 infants of GA ≤32 weeks with occurrence of ROP (group 4). Data from these infants with successful peripapillary choroidal thickness measurement were analyzed in the present study.

The GA, birth weight, age at examination, and sex for each group are displayed in Table 1. The average age at examination of all participants was 7.3 ± 1.9 years and 195 (50.3%) of 388 infants were male. Data about history of ROP and ophthalmologic findings are presented in Table 2 for the individual groups. Seventeen infants had a history of ROP of stage 1, nine

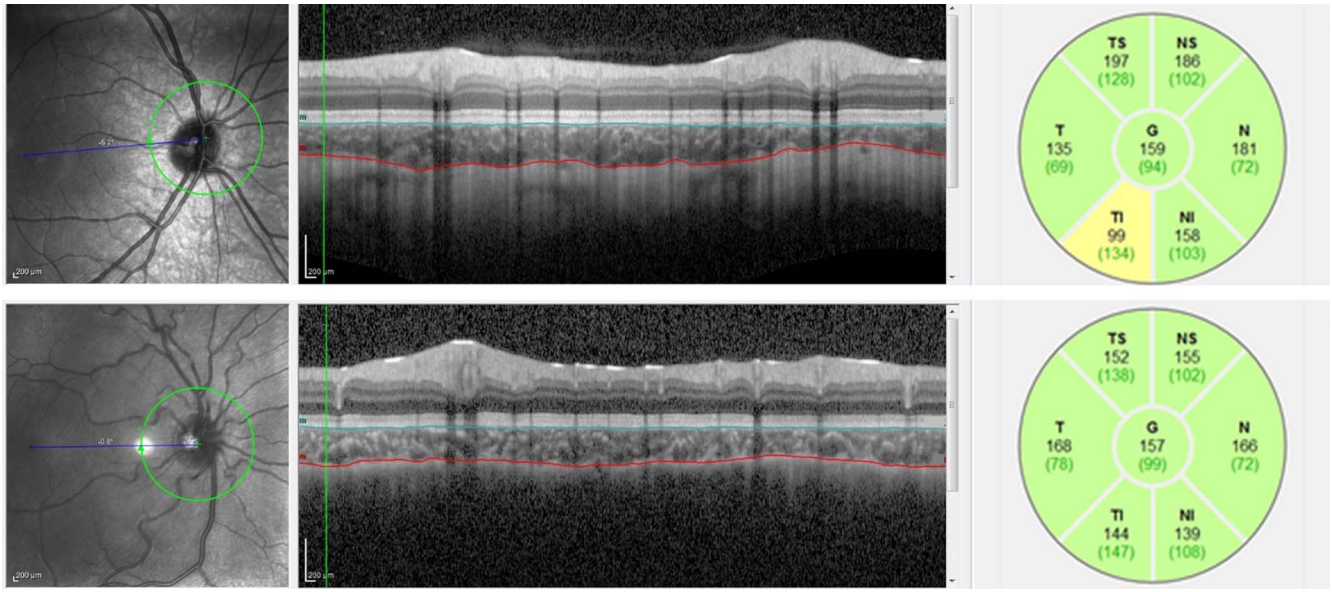

Figure. Illustrates the choroidal thickness measurement with the imaging and analysis tool of Heidelberg Engineering SD-OCT. The *top panel* displays an image and choroidal thickness profile of a 7-year-old full-term infant of group 1 (born at GA 38 weeks), and the *bottom panel* presents those of a 5-year-old former preterm infant of group 4 (born at GA 23 weeks with ROP stage 1). In the *left picture*, the location of the peripapillary scan is exposed in an infrared image, the *middle* illustrates the peripapillary SD-OCT scan displayed with the two borderlines of the choridea, the *right* presents the calculated thickness for each sector of peripapillary choroidal thickness. The numbers in the brackets and the colors of each sector display the standard values for the peripapillary RNFL thickness and not for the the peripapillary choroidea thickness. TS, temporal superior; T, temporal; TI, temporal inferior; NS, nasal superior; N, nasal; NI, nasal inferior; G, global.

of stage 2, and five infants of stage 3. Laser photocoagulation for ROP treatment was required in four infants.

Choroidal Thickness

Peripapillary choroidal thickness was manually delineated within the SD-OCT software by a second "masked" investigator for the first 40 eyes. The intraclass correlation coefficient was 0.991, indicating high delineation consistency. Global and sectoral peripapillary choroidal thickness measurements for each group are presented in Table 3. All results displayed were adjusted for sex, age at examination, spherical equivalent, and axial length. The global peripapillary choroidal thickness measurement was 151.5 ± 6.9 μm in group 1, 152.1 ± 6 μm in group 2, 143.9 ± 7.4 μm in group 3, and 151.6 ± 10.2 μm in group 4. In multivariable analysis comparing the groups, no difference was found in the global sector for preterm infants with GA less than 29 weeks compared with preterm infants with GA between 29 and 32 weeks ($P = 0.091$), as well as compared with full-term neonates ($P = 0.087$) independent of ROP occurrence. Furthermore, there was no difference between infants with and without ROP manifestation ($P = 0.67$).

Nine infants with available global peripapillary choroidal thickness measurement of both eyes had different degrees of ROP in the right and left eyes. Peripapillary choroidal thickness analysis showed no interocular differences in these patients ($P = 0.8$). In all groups, the inferior sector exposed the lowest and the temporal sector the highest values for peripapillary choroidal thickness. The comparison between the right and left eyes showed no differences ($P = 0.6$).

Small for GA

In infants born SGA ($n = 56$) compared with infants born AGA ($n = 332$), there was a tendency for a thinner peripapillary choroidal thickness for the global sector (144.6 ± 6.7 μm SGA versus 152.0 ± 7 μm AGA; $P = 0.067$). The peripapillary choroidal thickness in infants formerly born SGA was significantly thinner compared with infants formerly born AGA in the superior ($P = 0.033$) and the nasal ($P = 0.024$) sectors (Table 4).

Infants being SGA at birth presented with lower visual acuity than AGA infants (0.03 ± 0.07 logMAR SGA versus 0.01 ± 0.05 logMAR AGA; $P = 0.029$). For former preterm SGA infants ($n = 72$) compared with former preterm AGA infants ($n = 96$) at time of hospital discharge, no differences in terms of

Table 1. Patient Demographics for Former Full-Term Neonates With GA ≥37 Weeks (Group 1), Preterm Infants of GA Between 29 and 32 Weeks Without ROP (Group 2), Preterm Infants of GA ≤28 Weeks Without ROP (Group 3), and Preterm Infants With ROP Occurrence After Birth and GA ≤32 Weeks (Group 4)

Patient Demographics	Group 1, ≥37 wk	Group 2, 29–32 wk No ROP	Group 3, ≤28 wk No ROP	Group 4, ≤ 32 wk With ROP	*P* Value
n	220	100	37	31	
GA, wk	38.8 ± 1.4	30.5 ± 1.1	26.6 ± 1.3	26.6 ± 2.2	< 0.001
Birth weight, g	3258 ± 550	1527 ± 426	988 ± 251	956 ± 354	< 0.001
Age at examination, y	7.3 ± 1.9	7 ± 1.8	7.4 ± 2.1	8.0 ± 2.0	0.10
Male, *n* (%)	108 (49.1)	56 (56.0)	17 (45.9)	14 (45.2)	0.57

Variables are expressed as means ± SD.

Table 2. History of ROP and Ophthalmologic Findings for Each Group

Ophthalmologic Characteristics	Group 1, ≥37 wk	Group 2, 29–32 wk No ROP	Group 3, ≤28 wk No ROP	Group 4, ≤32 wk With ROP	*P* Value
n	220	100	37	31	
ROP stage (0/1/2/3)	(220/0/0/0)	(100/0/0/0)	(37/0/0/0)	(0/17/9/5)	< 0.001
Visual acuity, logMAR	0.01 ± 0.03	0.01 ± 0.04	0.04 ± 0.12	0.06 ± 0.1	< 0.001
Spherical equivalent, D	1.1 ± 1.1	1.4 ± 1.1	1.4 ± 1.2	1.1 ± 1.8	0.002
Axial length, mm	22.6 ± 0.8	22.4 ± 0.8	22.1 ± 1.0	22.3 ± 1.2	0.002

Variables are expressed as means ± SD.

global choroidal thickness ($P = 0.9$) and visual acuity ($P = 0.4$) were found at our follow-up examination.

Influence Factors

Univariate linear regression analysis revealed a positive association between global choroidal thickness and age at examination (0.164, confidence interval 1.210–4.880; $P = 0.001$) but no association with sex ($P = 0.8$), spherical equivalent ($P = 0.7$), or axial length ($P = 0.9$).

Univariate linear regression analysis of the other possible influencing factors on global peripapillary choroidal thickness adjusted for sex, age at examination, spherical equivalent, and axial length revealed no association with GA ($P = 0.18$), birth weight ($P = 0.11$), ROP occurrence ($P = 0.7$), stage of ROP ($P = 0.5$), laser treatment ($P = 0.3$), perinatal adverse events ($P = 0.7$), and best-corrected visual acuity in logMAR ($P = 0.8$).

Stepwise forward and backward multivariable linear regression analysis revealed no significant association of peripapillary choroidal thickness with birth weight, gestational age, ROP occurrence, perinatal adverse events, and best-corrected visual acuity in logMAR.

Discussion

The objective of the present study was to assess the peripapillary choroidal thickness profile in former preterm infants with ROP compared with preterm infants without ROP and that of full-term neonates. We also analyzed the associated morphologic influence factors. Peripapillary choroidal thickness showed no significant association with low GA, low birth weight, ROP occurrence, perinatal adverse events, and visual acuity. This suggests that prematurity itself does not influence choroidal thickness in the peripapillary region. However, infants born SGA had a smaller peripapillary choroidal thickness in two sectors and an impeded visual acuity compared with infants born AGA. This supports the hypothesis that growth restriction (SGA at birth) affects choroidal thickness development, possibly leading to impaired functional outcome. A positive association was found between peripapillary choroidal thickness and the age of the children at examination.

The present study proposes normative data and distribution of peripapillary choroidal thickness. To our knowledge, this is the first study to provide reference data of peripapillary choroidal thickness in a pediatric cohort including former preterm infants with and without ROP as well as full-term infants.

While no data exist on peripapillary choroidal thickness for premature infants, data on choroidal thickness in the macular region are limited and inconclusive. Anderson et al.[3] revealed that subfoveal and temporal choroidal thickness in former preterm infants with regressed ROP was significantly thinner than that of full-term neonates (control group). Park and Oh[10] investigated the macular choroidal thickness of 30 full-term infants compared with 31 former preterm infants with and without ROP aged between 4 and 10 years. They observed a choroidal thinning 3 mm temporal to the fovea in the preterm group. Shao and colleagues[16] observed an association between the choroidea and the pathogenesis of ROP in an animal model. The authors demonstrated that rats exposed to postnatal hyperoxia subsequently had choroidal involution, predominantly on the central posterior pole.

Few results have been reported for the influence of low birth weight and low GA on submacular choroidal thickness. Anderson et al.[3] analyzed subfoveal choroidal thickness in preterm infants compared with full-term neonates, reporting no significant correlation of low birth weight and low GA on subfoveal choroidal thickness. Furthermore, the Copenhagen Child Cohort 2000 Eye Study[2] investigated the subfoveal choroidal thickness in 1293 children aged between 11 and 12 years. The authors observed an association of a thinner

Table 3. Peripapillary Choroidal Thickness in Microns for Each Group Adjusted for Sex, Age at Examination, Spherical Equivalent, and Axial Length

Peripapillary Choroidal Thickness	Group 1, ≥37 wk	Group 2, 29–32 wk No ROP	Group 3, ≤28 wk No ROP	Group 4, ≤32 wk With ROP	*P1**	*P2**	*P3**
n	220	100	37	31			
Global	151.5 ± 6.9	152.1 ± 6	143.9 ± 7.4	151.6 ± 10.2	0.671	0.091	0.087
Sector superior	152.9 ± 8.1	152.2 ± 7	142.2 ± 8.4	147.3 ± 11.7	0.953	0.066	0.057
Sector inferior	137.7 ± 6.4	137.9 ± 5.6	129.1 ± 6.7	139.3 ± 9.7	0.462	0.079	0.067
Sector nasal	151.1 ± 7.1	153.3 ± 6.2	141.3 ± 7.2	155.6 ± 11.3	0.339	0.053	0.092
Sector temporal	162.8 ± 8.5	164 ± 7.7	157.4 ± 9.7	163.7 ± 13.9	0.704	0.202	0.166

Variables are expressed as means ± SD (microns).

* Data of choroidal thickness were adjusted for sex, age at examination, spherical equivalent, and axial length and compared in multivariable analysis.

*P1** indicates difference between infants with ROP and without ROP.

*P2** indicates difference between infants with GA below 29 weeks and infants with GA between 29 and 32 weeks.

*P3** indicates difference between infants with GA below 29 weeks and full-term infants.

Table 4. Peripapillary Choroidal Thickness in Microns for Infants Born AGA and SGA Adjusted for Sex, Age at Examination, Spherical Equivalent, and Axial Length

Peripapillary Choroidal Thickness	AGA	SGA	*P* Value
n	*n* = 332	*n* = 56	
Global	152.0 ± 7	144.6 ± 6.7	0.067
Sector superior	152.7 ± 7.8	142.6 ± 7.6	**0.033**
Sector inferior	137.9 ± 6.4	132.3 ± 6.2	0.137
Sector nasal	152.7 ± 7.3	141.5 ± 7.4	**0.024**
Sector temporal	163.5 ± 8.6	157.6 ± 9.7	0.192

Variables are expressed as means ± SD (microns). Bold numbers indicate significant *P* values.

subfoveal choroidea in infants with low birth weight, low birth length, and being SGA.

Peripapillary choroidal thickness was not measured in the above-mentioned studies. In the present investigation, we found no significant correlation of low GA, low birth weight, ROP manifestation, and perinatal adverse events with peripapillary choroidal thickness, indicating that prematurity itself does not affect choroidal thickness in the peripapillary region. Because only four infants of the ROP group received laser treatment, it is difficult to assess whether laser treatment has an impact on peripapillary choroidal morphology. Future studies are necessary to compare preterm infants who have had ROP treatment with corresponding full-term infants. The development of fetal choroidal vasculature starts at 4 weeks of menstrual age,[17] and at 6 weeks the entire optic cup is surrounded by a primitive choriocapillaris.[18] This underlines the importance of the peripapillary area in choroidal development. Our results demonstrate that only infants born SGA have a thinner peripapillary choroidal thickness in the superior and nasal sector as compared with infants born AGA. Furthermore, when the preterm infants of our study collective were divided into former AGA and SGA infants at time of hospital discharge, no differences in terms of our choroidal thickness measurements between the two groups were found at the age of 4 to 10 years. We suggest that not prematurity itself or postnatal growth development until hospital discharge, but that fetal growth restriction resulting with SGA at birth leads to long-term alterations of peripapillary choroidal thickness.

Our findings for low inferior and thicker superior choroidal thicknesses are congruent with previous findings in adults.[19] It is hypothesized that inferior thinning is a consequence of the location of embryologic inferior fetal fissure.[20,21] In support of this hypothesis, Read and colleagues[9] found inferior thinning in children aged between 11 and 16 years. The authors reported a higher choroidal thickness in the temporal sector compared with the nasal sector, assuming this to be a result of the high metabolic demand of the temporal region, possibly caused by the foveal region.[9] Overall, the results of the distribution of choroidal thickness around the optic nerve in our patients is consistent with previous reports of older children and in adults.[5,6,19,20,22,23] Read and colleagues[9] observed a mean peripapillary choroidal thickness of 191 ± 52 μm in the outermost annulus. Our lower peripapillary choroidal thickness values were likely caused by the lower mean age at examination of our infants. A comparison between studies determining peripapillary choroidal thickness is difficult because measurements were executed using different devices and scanning protocols and no data for peripapillary choroidal thickness in former preterm infants are currently available.

Regarding correlations between visual function and choroidal alterations, inconsistent findings have been reported for the foveal region. Wu et al.[4] found an association between foveal choroidal thinning and low visual function in infants with ROP. However, Anderson et al.[3] did not report any association between visual acuity and choroidal thickness in the foveal region in preterm and full-term infants. In the present report, growth-restricted infants being SGA at birth presented with worse visual acuity as compared with AGA infants. However, our data reveal that there is no correlation between morphologic changes of the peripapillary choroidea and visual function. It could be possible that fetal growth restriction leading to SGA at birth affects other choroidal regions, retinal layers, or neuronal structures as well, potentially contributing to low visual function.

Strengths and Limitations

The strength of our study is the large sample size of the study population, including 168 former preterm infants with and without ROP and 220 full-term neonates. Furthermore, importantly, a detailed assessment of possible confounding factors from patients' medical histories and parental interviews, as well as comprehensive ophthalmic examinations, especially for multivariable analysis, was performed in this study. As factors influencing choroidal thickness in the macular region, such as sex, age, refractive error, and axial length have been reported,[24,25] a further strength of our analysis is our adjustment for these factors via univariate and multivariable analysis. The high intraclass correlation coefficient demonstrates the solid reliability of our measurements.

A possible limitation of our investigation is that choroidal thickness measurements were executed at different times of the day and may be affected by diurnal variation, a phenomenon that has been reported by Tan and colleagues.[26] The use of a topical cycloplegic may have induced small changes in choroidal thickness that could probably have affected our results.[27] Further restrictions that may have led to selection bias include the cross-sectional design of our single-center study, the fact that the assessment of peripapillary choroidal thickness was not possible in some infants because of subject incompliance and refusal of some parents to participate in the study.

Conclusions

Our study reveals that there is no association between morphologic changes of the peripapillary choroidea and prematurity and/or ROP. As well, we have not found a direct correlation between peripapillary choroidal morphology and visual function. On the other hand, infants who were SGA at birth presented with limited visual acuity and peripapillary choroidal thinning.

Our data indicate that not prematurity and/or ROP itself affect choroidal thickness in the peripapillary area. Rather, SGA at birth determined peripapillary choroidal thinning in two sectors, highlighting the importance of fetal growth restriction, and its effect on altered peripapillary choroidal thickness development, as well as on visual acuity. The new normative data obtained in the present study for peripapillary choroidal thickness could help in the detection of choroidal abnormalities in preterm and full-term infants in the future.

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