Graefes Arch Clin Exp Ophthalmol (2017) 255:1433–1442
DOI 10.1007/s00417-017-3662-5

PEDIATRICS

Macular morphology in former preterm and full-term infants aged 4 to 10 years

Achim Fieß[1,2] · Johannes Janz[3] · Alexander K. Schuster[2] · Ruth Kölb-Keerl[1] · Markus Knuf[3] · Bernd Kirchhof[4] · Philipp S. Muether[4] · Jacqueline Bauer[3]

Received: 1 January 2017 / Revised: 20 March 2017 / Accepted: 27 March 2017 / Published online: 25 April 2017

Abstract
Objective To analyse macular retinal and choroidal layer thickness in former preterm and full-term infants and to assess associated perinatal influence factors and functional correlation.
Methods This prospective controlled, cross-sectional, hospital-based study in a tertiary center of maximum care examined former preterm infants with a gestational age (GA) ≤ 32 weeks and full-term neonates currently aged 4 to 10 years. We investigated data from 397 infants, analysing total foveal retinal thickness and six distinct macular retinal layer and choroidal layer measurements via spectral-domain optical coherence tomography. Multivariable linear regression analysis was performed to investigate associations of layer thickness with GA and retinopathy of prematurity (ROP).
Results Total retinal thickness in the fovea was thicker in former preterm infants with GA ≤ 28 weeks and in those with GA between 29–32 weeks compared to full-term infants independently of ROP. Occurrence of ROP was also associated with increased foveal thickness. Ganglion cell layer together with inner plexiform layer (GCL+IPL) was thinner in infants with GA ≤ 28 weeks than in full-term infants at 1000 and 2000μm distance from the fovea, but no association with ROP was present. Similar results were found for the photoreceptor layer. Total foveal retinal thickness was associated with low visual function.
Conclusion This study identified low gestational age and ROP occurrence as main determinants for foveal thickening. Furthermore, thinned GCL+IPL measurements were associated with lower gestational age. This study highlights the prognostic value of these maturity parameters influencing retinal morphology, which may affect visual function.

Keywords Retinal thickness · Retinal layer thickness · Choroidal thickness · Gestational age · Retinopathy of prematurity · Macula

✉ Achim Fieß
Achim.Fiess@gmail.com

[1] Department of Ophthalmology, Helios Dr. Horst Schmidt Klinik Wiesbaden, Ludwig-Erhard-Straße 100, 65199 Wiesbaden, Germany

[2] Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany

[3] Department of Paediatrics, Helios Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany

[4] Department of Ophthalmology, University of Cologne, Cologne, Germany

Introduction

Prematurity is one of the main reasons for low visual function in childhood. It is assumed that environmental changes related to prematurity disrupt retinal and choroidal development, consequently leading to impeded visual function. A migration disorder of the inner retinal layers has been distinguished in former preterm infants with a gestational age less than 28 weeks and regressed retinopathy of prematurity [1]. The initial stage of foveal development begins in the 22nd week of gestational age. Formation of foveal depression starts in the 24th to 28th week of gestational age with two opposed movements, while inner retinal neurons migrate laterally and outer segments move to the foveal centre [2–5]. Foveal maturation develops within 4 years after birth [4]. Some authors have reported significantly thicker central maculae, a higher rate of absence of the foveal depression [6–9]. However, other investigators have observed no differences between preterm

infants with and without ROP compared to full-term infants with regard to foveal and macular thickness [10].

Choroidal alterations may also cause impeded visual acuity and retinal alterations in preterm infants. The choroid provides nutrition and oxygen for the outer retinal layers and plays an important role in the emmetropisation process [11]. Significant choroidal thinning in preterm infants compared to full-term neonates has been detected [8, 12, 13]. Some authors have even suggested that choroidal thickness is a predictive factor of visual acuity in eyes with former ROP [14].

Data on other pathological conditions such as albinism show that there is an association of retinal thickness with visual acuity [15]. However, for former preterm infants there are only few studies with inconsistent results regarding retinal and choroidal development in the macular region, and the predictive value of these factors for visual acuity is still unclear.

The aim of the present study was to investigate macular retinal and choroidal layer thickness in preterm infants with ROP compared with preterm infants without ROP and full-term neonates by spectral-domain optical coherence tomography (SD-OCT) and to evaluate the influence of retinal and choroidal layer thickness on visual acuity in children born as preterm and full-term neonates.

Methods

This prospective, cross-sectional, observational, hospital-based study was conducted in a tertiary centre with maximum care in accordance with the Declaration of Helsinki. Study approval was obtained from the local ethics committee (Physician Chamber Hessen). Written informed consent was obtained from the parents or the legal guardians of each child prior to study entry. The authors declare no financial or proprietary interests.

Patients

Five hundred and three subjects were initially enrolled in the Wiesbaden Prematurity Study (WPS) in the period between July 2014 and March 2015. The children included in the WPS were aged between 4 and 10 years and were born in our hospital in the years between 2004 and 2010 with a gestational age below 33 weeks or randomly selected full-term neonates with gestational age ≥ 37 weeks. Exclusion criteria were the presence of severe congenital anomalies since birth. Severe congenital anomalies were defined as infants with congenital chromosomal disorders or/and congenital heart diseases, or/and neural tube defects.

The outcome of the present study, a sub-analysis of WPS, was the measurement of macular retinal and choroidal layer thicknesses and the associated influencing factors.

Participants were included (1) if macular retinal and choroidal thickness layer measurements were possible, (2) if spectral-domain optical coherence tomography (SD-OCT) signal strength was of good quality, and (3) if the implementation of layer measurements on SD-OCT scans was feasible without significant movement or acquisition artefacts.

Infants in which (1) SD-OCT could not be executed and (2) low SD-OCT quality was obtained were excluded from the present sub-analysis. All scans were checked for correct interface delineations. When manual correction of inaccurate automated delineation was not possible due to limited SD-OCT quality, children were excluded from the study. For comparison, infants were classified according to gestational age (GA) as full-term infants with GA ≥ 37 weeks (group 1 – control group), preterm infants with GA between 29 and 32 weeks without ROP (group 2), preterm infants with GA ≤ 28 weeks without ROP (group 3), and preterm infants with GA ≤ 32 weeks with occurrence of ROP (group 4).

Assessment of prenatal and postnatal history

The medical records of each subject were analysed and at the follow-up examination, parents had to complete a standardized questionnaire. According to German guidelines, postnatal ROP screening was started 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. Diode laser photocoagulation was performed if therapy was necessary [16].

Ophthalmologic examination

For the current analysis, the results of detailed ophthalmologic assessments performed routinely in every WPS participant were extracted. This included measurements of best corrected visual acuity (tested with Lea symbols until school enrolment and with landolt rings after that), orthoptic examination, cycloplegic refraction, keratometry analysed with a Nikon Nidek ARK-1s keratometer (NIDEK CO., LTD., Gamagori, Japan), eye length measurement analysed with an IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany), and a foveal SD-OCT scan with and without enhanced deep imaging mode acquired by Spectralis-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany).

Spectral domain optical coherence tomography

In every subject, one horizontal and vertical scan through the fovea with SD-OCT with and without enhanced deep imaging mode were performed (macular cross hair scan). The deepest foveal depression was assumed to be the foveal centre. Participants had to fixate on an internal blue spot while the

other eye was covered, if possible. SD-OCT scans had an axial resolution of about 4 μm.

Thickness measurements of the retinal layers were conducted with Heidelberg eye explorer segmentation software (Version 6.0.7.0; Heidelberg Engineering GmbH, Heidelberg, Germany). This included measurements of the total retinal layer (TR), the retinal nerve fibre layer (RNFL), the ganglion cell layer plus the inner plexiform layer (GCL + IPL), the inner nuclear layer plus the outer plexiform layer (INL + OPL), the outer nuclear layer (ONL), the photoreceptor layer (PR), and the retinal pigment epithelium (RPE). Retinal layer thicknesses were recorded in microns. The total retinal thickness was displayed by the software as vertical distance from the internal membrane limitans to Bruch's membrane (Fig. 1).

Additionally, enhanced depth imaging SD-OCT for manual choroidal thickness measurements was completed on every subject. A masked investigator for gestational age and to study group classification manually measured choroidal thickness. Choroidal thickness was defined as the vertical distance from the outer border of the retinal pigment epithelium and the inner surface of the sclera. In every child, retinal and choroidal thickness measurements were conducted at the fovea and at 1000 μm and 2000 μm distances away from the fovea in the superior, inferior, nasal, and temporal directions. To avoid bias, the average value of four measurements at each distance was calculated. The average value at 1000 μm was defined as the inner location and at 2000 μm as the outer location. For 40 right eyes, subfoveal choroidal thickness measurement was performed by a second masked investigator to test the repeatability of the measurements. In addition, intra-rater reliability was determined on 40 right eyes in a masked manner, which were imaged with SD-OCT twice. Only data for the right eye were included in the analysis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). The normal distribution was tested with the Kolmogorov-Smirnov-Test. Categorical variables are stated as proportions. The chi-squared test was used to analyse the association between categorical variables. 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. Retinal and choroidal layer thickness values were compared for different gestational age (GA ≥ 37 weeks, GA 29–32 weeks, and GA ≤ 28 weeks) and for presence of ROP using multivariable linear regression

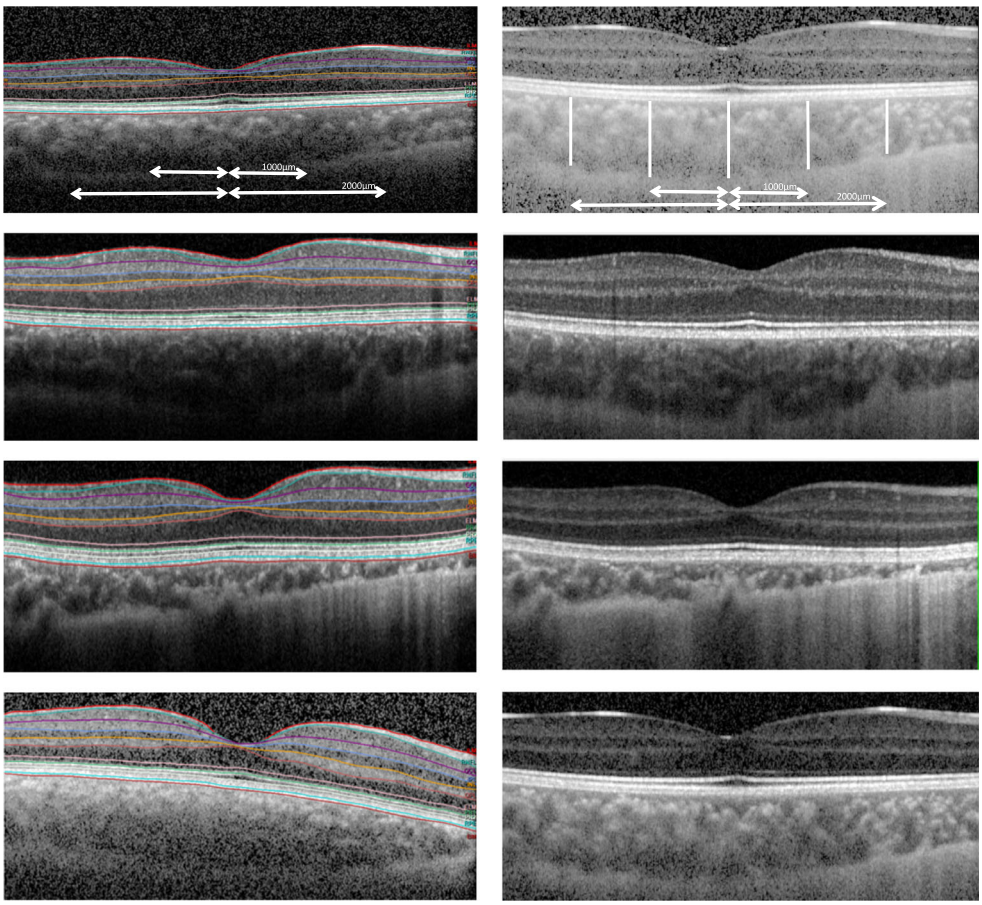

Fig. 1 A 1:1 pixel view of horizontal SD-OCT retinal and choroidal layer thickness measurements. Images on the left present the macular B-scan with coloured lines demarcating each retinal layer. In the right column images present the macular B-scans with EDI, which were used for choroidal thickness measurement. Image acquisition was performed first without and then with EDI-mode and, therefore, scan orientation can be slightly different. Thickness measurements were performed in the fovea and 1000 and 2000 μm away to the fovea in the superior, inferior, nasal, and temporal directions. Top (Group 4): 5-year-old boy born at 23 weeks gestational age with ROP. Top middle (Group 3) a 6-year-old boy of 25 weeks gestational age without ROP. Bottom middle (Group 2) a 7-year-old girl of 30 weeks gestational age without ROP. Bottom (Group 1): a 4-year-old girl of 38 weeks gestational age

models with adjustment for gender, age at examination, spherical equivalent, and axial length. A similar statistical approach was used to investigate the association of visual acuity (in logMAR) with retinal/choroidal layer thickness. This multivariable linear regression analysis with visual acuity as dependent variable and retinal/choroidal layer thickness as independent variable (one model per variable) was adjusted for ROP occurrence, GA groups (GA ≥ 37 weeks, GA 29–32 weeks, and GA ≤ 28 weeks), gender, age at examination, spherical equivalent, and axial length. In addition, one statistical model was performed including all univariate associated retinal/choroidal layer thicknesses ($p < 0.05$) and the same adjustment parameters. Multicollinearity was investigated by computing variation inflation factors. The non-standardized coefficient beta was operated to describe the association, and 95% confidence intervals are given. Post hoc power calculation was performed for our main hypothesis of different total foveal thickness and GCL + IPL segmented retinal layer between the three different groups of premature children (GA 29–32 weeks without ROP, GA ≤ 28 weeks without ROP, GA ≤ 32 weeks with ROP) and controls. The included study participants of the WPS revealed a power of >99% for foveal total retinal thickness (ANOVA-analysis) using the means and standard deviation as described in Table 2, 85% for GCL + IPL at inner location and 77% for GCL + IPL at outer location. As this is an explorative study, *p*-values should be regarded as a continuous parameter reflecting the level of evidence and are, therefore, reported exactly. Statistical calculations were performed using the program IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Macular cross hair scans with and without enhanced depth imaging mode were possible in 397 of 503 WPS participants. Accordingly, thickness measurements were possible in 224 of 264 full-term infants, in 99 of 125 preterm infants with GA between 29 and 32 weeks without ROP, in 37 of 59 preterm infants with GA ≤ 28 weeks without a history of ROP, and in 37 of 55 preterm infants with GA ≤ 32 weeks with a history of ROP (Fig. 2). Patient characteristics for each group are presented in Table 1. The mean age of all infants at study examination was 7.3 ± 2.0 years, 200 (50.4%) children were male. ROP occurrence and ophthalmologic follow-up results are presented in Table 1. Of the 37 infants in the ROP group (group 4), 11 infants had a GA between 29 and 32 weeks, nine of them with a history of ROP stage 1 and two infants of ROP stage 2. Laser photocoagulation was necessary in three subjects with a history of ROP. None of the infants with successful macular retinal and choroidal thickness measurements had congenital glaucoma, cataract, or idiopathic nystagmus.

Description of retinal and choroidal thickness

Unadjusted thickness parameters for each retinal and choroidal layer thickness are displayed in Table 2. Examples of these measurements are shown in Fig. 1. Foveal choroidal thickness was measured within the SD-OCT software by a second masked investigator for 40 eyes. The intraclass correlation coefficient (ICC) for inter-rater reliability was 0.90. Additionally, the ICC for intra-rater reliability in this measurement was 0.81, both indicating high delineation consistency.

Total retinal thickness in the fovea was thicker in former preterm infants with GA ≤ 28 weeks and in infants with GA between 29 and 32 weeks compared to full-term infants independent of ROP manifestation. At inner (1000 μm apart from fovea) and outer (2000 μm apart from fovea) location, infants with GA ≤ 28 weeks had descriptively slightly thinner total retinal thickness (Table 2). GCL + IPL layer was thinner in infants with GA ≤ 28 weeks and ROP at inner and similar at outer location, while the choroid appeared to be thinner in infants with GA ≤ 28 weeks (Table 2).

Multivariable analysis for retinal layer thickness

Statistical differences were explored with multivariable linear regression models including adjustment for gender, age at examination, spherical equivalent, and axial length.

At foveal centre, total retinal thickness was thicker in infants with GA ≤ 28 weeks and in infants with GA between 29 and 32 weeks compared to full-term infants independent of ROP manifestation. ROP manifestation itself was also associated with a significantly thicker total retinal thickness at foveal centre. Total retinal thickness was thinner at outer location in infants with GA ≤ 28 weeks (Table 3).

With respect to segmented retinal layers, the GCL + IPL was thinner in infants with GA ≤ 28 weeks at inner and outer location, but not in in infants with GA 29–32 weeks compared to full-term infants, or for ROP independent of GA (Table 3). Photoreceptor layer showed similar findings: layer measurement was thinner in infants with GA ≤ 28 weeks at all locations (foveal, inner and outer), but not in in infants with GA 29–32 weeks, compared to full-term infants. Analysis of the other segmented retinal layer measurements and choroidal thickness did not show consistent associations with GA or ROP (Table 3).

Multivariable analysis for visual acuity

In multivariable analysis assessing the association between visual acuity and retinal thickness data was adjusted for ROP, GA groups, gender, age at examination, spherical

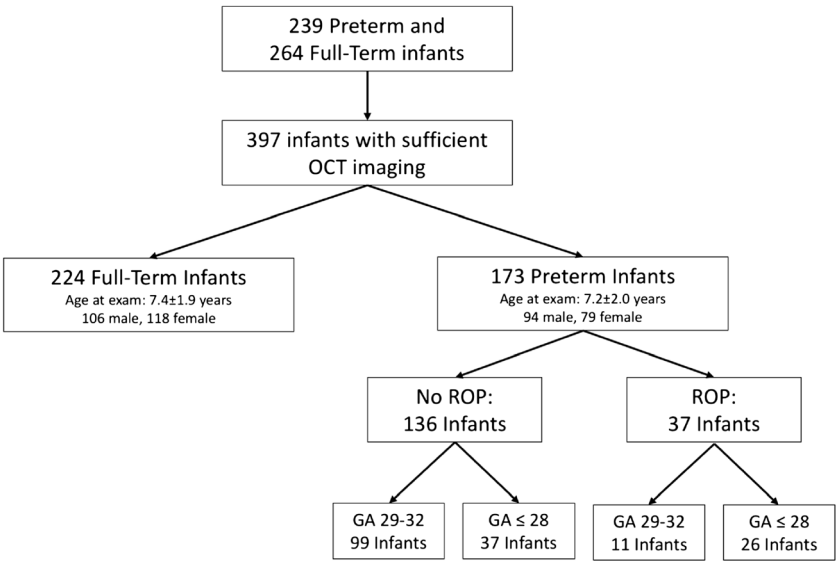

Fig. 2 This figure presents the number of participants of each group with successful macula retinal and choroidal thickness measurements

equivalent and axial length. An association between reduced visual acuity (in logMAR) and the entire foveal thickness was found (Table 4). Furthermore, decreasing total retinal thickness in the inner location, and GCL + IPL thickness in the inner location were associated with better visual function while RNFL thickness increase in the inner location was associated with reduced visual acuity. A decrease of the outer nuclear layer at the inner and outer location was also associated with better visual function. When including all associated layers into one model, only entire retinal thickness at the fovea, GCL + IPL layer at the inner location and RNFL at the inner location remained associated with visual function.

Discussion

The aim of the present study was to investigate macular retinal and choroidal layer thickness in former preterm infants and full-term neonates, as well as to assess the associated factors for morphological changes. We observed in multivariable analysis that low gestational age and ROP occurrence are the main factors for foveal thickening. Furthermore, a significant association was found between increasing retinal thickness and decreased visual acuity. This indicates that impeded retinal development is potentially associated with poor visual outcome.

Retinal layer thickness

This increased foveal thickness in former preterm infants compared to former full-term neonates was detected in our study in accordance to previous reports [6–9, 17–20]. The special feature of our analysis is that we could compare preterm infants with GA ≤ 28 weeks and infants with GA between 29 and 32 weeks independent of ROP to formerly full term born neonates demonstrating that both preterm groups revealed a

Table 1 Patient characteristics for 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 GA ≤ 32 weeks and ROP occurrence after birth (group 4)

	Group 1 ≥ 37 wks n = 224	Group 2 29–32 wks no ROP n = 99	Group 3 ≤ 28 wks no ROP n = 37	Group 4 ≤ 32 wks ROP n = 37
Gestational age (weeks)	38.8 ± 1.4	30.4 ± 1.1	26.4 ± 1.4	27.0 ± 2.2
Gestational age (range)	37–43	29–32	24–28	23–30
Birth weight (g)	3241 ± 563	1506 ± 376	939 ± 244	973 ± 328
Age at examination (years)	7.4 ± 1.9	7.0 ± 1.8	6.9 ± 2.1	7.7 ± 2.2
Male (n (%))	106 (47.3%)	54 (54.5%)	19 (51.4%)	21 (56.8%)
ROP stage (0/1/2/3)	(224/0/0/0)	(99/0/0/0)	(37/0/0/0)	(0/23/8/6)
Visual acuity (logMAR)	0.005 ± 0.02	0.01 ± 0.03	0.03 ± 0.06	0.09 ± 0.18
Spherical equivalent (D)	1.1 ± 1.3	1.4 ± 1.2	1.3 ± 1.3	1.1 ± 2.5
Axial length (mm)	22.6 ± 0.8	22.4 ± 0.8	22.1 ± 1.0	22.4 ± 1.2

Variables are expressed as means ± standard deviation

wks weeks of gestational age; ROP retinopathy of prematurity; n number of children; g grams

D Dioptre; mm millimetre

Table 2 Unadjusted retinal and choroidal layer thickness for each group

	Group 1 ≥ 37 wks n = 224	Group 2 29–32 wks no ROP n = 99	Group 3 ≤ 28 wks no ROP n = 37	Group 4 ≤ 32 wks ROP n = 37
Thickness (μm)				
Foveal centre				
Total TR	222.6 ± 31.3	240.3 ± 24.8	250.8 ± 32.2	262.9 ± 29.0
PR	94.6 ± 6.8	94.2 ± 10.7	91.5 ± 8.8	93.0 ± 7.1
RPE	17.1 ± 5.9	17.5 ± 4.6	16.0 ± 4.4	14.8 ± 3.6
Choroid	310.2 ± 53.6	313.7 ± 62.4	294.5 ± 57.1	321.6 ± 61.9
Inner locations#				
Total TR	342.4 ± 15.6	344.2 ± 13.2	337.7 ± 20.2	341.1 ± 19.9
RNFL	18.2 ± 4.5	18.0 ± 2.1	17.9 ± 1.8	19.9 ± 4.6
GCL + IPL	96.9 ± 8.3	96.7 ± 7.2	92.2 ± 10.9	91.9 ± 11.1
INL + OPL	77.2 ± 6.8	78.0 ± 6.1	77.1 ± 6.2	77.9 ± 7.4
ONL	69.9 ± 10.1	71.4 ± 8.5	70.5 ± 11.0	68.9 ± 12.1
PR	80.6 ± 2.4	80.3 ± 2.2	79.3 ± 3.7	80.9 ± 2.5
RPE	13.4 ± 1.6	12.9 ± 1.4	12.9 ± 1.7	13.0 ± 1.7
Choroid	302.3 ± 50.5	303.9 ± 61.9	289.3 ± 53.0	308.1 ± 48.3
Outer locations##				
Total TR	312.5 ± 14.6	310.9 ± 12.3	306.5 ± 16.6	309.0 ± 13.9
RNFL	94.6 ± 18.8	98.3 ± 19.1	96.4 ± 6.5	91.6 ± 20.3
GCL + IPL	77.0 ± 7.7	75.6 ± 6.4	73.7 ± 7.5	72.4 ± 9.2
INL + OPL	67.8 ± 4.6	68.0 ± 4.5	67.9 ± 5.7	68.6 ± 5.6
ONL	61.6 ± 8.6	62.3 ± 6.9	61.8 ± 8.0	61.3 ± 10.5
PR	78.7 ± 2.5	78.5 ± 2.6	77.5 ± 2.3	78.8 ± 2.4
RPE	12.1 ± 1.6	11.9 ± 1.5	11.5 ± 1.2	11.8 ± 1.6
Choroid	278.5 ± 44.7	276.6 ± 54.6	265.2 ± 46.7	284.5 ± 48.8

Variables are expressed as means ± standard deviation

(GA gestational age, ROP retinopathy of prematurity, wks weeks of gestational age, n number of children, TR total retinal thickness, RNFL retinal nerve fibre layer, GCL + IPL the ganglion cell layer plus the inner plexiform layer, INL + OPL the inner nuclear layer plus the outer plexiform layer, ONL outer nuclear layer, PR photoreceptor layer, RPE retinal pigment epithelium)

1000 μm away from fovea

2000 μm away from fovea

significantly thicker retina compared to full-term born infants. Several authors assume that increased foveal thickness especially in preterm infants born in the critical period of foveal development (22 to 28 weeks of gestational age) is a consequence of a disorder in lateral cell migration of the inner retinal layers away from the fovea [1, 6–8]. In accordance with these reports, we found thinner inner retinal layers (ganglion cell layer together with inner plexiform layer) in infants with GA ≤ 28 weeks in the inner and outer locations.

With respect to ROP, previous studies reported that infants with regressed ROP showed thicker foveae, a smaller avascular zone in the fovea, and the absence of a foveal depression [1, 6, 7, 9, 18, 21]. Accordingly, our data identifies ROP occurrence as a main factor for total retinal thickening in the fovea independent of gestational age. Foveal thickening being caused by laser treatment is unlikely, as only three patients in the ROP group had required retinal laser coagulation therapy. Further investigations are necessary to evaluate why ROP affects foveal retinal layer thickness.

Furthermore, we found significantly thinner foveal photoreceptor layer for infants with GA ≤ 28 weeks compared to full-term infants independent of ROP manifestation in the fovea, inner and outer location which is in contrast to Bowl et al. [7] highlighting the impact of very low gestational age on normal photoreceptor layer development.

For some ocular morbidities an association between individual retinal layers and visual acuity is described [15]. However, several studies reported no correlations between visual acuity and foveal thickness in former preterm infants [6–8, 18, 21]. Some authors speculate that this is because there is photoreceptor maturation although an abnormal foveal depression exists. Foveal thickening in premature infants might indicate former prematurity, but is not necessarily connected with reduced visual function [21]. Bowl and colleagues [7] investigated in a large collective of 150 former preterm and 30 full-term infants aged from 6 to 13 years the association between retinal layer thickness with visual acuity and light increment sensitivity threshold (assessed with a fundus-controlled microperimetry to determine the subjective recognition of "light changes" at defined loci) and did not find a relationship between retinal layer thickness and functional parameters. Nevertheless, they found a correlation between the ratio

Table 3 Linear regression model analysing the association of retinal and choroidal layer thickness (fovea, inner, and outer location) of the different gestational age groups and ROP

Linear regression model	GA ≥ 37 wks	GA 29–32 wks		GA ≤ 28 wks		ROP (yes)	
N = 397	Reference	ß [95% CI]	*P*-value	ß [95% CI]	*P*-value	ß [95% CI]	*P*-value
Foveal centre							
Total TR		16.9 [9.9; 23.8]	**<0.001**	27.9 [18.2; 37.7]	**<0.001**	14.2 [2.5; 25.8]	**0.017**
PR		−0.4 [−2.3; 1.5]	0.66	−3.4 [−6.1; −0.7]	**0.01**	0.6 [−2.6; 3.8]	0.72
RPE		0.4 [−0.8; 1.7]	0.50	−1.5 [−3.2; 0.3]	0.11	−1.6 [−3.7; 0.5]	0.13
Choroid		−0.8 [−13.9; 12.4]	0.91	−15.1 [−33.6; 3.5]	0.11	16.9 [−5.2; 39.1]	0.13
Inner locations[#]							
Total TR		0.6 [−3.0; 4.2]	0.75	−4.0 [−9.1; 1.0]	0.12	0.3 [−5.7; 6.3]	0.92
RNFL		−0.5 [−1.3; 0.4]	0.28	−0.17 [−1.4; 1.1]	0.80	2.0 [0.6; 3.5]	**0.007**
GCL + IPL		−0.2 [−2.2; 1.8]	0.83	−4.2 [−7.0; −1.5]	**0.003**	−1.8 [−5.1; 1.5]	0.29
INL + OPL		0.4 [−1.2; 1.9]	0.64	0.7 [−1.5; 2.9]	0.53	0.4 [−2.2; 3.0]	0.77
ONL		0.9 [−1.4; 3.3]	0.42	−0.6 [−3.9; 2.6]	0.70	−2.1 [−6.0; 1.7]	0.28
PR		−0.4 [−0.9; 0.2]	0.23	−1.1 [−1.9; −0.3]	**0.01**	1.1 [0.1; 2.0]	**0.03**
RPE		−0.5 [−0.8; −0.1]	**0.02**	−0.4 [−0.9; 0.1]	0.13	0.0 [−0.6; 0.6]	0.98
Choroid		−2.4 [−15.0; 10.2]	0.71	−11.8 [−29.4; 5.8]	0.19	9.8 [−11.2; 30.8]	0.36
Outer locations[##]							
Total TR		−2.9 [−6.3; 0.3]	0.07	−6.5 [−11.1; −1.9]	**0.006**	0.8 [−4.7; 6.3]	0.78
RNFL		−0.3 [−4.6; 4.0]	0.90	−0.1 [−6.2; 5.9]	0.97	−2.9 [−10.2; 4.4]	0.43
GCL + IPL		−1.3 [−3.0; 0.5]	0.15	−4.1 [−6.6; −1.6]	**0.001**	−1.6 [−4.5; 1.4]	0.30
INL + OPL		−0.3 [−1.4; 0.8]	0.61	0.3 [−1.2; 1.9]	0.69	0.7 [−1.2; 2.5]	0.49
ONL		−0.2 [−2.1; 1.7]	0.87	−0.7 [−3.3; 2.0]	0.63	−0.9 [−4.1; 2.3]	0.58
PR		−0.2 [−0.8; 0.4]	0.48	−1.1 [−1.9; −0.2]	**0.01**	0.9 [−0.2; 1.9]	0.10
RPE		−0.2 [−0.6; 0.2]	0.27	−0.7 [−1.2; −0.2]	**0.01**	0.3 [−0.3; 0.9]	0.37
Choroid		−5.4 [−16.5; 5.6]	0.33	−10.9 [−26.5; 4.8]	0.18	10.9 [−7.7; 29.6]	0.25

Retinal and choroidal layer thickness values were compared for different gestation age (GA ≥ 37 weeks, GA 29–32 weeks and GA ≤ 28 weeks) and for presence of ROP using multivariable linear regression models with the inclusion of all preterm and full term born infants and data adjustment for gender, age at examination, spherical equivalent and axial length. *P*-values ≤0.05 were pesented in bold

(GA gestational age, ROP retinopathy of prematurity, wks weeks of gestational age, n number of children, TR total retinal thickness, RNFL retinal nerve fibre layer, GCL + IPL the ganglion cell layer plus the inner plexiform layer, INL + OPL the inner nuclear layer plus the outer plexiform layer, ONL outer nuclear layer, PR photoreceptor layer, RPE retinal pigment epithelium)

1000 μm away from fovea

2000 μm away from fovea

of the ONL and total retinal layer thickness with light increment sensitivity in former preterm infants. In contrast to our study, infants with psychological and neuronal disorders, intraventricular haemorrhage, and some other comorbidities were excluded from the investigation, which might explain the discrepancy to our results.

We found that reduced visual function is linked to retinal layers in the macula and it is also linked to peripapillary RNFL thinning in our cohort [22]. Taking these findings together, functional correlation between peripapillary RNFL thickness and foveal thickness might be linked via the papillo-macular area. Congruently, Wang et al. [23] found an association between the peripapillary RNFL thickness in the temporal sector and foveal thickness and hypothesised that prematurity disturbs normal axonal distribution of retinal ganglion cells around the fovea. In contrast to Bowl et al. [7], we did not exclude infants with neuronal disorders and other specific comorbidities as this would reduce the representativeness of our cohort. Therefore, it is difficult to state if macular and/or peripapillary RNFL thickness changes finally cause reduced visual outcome. Additional cerebral changes might have led to alteration in RNFL thickness and then secondarily to decreased visual acuity or the cerebral changes itself did lead to decreased visual acuity. Rothman et al. [24] reported that prematurity is associated with brain structure and neurodevelopment alterations which could support the hypothesis that reduced visual function in our study collective is rather caused by neurologic changes accompanied by morphologic retinal changes in our collective.

Choroid

In the present study, we observed no significant differences in foveal choroidal thickness between preterm infants with and without ROP and full-term neonates, nor in 1000 or 2000 μm distance from the fovea. In contrast, several authors reported of choroidal thinning in former preterm infants with or without ROP compared to full-term infants [8, 12–14].

Table 4 Association of visual acuity and retinal and choroidal layer thickness (fovea, inner, and outer location). The linear regression model (one model per layer) was adjusted for ROP, GA groups and gender, age at examination, spherical equivalent, and axial length

Visual acuity (change of logMAR per 10 μm of retinal layer)	Effect estimates adjusted with 1*	
N = 397	ß [95% CI]	*P*-value
Foveal centre		
Total TR	0.00 [0.00; 0.00]	**0.039**
PR	0.00 [−0.01; 0.01]	0.643
RPE	−0.01 [−0.02; 0.00]	0.177
Choroid	0.00 [−0.00; 0.00]	0.109
Inner locations#		
Total TR	−0.01 [−0.01; −0.00]	**0.002**
RNFL	0.03 [0.02; 0.05]	**0.000**
GCL + IPL	−0.02 [−0.02; −0.01]	**0.000**
INL + OPL	0.00 [−0.01; 0.01]	0.772
ONL	−0.01 [−0.01; −0.00]	**0.022**
PR	0.00 [−0.03; 0.02]	0.872
RPE	−0.02 [−0.06; 0.02]	0.322
Choroid	0.00 [0.00; 0.00]	0.137
Outer locations##		
Total TR	0.00 [−0.01; 0.00]	0.118
RNFL	0.00 [−0.01; 0.00]	0.199
GCL + IPL	−0.01 [−0.01; 0.00]	0.192
INL + OPL	0.00 [−0.01; 0.02]	0.666
ONL	−0.01 [−0.02; −0.00]	**0.012**
PR	0.00 [−0.02; 0.03]	0.774
RPE	0.00 [−0.04; 0.05]	0.823
Choroid	0.00 [0.00; 0.00]	0.408

Retinal and choroidal layer thickness values were analysed for the association with visual function in logMAR using multivariable linear regression models (for each analysed layer one model) with the inclusion of all preterm and full-term born infants and data adjustment with 1*

*1: Adjustment variables were ROP, GA groups, gender, age at examination, spherical equivalent, and axial length

(GA gestational age, ROP retinopathy of prematurity, wks weeks of gestational age, n number of children, TR total retinal thickness, RNFL retinal nerve fibre layer, GCL + IPL the ganglion cell layer plus the inner plexiform layer, INL + OPL the inner nuclear layer plus the outer plexiform layer, ONL outer nuclear layer, PR photoreceptor layer, RPE retinal pigment epithelium). *P*-values ≤0.05 were presented in bold

1000 μm away from fovea

2000 μm away from fovea

Furthermore, Li et al. [25] observed that children aged from 11 to 12 years with a low birth weight, small for gestational age, or shorter at birth had an association with a thinner subfoveal choroid. Wu and colleagues [14] noticed an association between visual acuity and choroidal thickness in infants with threshold ROP and laser or cryotherapy treatment and with regressed ROP, suggesting that the choroid could be a potential extraretinal factor influencing visual function in former preterm infants. Measurement of subfoveal choroidal thickness can vary due to the use of different SD-OCT devices in studies. These problems may also explain the variable results to previous reports. Future studies are necessary to analyse the influence of prematurity on choroidal thickness with homogenous and large study collectives.

In an animal model, Shao and colleagues [26] detected that postnatal hyperoxia plays an important role in the pathogenesis of ROP, and induces choroidal involution mainly in the central posterior pole. Nevertheless, we did not observe an association between presence of ROP and macular choroidal thickness.

Strengths and limitations

The strengths of the present study include its large sample population, as well as the use of high resolution SD-OCT to measure retinal and choroidal thickness. The analysis of medical records, detailed parental interviews, and extensive ophthalmologic examination for each child contributed to the accurate, detailed data assessment and statistical analysis. Gender, age at examination, spherical equivalent, and axial length are possible determinants influencing retinal [27–31] and choroidal [32–34] thickness measurements; therefore, our analysis was adjusted for these factors. High intra- and inter-observer reproducibility was observed in previous studies [35], similar to our study.

A limitation of our study is its single-centre, hospital-based, cross-sectional design. Although we invited all children and their parents systematically, some parents refused to cooperate in our study. This is not uncommon for a sample of impaired and potentially disabled children, but consequently our study population may not be a strict representative sample. A similar limitation exists for imaging with SD-OCT: acquisition of SD-OCT scans with sufficient image quality was not possible in every patient, especially in infants with poor visual acuity without fixation. Because infants with very low GA and ROP are predisposed not to fixate at our measurements this could reduce a possible difference between the groups. Furthermore, measurements of the choroid taken at various points can be affected by local variation and impact the results of local choroidal thickness measurements. Diurnal variations [33] and the use of topical cycloplegia [36] may also have influenced the results of choroidal thickness measurements.

Conclusion

This study identified as main determinants for foveal thickness low gestational age and ROP occurrence. Supporting the hypothesis of a disorder in lateral cell migration of the inner retinal layers away from the fovea in preterm infants, we observed thinner inner retinal layer structures (ganglion cell layer with inner plexiform layer) at 1000 and 2000 μm distance from the fovea. We observed that preterm infants with GA ≤ 28 weeks and infants with GA between 29 and 32 weeks

revealed a significant thicker retina compared to full-term born infants independent of ROP manifestation. The observed photoreceptor thinning at all positions in infants with very low GA (≤ 28 weeks) highlights the impact of prematurity on this retinal layer. Furthermore, an association between visual acuity and total foveal retinal thickness was found highlighting that retinal thickness changes might lead to reduced visual function in preterm infants. Overall, this study underlines the prognostic value of low gestational age and ROP influencing retinal morphology.

Acknowledgements Participating investigators or Collaborators who collected data or provided and cared for study patients (in alphabetical order): Luca Christian, Serife Demirbas, Paula Divis Di Oliveira, Lisa Ernst, Shirin Ghafoori, Saskia Jordan, Petra Nikolic, David Scheele, Florian Tlucynski, Christine Zeymer.

This study contains parts of the thesis of Johannes Janz.

Compliance with ethical standards

Competing interests No funding was received for the study. The authors report no conflicts of interest. The authors declare that they have no competing interests.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licencing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent "Informed consent was obtained from all individual participants included in the study."

References

1. Wang J, Spencer R, Leffler JN et al (2012) Critical period for foveal fine structure in children with regressed retinopathy of prematurity. Retina 32:330–339
2. Yuodelis C, Hendrickson A (1986) A qualitative and quantitative analysis of the human fovea during development. Vis Res 26:847–855
3. Hendrickson AE, Yuodelis C (1984) The morphological development of the human fovea. Ophthalmology 91:603–612
4. Provis JM, Diaz CM, Dreher B (1998) Ontogeny of the primate fovea: a central issue in retinal development. Prog Neurobiol 54: 549–580
5. Springer AD (1999) New role for the primate fovea: a retinal excavation determines photoreceptor deployment and shape. Vis Neurosci 16:629–636
6. Akerblom H, Larsson E, Eriksson U et al (2011) Central macular thickness is correlated with gestational age at birth in prematurely born children. Br J Ophthalmol 95:799–803
7. Bowl W, Stieger K, Bokun M et al (2016) OCT-based macular structure-function correlation in dependence on birth weight and gestational age-the Giessen long-term ROP study. Invest Ophthalmol Vis Sci 57:235–241
8. Park KA, Oh SY (2012) Analysis of spectral-domain optical coherence tomography in preterm children: retinal layer thickness and choroidal thickness profiles. Invest Ophthalmol Vis Sci 53:7201–7207
9. Yanni SE, Wang J, Chan M et al (2012) Foveal avascular zone and foveal pit formation after preterm birth. Br J Ophthalmol 96:961–966
10. Pueyo V, Gonzalez I, Altemir I et al (2015) Microstructural changes in the retina related to prematurity. Am J Ophthalmol 159:797–802
11. Nickla DL, Wallman J (2010) The multifunctional choroid. Prog Retin Eye Res 29:144–168
12. Moreno TA, O'Connell RV, Chiu SJ et al (2013) Choroid development and feasibility of choroidal imaging in the preterm and term infants utilizing SD-OCT. Invest Ophthalmol Vis Sci 54:4140–4147
13. Anderson MF, Ramasamy B, Lythgoe DT et al (2014) Choroidal thickness in regressed retinopathy of prematurity. Eye (Lond) 28: 1461–1468
14. Wu WC, Shih CP, Wang NK et al (2013) Choroidal thickness in patients with a history of retinopathy of prematurity. JAMA Ophthalmol 131:1451–1458
15. Mohammad S, Gottlob I, Kumar A et al (2011) The functional significance of foveal abnormalities in albinism measured using spectral-domain optical coherence tomography. Ophthalmology 118:1645–1652
16. Jandeck C (2008) [Guidelines for ophthalmological screening of premature infants]. Ophthalmologe 105: 81–86, 88–90
17. Hammer DX, Iftimia NV, Ferguson RD et al (2008) Foveal fine structure in retinopathy of prematurity: an adaptive optics Fourier domain optical coherence tomography study. Invest Ophthalmol Vis Sci 49:2061–2070
18. Recchia FM, Recchia CC (2007) Foveal dysplasia evident by optical coherence tomography in patients with a history of retinopathy of prematurity. Retina 27:1221–1226
19. Ecsedy M, Szamosi A, Karko C et al (2007) A comparison of macular structure imaged by optical coherence tomography in preterm and full-term children. Invest Ophthalmol Vis Sci 48:5207–5211
20. Lago A, Matieli L, Gomes M et al (2007) Stratus optical coherence tomography findings in patients with retinopathy of prematurity. Arq Bras Oftalmol 70:19–21
21. Villegas VM, Capo H, Cavuoto K, et al. (2014) Foveal structure-function correlation in children with history of retinopathy of prematurity. Am J Ophthalmol 158: 508–512 e502
22. Fieß A, Christian L, Janz J et al (2017) Functional analysis and associated factors of the peripapillary retinal nerve fibre layer in former preterm and full-term infants. Br JOphthalmol. doi:10.1136/bjophthalmol-2016-309622
23. Wang J, Spencer R, Leffler JN, et al. (2012) Characteristics of peripapillary retinal nerve fiber layer in preterm children. Am J Ophthalmol 153: 850–855 e851
24. Rothman AL, Sevilla MB, Mangalesh S, et al. (2015) Thinner retinal nerve fiber layer in very preterm versus term infants and relationship to brain anatomy and neurodevelopment. Am J Ophthalmol 160: 1296–1308.e1292
25. Li XQ, Munkholm A, Larsen M et al (2015) Choroidal thickness in relation to birth parameters in 11- to 12-year-old children: the Copenhagen child cohort 2000 eye study. Invest Ophthalmol Vis Sci 56:617–624

26. Shao Z, Dorfman AL, Seshadri S et al (2011) Choroidal involution is a key component of oxygen-induced retinopathy. Invest Ophthalmol Vis Sci 52:6238–6248
27. Alasil T, Wang K, Keane PA et al (2013) Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. J Glaucoma 22:532–541
28. Bendschneider D, Tornow RP, Horn FK et al (2010) Retinal nerve fiber layer thickness in normals measured by spectral domain OCT. J Glaucoma 19:475–482
29. Budenz DL, Anderson DR, Varma R et al (2007) Determinants of normal retinal nerve fiber layer thickness measured by stratus OCT. Ophthalmology 114:1046–1052
30. Parikh RS, Parikh SR, Sekhar GC et al (2007) Normal age-related decay of retinal nerve fiber layer thickness. Ophthalmology 114: 921–926
31. Oner V, Ozgur G, Turkyilmaz K et al (2014) Effect of axial length on retinal nerve fiber layer thickness in children. Eur J Ophthalmol 24:265–272
32. Barteselli G, Chhablani J, El-Emam S et al (2012) Choroidal volume variations with age, axial length, and sex in healthy subjects: a three-dimensional analysis. Ophthalmology 119: 2572–2578
33. Tan CS, Ouyang Y, Ruiz H et al (2012) Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 53:261–266
34. Fujiwara T, Imamura Y, Margolis R et al (2009) Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. Am J Ophthalmol 148:445–450
35. Shao L, Xu L, Chen CX et al (2013) Reproducibility of subfoveal choroidal thickness measurements with enhanced depth imaging by spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 54:230–233
36. Sander BP, Collins MJ, Read SA (2014) The effect of topical adrenergic and anticholinergic agents on the choroidal thickness of young healthy adults. Exp Eye Res 128:181–189