Long-Term Effect Of Gestatıonal Age And Bırth Weıght On Macular Development

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ABSTRACT

Objective: To evaluate macular structure in childhood due to their birth history, and analyse possible effects of prematurity and birth weight for gestatinonal age.

Design:A cohort, case-control study

Methods: Children who were between 5 and 18 years old age were divided into the following 3 groups due to their birth histories: Patients who were preterm (Preterm: Group 1), full-term and small for gestational age (Full-term-SGA: Group 2), and full-term and average for gestational age (Full-term-AGA: Group 3,Control group). 398 eyes of 199 children were included. Their macular parameters were analysed by spectral-domain optical coherence tomography (SD-OCT). Mean outcome measures were central foveal thickness (CFT), minumum foveal thickness (MFT), inner retinal thickness (IRT), outer retinal thickness (ORT), central foveal volume (CFV), total macular volume (TMV), and parafoveal volume (PV).

Results: There was no statistically significant difference in age between the groups. The mean gestational age was 30,68±2,76; 38,82±0,75; and 39,59±0,56 weeks in Group 1, 2, and 3, respectively.

Keywords: Birth weight, gestational age, macular development.

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The mean CFT and MFT in Group 1 were significantly thicker than Group 1 (p=0.020, p=0,017). The mean IRT in Group 3 was significantly thicker than Group 1 (p=0.034;) and Group 2 (p=0.013). There was no statistically significant difference between the groups according to CFV, TMV, and PV.

Conclusions: Prematurity might be more associated with thicker CFT than small for gestational age, whereas both parameters seem to be associated with thinner parafoveal thickness in childhood.

INTRODUCTION

Prematurity and being small for gestational age (SGA) have been associated with many diseases, including hypertension, diabetes mellitus, neurologic and kidney (1-5). Ophthalmologic disorders are also widespread among children that were premature or SGA. However, the risk factors for these disorders have not been analyzed exactly and the result of central retinal morphologic alterations has not yet been investigated.

Preterm birth is the birth of a baby of less than 37 weeks gestational age. Although many risk factors seem to be linked with the development of preterm birth, the cause is unknown in many situations (1-4). SGA usually refers to a birth weight less than 2500 grams. Fetal growth restriction results in the birth of an infant who is SGA. Morbidity and mortality are increased in SGA babies when compared to the babies that were appropriate for gestational age (AGA).

Preterm babies are at high risk of amblyopia, myopia, retinopathy of prematurity, and optic nerve abnormalities (6-8). Preterm babies have been also reported to have impairment in color vision (9,10) and contrast sensitivity (8). All these studies (11,12) investigating the development of the macula propose that prematurity itself makes change to the development

of the central retina. Spectral domain optical coherence tomography (SD-OCT) imaging of the retina is highly reproducible, and also a helpful instrument for the measurement of macular volume and foveal thickness (13,14) . The main aim of this study was to compare the macular thickness of prematurely or SGA born children with full-term children.

MATERİALS AND METHODS

Children who were born between January 1, 1995, and January 1, 2009, and had follow-up at Ataturk University Hospital, Erzurum, Turkey, were selected for this retrospective cohort study. Patients treated and observed at the department of pediatrics were chosen from the records. Infants who born at post-conception age of less than 37 weeks were defined as preterm and whose birth weight of less than 2500 grams were defined as SGA. Written, informed consent was obtained from the parents of each study case. The study satisfied to the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

Subjects and Grouping

Three hundred and eighty eight eyes of 199 children included in to this study. Medical files were reviewed to accumulate information regarding birth history (birth weight, gestational age), presence of systemic disorders, and critical complications developing in the neonatal age. The children divided into 3 groups according to their birth history that was obtained from their madical records. Patients who were born before than 37 weeks were included in Group 1 (Preterm), who were born after 37 weeks and were small for gestational age constituted Group 2 (SGA). Group 3 (Control group) composed of an age-matched group of healthy children that were appropriate for gestational age (AGA). All control cases were healthy, without any ocular disease. Both eyes of all subjects were eligible for the study. There were 132 eyes (66 children) in Group 1, 88 eyes (44 children) in Group 2 and 178 eyes (89 children) in Group 3.

The patients, who had a history of cerebral disease, residua of ROP, amblyopia, and myopia higher than -3.0 D, were excluded from the study. Patients who had mother with diabetes mellitus or gestational diabetes during pregnancy were also excluded from the study.

Clinical Examination and SD-OCT Imagining

All children underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), refraction error after instilling cycloplegic drug, and the measurement of macula parts by SD-OCT. Refraction was obtained with a calibrated autokeratorefractometer. BCVA was measured at 5 meter by using Snellen chart. An orthoptic examination was also performed in each case. The SD-OCT measurements **(**Optovue Inc., Fremont, CA, USA**)** were performed in a dim room after mydriasis with tropicamide 0.5% (Tropamid; Bilim, Istanbul, Turkey) drops. The pupils were dilated to minimum 5 mm diameter before the macular measurements. A medical history was taken, including neurological complications defined as epilepsy, cerebral haemorrhage, leucomalacia, and cerebal palsy.

Macular measurements were performed with the macular mapping protocol of Early Treatment of Diabetic Retinopathy Study (ETDRS) that şncludes of 6 individual line scans ordered in a radial design. The patients were asked to fixate an internal target and the same ophthalmologist focused the macular scans on the foveal pit. The scans were approved if free of artifacts. Retinal thickness, the distance between the internal limiting membrane and retinal pigment epithelium, was automatically determined by the instrument's software. Measurements were provided for three concentric regions. All OCT assessments were performed by one of the authors (OOO). Mean outcome measures were central foveal thickness (CFT), minumum foveal thickness (MFT), inner retinal thickness (IRT), outer retinal thickness (ORT), total macular volume (TMV), inner retinal volume (IRV), and outter retinal volume (ORV).

Statistical Methods

The groups were compared by using the independent t test and for continuous data by one-way ANOVA test. The Pearson correlation was used for bivariate correlations. Right and left eyes were analyzed separately. Statistical analysis was performed with commercial software (SPSS version 15.0 for Windows; SPSS, Chicago, IL), and $p < 0.05$ was considered statistically significant.

RESULTS

Demographics and General Information

Among the 199 children, there were 120 boys and 79 girls. The proportions of boys and girls were alike in Group 1 and 3. Female:male ratio in Group 2 was significantly lower than Group 1 (p=0,043). The range of ages was the similar in the three groups, although the mean age was a little lower in the prematurely born children. The mean age of children was 9,01±2,54 years in Group 1, 9,03±2,90 years in Group 2, and 9,65±2,55 years in Group 3. The mean gestational age was 30,68±2,76 weeks in Group 1, 38,82±0,75 weeks in Group 2, and 39,59±0,56 weeks in Group 3. The mean birth weight was 1528,18±536,01 grams in Group 1, 2152,16±386,52 grams in Group 2, and 3417,36±569,55 grams in Group 3. No significant difference was found in gender and age among the groups. Demographic data of the groups are shown in table 1.

Refractive Status

The BCVA was 20/20 bilaterally in all children. The refractive error ranged from +1.25 to -3.00 D spherical equivalent, and there was no significant difference among the groups.

Macular Measurements

Posterior pole was appearing within normal limits in all eyes. The CMT was 239,85±23,18 µm in Group 1, 228,07±19,67 µm in Group 2, and 235,63±23,07 µm in Group 3. The mean

MFT was 208,80±27,68 µm in Group 1, 194,28±28,69 µm in Group 2, and 199,95±25,72 µm in Group 3. The mean IRT was 301,11±17,38 µm in Group 1, 301,63±12,38 µm in Group 2, and 306,91±15,17 µm in Group 3. The mean ORT was 279,17±23,63 µm in Group 1, 282,36±15,99 µm in Group 2, and 283,21±29,63 µm in Group 3. The mean CFT and MFT in Group 1 were significantly thicker than Group 1 (p=0.020, p=0,017). The mean IRT in Group 3 was significantly thicker than Group 1 (p=0.034;) and Group 2 (p=0.013). The mean CMT, MFT, IRT, ORT, and the results of the Post Hoc test for comparison of three groups are shown in table 2.

The mean TMV was 6,97±0,41 mm^3 in Group 1, 6,94±0,41 mm^3 in Group 2, and 6,97±0,49 mm^3 in Group 3. The mean IRV was 1,90±0,10 mm^3 in Group 1, 1,90±0,08 mm^3 in Group 2, and 1,92±0,11 mm^3 in Group 3. The mean ORV was 3,53±0,23 mm^3 in Group 1, 3,56±0,19 mm^3 in Group 2, and 3,53±0,33 mm^3 in Group 3. The mean volumes of total macula, inner and outer retina, and the results of the Post Hoc test for comparison of three groups are shown in table 3. There was no statistically significant difference bwtween the groups according to TMV, IRV, and ORV.

DİSCUSSİON

The fovea is responsible for high spatial resolution and for central and color vision (15). Retinal structures undergo a continuous development and remodeling activity before and after birth (16,17). Before and during foveal generation, cones become firmly packed, extend, and migrate centripetally (18-20). The processes of cone packing and pit development in humans have been examined in many histological studies (18-24). Later gestational alterations consist of centrifugal migration of inner retinal neurons, resulting in depletion of the ganglion and bipolar cell layers at the fovea. During the third trimester, photoreceptors are comparatively immature at the foveal center than parafoveal and perifoveal locations (25). After birth, the foveal pit profile continues to be altered by cellular migration, reaching maturity

approximately at 18 months (19). Reports demonsrate that foveal cone density reaches the lower range reported for adults by 4 years of age (18,19) , but the exact relationship between foveal pit development and photoreceptor maturation still remains unclear (20,26,27).

Histologically, the term macula refers to that area of the retina where the ganglion cell layer is thicker than a single cell. Clinically, this area corresponds approximately with the area of the retina bound by the inferior and superior vascular arcades. The macula is subdivided into the foveola, the fovea, the parafovea, and the perifovea. Only photoreceptor cells appear in the central foveola; the ganglion cells, other nucleated cells including Müller cells, and blood vessels are not present. The neurosensory retina can be divided into the photoreceptor layer (outer retina) and the processing and transmitting layers (inner retina). In our study we analyzed and compared CMT, MRT, IRT, ORT, TMV, IRV, ORV among three groups.

OCT permits visualization of retinal layers and the structuring of the outer retina (28-30). Evolution in OCT image obtaining (31,32) has raised questions about the earlier anatomical assignment of layers observed with OCT (28,30,31,33). Determining the correlation between OCT bands and photoreceptor structure is important for understanding foveal development. Maldonado et al reported absence and variations in many of these layers as proof of the dynamic morphologic changes associated with development of human fovea (33). Vajzovic et al reported first correlation of SD-OCT scans and histology images in normal human foveal development (34). According to their study, the most obvious finding was the extreme immaturity of the outer retina before and after birth, especially in the fovea.

Major pulmonary, neurological and ophthalmological dysfunctions are widespread in prematurely born children. However, minor dysfunctions of preterm are less well known. Numerous factors may influence foveal development: prematurity (35,42), development of vasculature (43), foveal tissue elasticity, intraocular pressure, retinal stretching (43). In a recent study, Wu et al reported significantly thicker foveas in the patients with the history of

threshold ROP who had been treated using laser therapy or cryotherapy (37). In our study we aimed to evaluate the possible long-term effects of prematurity and birth weight on macular development.

In the present study, we found thicker central foveas in the prematurely born children than in those born at term and were AGA. Our findings accord with those of Hammer et al (45), Ecsedy et al (35), and Akerblom et al (38). Ecsedy et al, in a prospective case-control study that was made among the children between 7 and 14 years old, reported thicker CFT in preterm groups than full-term groups. They found larger central retinal region and decreased the foveal depression was reduced due to the continuity of the inner retinal layers observed beneath the foveal pit, and anticipated these changes might be owing to impairment of the normal centrifugal movement of foveal cone nucleus and inner retinal cells during the development of the macula (19,35,46).

Akerblom found this macular modification was mainly related to ROP, prematurity had only a marginally important role. Akerblom et al also reported significantly thicker CFT in prematurely born children than in those born at term, especially in children that had previous ROP (38). In our study, presence on ROP was an excluding criteria, and we found prematurity was solely risk factor for thicker CFT (p=0,020). One of the important results of our study was about IRT that was significantly thinner in Group 1 and 2 when compared to Group 3 (p=0,013; p=0,034). According to this result SGA seems to be an independent risk factor for thinner IRT.

We found no association between foveal thickness and visual acuity or refraction in the this study. This is in accordance with the study of 12 cases by Recchia et al (47), who found no association between a decrease in visual acuity and absence of a foveal depression. This result concurs the idea of Marmor et al (49), who declare that abnormality in foveal morphology is not usually related with a decrease in visual acuity.

In conclusion, according to our results, prematurity seem to be more associated with thicker central foveal thickness when compared to SGA, whereas both parameters might be associated with thinner parafoveal thickness in childhood. We think that this may be owing to a halt in the peripheral migration of cells in the time of development of the fovea. Large-scale, controlled and prospective studies are needed to evaluate the clinical significance of a thickened central fovea and thinned parafovea in children who were preterm and small for gestational age.

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Table 1: Demographics of the groups (Age, Gender, Gestational age, Birth weight)

		[1]Preterm (n=66)	[2]Term-SGA (n=44)	[3]Term-AGA (n=89)	*p*	*Binary Comparison (Post Hoc Test)*
Age (year)	***Min-Max***	5-18	5-15	5-15	[a]***0,45***	[c1-2]***p:0,7**** [c1-3]***p:0,35*** [c2-3]***p:0,404***
	Mean± SD	9,01±2,54	9,03±2,90	9,65±2,55		
Birth Weight (gram)	***Min-Max***	750-2500	1100-2500	2600-5000	[a]***0,001 ****	[c1-2]***p:0,001*** [c1-3]***p:0,001*** [c2-3]***p:0,001***
	Mean± SD	1528,18±536, 01	2152,16±386, 52	3417,36±569, 55		
Gestational Age (week)	***Min-Max***	25-36	37-40	38-41	[a]***0,001 ****	[c1-2]***p: 0,001*** [c1-3]***p: 0,001*** [c2-3]***p:0,033****
	Mean± SD	30,68±2,76	38,82±0,75	39,59±0,56		
Gender; *n (%)*	**Female**	32 (%48,5)	12 (%27,3)	35 (%39,3)	[b]***0,083***	[d1-2]***p:0,043**** [d1-3]***p:0,330* [d2-3]***p:0,240***
	Male	34 (%51,5)	32 (%72,7)	54 (%60,7)		

*[a]One-way ANOVA Test, [b]Pearson Ki-kare Test, **p<0,01, [c]Post Hoc Test: Tukey HSD test, [d]Yates Continuity Correction Test , *p<0,05, SGA: Small for gestational age, AGA: Appropriate for gestational age, SD: Standardized deviation, n: Number, Min: Minimum, Max: Maximum*

Table 2: Macular thicknesses of the groups

	[1]Preterm (n=66) Mean±SD (Min-Max)	[2]Term-SGA (n=44) Mean±SD (Min-Max)	[3]Term-AGA (n=89) Mean±SD (Min-Max)	[a]p	*Binary Comparison (Post Hoc Test)*
Mean Central Foveal Thickness (µm)	239,85±23,18 (197,5-313,5)	228,07±19,67 (185,5-263,0)	235,63±23,07 (157,5-296,0)	***0,028****	*[1-2]p:0,020** *[1-3]p:0,479* *[2-3]p:0,162*
Mean Minimum Foveal Thickness (µm)	208,80±27,68 (162-305)	194,28±28,69 (141,5-259,5)	199,95±25,72 (129-266)	***0,018****	*[1-2]p:0,017** *[1-3]p:0,112* *[2-3]p:0,492*
Mean Parafoveal Thickness (µm) (Inner Retinal Thickness)	301,11±17,38 (226-339)	301,63±12,38 (280,5-325)	306,91±15,17 (259,5-357)	***0,041****	*[1-2]p:0,984* *[1-3]p:0,013** *[2-3]p:0,034**
Mean Perifoveal Thickness (µm) (Outter Retinal Thickness)	279,17±23,63 (169-332,5)	282,36±15,99 (249-338,5)	283,21±29,63 (115-450)	***0,603***	*[1-2]p:0,793* *[1-3]p:0,586* *[2-3]p:0,982*

*[a]One-way ANOVA Test, Post Hoc Test: Tukey HSD test , *p<0,05, **p<0,01, SGA: Small for gestational age, AGA: Appropriate for gestational age, SD: Standardized deviation, n: Number, Min: Minimum, Max: Maximum*

Table 3: Macular volumes of the groups

	[1]**Preterm (n=66)** **Mean±SD (Min-Max)**	[2]**Term-SGA (n=44)** **Mean±SD (Min-Max)**	[3]**Term-AGA (n=89)** **Mean±SD (Min-Max)**	[a]***p***	***Binary Comparison (Post Hoc Test)***
Mean Total Macular Volume (mm^3)	6,97±0,41 (5,40-7,94)	6,94±0,41 (5,39-8,16)	6,97±0,49 (4,69-8,34)	***0,917***	$^{1-2}$***p:0,948*** $^{1-3}$***p:0,995*** $^{2-3}$***p:0,911***
Mean Parafoveal Volume (Inner Retinal Volume) (mm^3)	1,90±0,10 (1,56-2,13)	1,90±0,08 (1,76-2,04)	1,92±0,11 (1,45-2,22)	***0,216***	$^{1-2}$***p:0,999*** $^{1-3}$***p:0,263*** $^{2-3}$***p:0,381***
Mean Perifoveal Volume (Outter Retinal Volume) (mm^3)	3,53±0,23 (2,44-4,04)	3,56±0,19 (3,25-4,25)	3,53±0,33 (1,64-4,33)	***0,803***	$^{1-2}$***p:0,798*** $^{1-3}$***p:0,987*** $^{2-3}$***p:0,852***

[a]*One-way ANOVA Test, Post Hoc Test: Tukey HSD test, SGA: Small for gestational age, AGA: Appropriate for gestational age, SD: Standardized deviation, n: Number, Min: Minimum, Max: Maximum*