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Macular thickness analysis using optical coherence tomography data, stereopsis and binocular vision in premature infants who underwent retinal laser photocoagulation due to retinopathy of prematurity in an age-related perspective

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The purpose *was to establish reference values for macular thickness, binocular vision, and stereopsis in premature infants aged 5-9 years and 10-13 years who underwent laser photocoagulation of avascular retinal zones due to retinopathy of prematurity (ROP); to assess and compare the data in an age-related perspective.*

Methods. *Data from 24 premature infants who underwent ophthalmological examination, including optical coherence tomography, Titmus Stereo Fly Test, and the Worth 4 Dot Test, at ages 5-9 years and again at ages 10-13 years were analyzed. All children had undergone laser photocoagulation of avascular retinal zones due to ROP in infancy.*

Results. *At ages 5-9 years, the mean central macular volume was 9.2 mm^3, and the retinal thickness in the central fovea was 313.7 μm. At ages 10-13 years, the mean central macular volume was 9.1 mm^3, and the retinal thickness in fovea was 320.8 μm. Normal binocular vision and stereopsis were observed in 79.2% and 33.3% of the children at the first time point, and in 87.5% and 45.8% at the second time point.*

Conclusions. *No statistically significant difference in the central macular volume and macular thickness was detected between the two time points, ($p>0.05$). The thickest part of the macula was identified in the inner macula, followed by the outer macula, with the nasal quadrant being the thickest. Despite the anatomical peculiarities, high rates of binocular vision were observed at both time points, along with stereopsis at the second examination.*

Key words:

retinopathy of prematurity, macular thickness, stereopsis, binocular vision

Introduction. The formation of the macula is a crucial process for developing clear central, binocular, and stereoscopic vision. The process of macular development involves the centrifugal displacement of inner retinal cells and the centripetal displacement of photoreceptors, illustrating its complexity [1]. The formation of the macula begins intrauterinely, with the development of the fovea initiating approximately during the 22 week of gestation as a thickened region comprised of ganglion cells [1]. Premature birth disrupts the normal process of macular formation, consequently leading to impairments in visual functions.

Retinopathy of prematurity (ROP) is recognized for its influence on the maturation of the central retinal area and correlates with a high frequency of refractive errors and impairments in acuity of vision [2]. Additionally, macular development typically does not conclude by 3-4 years of age, as in healthy children, with the fovea being the final structure to reach full maturation [1]. Therefore, it is understandable that children with a history of ROP may exhibit macular abnormalities [1]. As a rule, among children who have experienced ROP in the past, the inner retinal layers of the fovea persist, the depth of the foveal pit diminishes, the diameter of the foveal avascular zone shrinks, central macular thickness measurements increase, the ganglion cell layer and inner plexiform layer complex become thinner, photoreceptor development is delayed, and the photoreceptor layers thin out [2]. However, deviations from normal foveal morphology do not consistently decrease visual acuity and other visual functions [3].

The purpose of the current study was to establish reference values of macular thickness, binocular vision, and stereopsis in premature infants aged 5-9 years and 10-13 years who underwent laser photocoagulation of avascular retinal zones due to ROP; to assess and compare the data in an age-related perspective.

Methods

The study used a combination of retrospective medical record data and prospective ophthalmological evaluations. It included 24 premature infants (48 eyes) who underwent evaluations at ages 5-9 years and subsequently at ages 10-13 years. The inclusion criteria consisted of premature infants diagnosed with prethreshold ROP Type 1, threshold ROP, or aggressive ROP (A-ROP), who underwent laser photocoagulation (LPC). The diagnosis of ROP was de-

termined based on the International Classification of Retinopathy of Prematurity [4]. LPC was performed using a semiconductor laser (Purepoint Laser; Alcon, Fort Worth, TX, USA) with diode pumping at a wavelength of 532 nm within 48-72 hours after establishing the diagnosis. The exclusion criteria were children with Stage 4 or 5 ROP, who were not included in the study.

The ophthalmological examination, in addition to standard diagnostic procedures, necessarily included the following methods: optical coherence tomography (OCT) for assessing macular thickness and macular volume, The Worth 4 Dot Test for evaluating binocular vision, and the Titmus Stereo Fly Test (Graded circle test) for evaluating stereopsis and depth perception. High-resolution OCT was used to obtain images of the macular area. Macular measurements were acquired with dilated pupils using the Spectralis Tracking Laser (Heidelberg Engineering, Inc., Heidelberg, Germany). The ophthalmic imaging platform Spectralis scans the optic disc and macular thicknesses in 20 × 20° area. The macula area was divided into 3 concentric circles centered on the fovea, which corresponded to the Early Treatment Diabetic Retinopathy Study (ETDRS) map overlaid on the OCT map of the macula. These circles comprised the fovea (<1 mm in diameter), the inner macula (1-3 mm), and the outer macula (3-6 mm). The inner and outer macula were subdivided into the superior, inferior, nasal, and temporal quadrants. All scans underwent automatic evaluation by the software of the Spectralis OCT system for nine ETDRS areas.

For the evaluation of stereopsis and depth perception, we used the Titmus Stereo Fly Test (Stereo Optical Company, Inc., Chicago, IL, USA), specifically the Graded Circle Test. Results were presented from 40 to 800 seconds of arc. We divided the results into three groups: high stereovision – 40-60 seconds of arc, normal – 80-140 seconds of arc, and decreased stereovision – 200-800 seconds of arc. For the evaluation of binocular vision, we used The Worth 4 Dot Test. During the test, the distance was adjusted depending on the individual characteristics of the patient, particularly their best correction vision acuity.

Statistical analysis was conducted using MedCalc® Statistical Software version 20.106 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). Quantitative data with a normal distribution were presented as (mean value of the parameter) ± SD (standard deviation). For data with a non-normal distribution, the median (Me) and interquartile range (QI – QIII) were calculated. For comparison, the Student's t-test or the Mann-Whitney U test is suitable. The significance level was predetermined at $p = 0.05$.

All stages of the research adhered strictly to ethical standards and regulations. The study was conducted in accordance with the principles outlined in the Helsinki Declaration of Human Rights, as specified in the document "Terms of Bioethics of the Helsinki Declaration on Ethical Regulation of Medical Research" by the Council of Europe on Human Rights and Biomedicine, as well as relevant laws of Ukraine. Approval for the study protocol was granted by the Institutional Review Board and the Bioethics Committee of the SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine".

Results

A total of 48 eyes of 24 premature children who underwent LPC due to ROP were included in this study. The average gestational age of the children at birth was Me = 29 weeks (QI = 28 weeks – QIII = 30 weeks). The average birth weight was Me = 1150 grams (QI = 985 grams – Q3 = 1295 grams).

The average age of children at the time of the first examination (5-9 years) was Me = 7.3 years (QI = 6.2 years – QIII = 9.0 years), the minimum and maximum age was 5 and 9.9 years, respectively. At the time of the second examination (10-13 years), the average age of the children was Me = 11.05 years (QI = 10.4 years – QIII = 12.3 years), the minimum and maximum age was 10.1 years and 13.8 years, respectively.

At the age of 5-9 years, the average value of the spherical equivalent (SE) in the right eye was -1.05 ± 3.12 D (minimum value -7.75 D, maximum value +2.87 D), and in the left eye was -0.69 ± 3.17 D (minimum value -7.71 D, maximum value +4.5 D). Strabismus was observed in 4 children (12.9%) during the first examination period, with 2 children having convergent strabismus and 2 children having divergent strabismus.

At the age of 10-13 years, the average value of the SE in the right eye was -1.56 ± 3.28 D (minimum value -7.0 D, maximum value +2.00 D), and in the left eye was -1.79 ± 3.93 D (minimum value -10.37 D, maximum value +3.62 D). The same proportion of children (12.9%) continued to show strabismus, with 2 children having convergent strabismus and 2 children having divergent strabismus.

At the age of 5-9 years, the average uncorrected visual acuity in the right eye was Me = 0.6 (QI = 0.2 – QIII = 0.82), and in the left eye Me = 0.6 (QI = 0.35 – QIII = 0.75). The average corrected visual acuity in the right eye was Me = 0.8 (QI = 0.5 – QIII = 1.0), in the left eye Me = 0.7 (QI = 0.55 – QIII = 0.95).

At the age of 10-13 years, the average uncorrected visual acuity in the right eye was Me = 0.6 (QI = 0.08 – QIII = 0.95), in the left eye Me = 0.6 (QI = 0.09 – QIII = 0.85). The average corrected visual acuity in the right eye was Me = 1.0 (QI = 0.65 – QIII = 1.0), in the left eye Me = 0.9 (QI = 0.55 – QIII = 1.0).

At the first stage of the study, we conducted an assessment and comparison of the central macular volume and macular thickness of the central foveal area and all quadrants of the outer and inner macula in prematurely born children who underwent LPC due to ROP at two time points.

At the age of 5-9 years, the mean central macular volume was 9.3 ± 0.6 mm^3 in the right eye and 9.2 ± 0.5 mm^3 in the left eye. At the age of 10-13 years, the mean central macular volume was 9.2 ± 0.4 mm^3 in the right eye and 9.1 ± 0.5 mm^3 in the left eye. The ranges, mean values,

and standard deviations (SD) of central foveal thickness, as well as thickness in the inner and outer macula in all quadrants, were determined in premature children at two age points. The results are presented in Tables 1 and 2.

According to Table 1, differences in the macular thickness values of premature children after LPC due to ROP aged 5-9 years between the two eyes are not statistically significant, ($p>0.05$).

According to Table 2, differences in the macular thickness values of premature children after LPC due to ROP aged 10-13 years between the two eyes are not statistically significant, ($p>0.05$).

Subsequently, we compared the OCT parameters between two time points. The results are presented in Table 3.

According to the data in Table 3, no statistically significant difference in central macular volume and macular thickness was detected for both eyes between the two time points, ($p>0.05$).

At the second stage of the study, we assessed binocular vision and stereopsis at two time points among premature children who underwent LPC due to ROP. The results are presented in Table 4.

Discussion

OCT is becoming more prevalent as a diagnostic and monitoring tool for vision impairment in pediatric patients. In this study, we investigated 48 eyes of 24 premature infants who underwent LPC for ROP during infancy, with follow-up evaluations conducted at ages 5-9 years and again at 10-13 years. We determined the average values of the OCT indicators for these children and compared them in an age-related perspective. Our study lacked a control

Table 1. Values of macular thickness of premature children after LPC due to ROP aged 5-9 Years

OCT Parameters	Right Eye (n=24 eyes)			Left Eye (n=24 eyes)		
	Range	Mean	SD	Range	Mean	SD
Central Foveal Thickness, μm	249 – 385	313.9	32.8	251-378	313.5	33.1
	Inner macula					
Nasal, μm	327 – 407	359.6	23.3	324 – 402	359.9	21.9
Temporal, μm	309 – 387	349.2	22.5	310 – 380	344.5	19.5
Superior, μm	316 – 408	358.4	23.9	321 – 397	356.8	22.2
Inferior, μm	314 – 401	357	22.9	307 – 395	353.9	21.2
	Outer macula					
Nasal, μm	298 – 370	330.5	23.1	291 – 380	335	21.3
Temporal, μm	278 – 344	311.5	20.7	277 – 343	308.6	16.7
Superior, μm	284 – 356	317	20.6	277 – 359	319.2	20.1
Inferior, μm	281 – 347	311.7	18.4	274 – 357	310.8	19.6

Table 2. Values of macular thickness of premature children after LPC due to ROP aged 10-13 Years

OCT Parameters	Right Eye (n=24 eyes)			Left Eye (n=24 eyes)		
	Range	Mean	SD	Range	Mean	SD
Central Foveal Thickness, μm	279 – 388	320	27.6	278-374	321.7	25.4
	Inner macula					
Nasal, μm	304 – 404	360.5	21.4	298 – 399	358.9	26
Temporal, μm	279 – 383	345.3	23.2	307 – 377	345.8	20.6
Superior, μm	294 – 393	355.2	21.7	315 – 395	356.8	21.9
Inferior, μm	332 – 392	357.4	16.6	274 – 387	351.7	27.5
	Outer macula					
Nasal, μm	267 – 362	330.7	21.2	235 – 367	327.5	30.8
Temporal, μm	262 – 331	304.3	17.5	263 – 329	304.2	18.4
Superior, μm	291 – 345	316.5	14.7	282 – 351	317.7	18.9
Inferior, μm	277 – 246	311.2	17.2	275 – 331	304.3	17.7

Table 3. Comparison of OCT parameters between two time points

OCT Parameters	First visit at 5-9 years	Second visit at 10-13 years	p
Central macular volume for RE, μm	9.08 (8.825 – 9.745)	9.25 (8.873 – 9.443)	0.883
Central Foveal Thickness for RE, μm	313.9±32.8	320±27.6	0.521
Nasal Inner Macula Thickness for RE, μm	351.5 (345.5 – 377)	361 (352.25 – 372.5)	0.346
Temporal Inner Macula Thickness for RE, μm	349.2±22.5	345.3±23.2	0.585
Superior Inner Macula Thickness for RE, μm	354 (341.5 – 375)	361 (341 – 368)	>0.999
Inferior Inner Macula Thickness for RE, μm	357±22.9	357.4±16.6	0.947
Nasal Outer Macula Thickness for RE, μm	328 (315.5 – 348)	332 (320.25 – 344.25)	0.750
Temporal Outer Macula Thickness for RE, μm	311.5±20.7	304.3±17.5	0.237
Superior Outer Macula Thickness for RE, μm	311 (302 – 337.5)	318 (305 – 322.25)	0.874
Inferior Outer Macula Thickness for RE, μm	311.7±18.4	311.2±17.2	0.927
Central macular volume for LE, μm	9.07 (8.915 – 9.553)	9.16 (8.780 – 9.600)	0.694
Central Foveal Thickness for LE, μm	313.5±33.1	321.7±25.4	0.384
Nasal Inner Macula Thickness for LE, μm	359.9±21.9	358.9±26	0.899
Temporal Inner Macula Thickness for LE, μm	344.5±19.5	345.8±20.6	0.828
Superior Inner Macula Thickness for LE, μm	356.8±22.2	356.8±21.9	0.992
Inferior Inner Macula Thickness for LE, μm	350 (341.75 – 363.5)	354 (338 – 371)	0.971
Nasal Outer Macula Thickness for LE, μm	330 (324.75 – 347)	331.5 (315 – 349)	0.571
Temporal Outer Macula Thickness for LE, μm	309 (294.75 – 320.5)	306 (291 – 322)	0.530
Superior Outer Macula Thickness for LE, μm	314 (306.5 – 333.75)	314.5 (309 – 333)	0.980
Inferior Outer Macula Thickness for LE, μm	310.8±19.6	304.3±17.7	0.270

Notes: in the normal division, the median value and standard deviation (± SD) or median value (Me) and interquartile range (QI – QIII) are indicated. For comparison, the Student's t-test or the Mann-Whitney U test is suitable.

Table 4. Comparison of stereopsis and binocular vision parameters between two time points

Indicator	First visit at 5-9 years	Second visit at 10-13 years
The Worth 4 Dot Test, n (%)		
Normal binocular vision	19 (79.2%)	21 (87.5%)
Abnormal binocular vision	5 (20.8%)	3 (12.5%)
Titmus Stereo Fly Test, n (%)		
High stereovision	3 (12.5%)	6 (25%)
Normal stereovision	5 (20.8%)	5 (20,8%)
Decreased stereovision	7 (29.2%)	8 (33,4%)
Test could not be performed	9 (37.5%)	5 (20,8%)

group consisting of healthy full-term children. Therefore, for comparison with healthy full-term children, we used data from the literature [5]. Nigam et al. conducted OCT scans of healthy full-term children aged 5-9 years and 10-13 years without any refractive errors, ocular pathologies, family history of eye diseases, history of eye trauma, or any form of treatment, as well as any systemic diseases that could affect the eyes [5].

Based on our findings, at all age points for both eyes, the greatest thickness was observed in the inner macula, followed by the outer macula. Specifically, the nasal quadrant exhibited the highest thickness, followed by the superior, inferior, and temporal quadrants in both the inner and outer macula. These results align with those reported by Nigam et al. [5], who reported that the inner macula was the thickest, followed by the outer macula in both age groups, with the nasal segment being the thickest, followed by the superior, inferior, and temporal quadrants.

For healthy full-term children aged 5 to 9 years, Nigam et al. reported the following mean thickness values: nasal inner segment is 311.3 μm, inferior inner segment is

306.8 μm, superior inner segment is 306.6 μm, temporal inner segment is 293.5 μm, nasal outer segment is 295.1 μm, superior outer segment is 270.3 μm, inferior outer segment is 267.1 μm and temporal outer segment is 257.1 μm [5]. For children aged 10 to 13 years, the mean thickness values were as follows: nasal inner segment is 314.6 μm, superior inner segment is 309.1 μm, inferior inner segment is 308.1 μm, temporal inner segment is 299.1 μm, nasal outer segment is 298.1 μm, superior outer segment is 274.2 μm, inferior outer segment is 265.1 μm and temporal outer segment is 260.1 μm [5]. The retinal thickness in all quadrants was thicker in premature infants who underwent laser treatment due to ROP than in full-term healthy infants of the same age.

The central foveal thickness in premature children who underwent laser treatment due to ROP was also notably thicker compared to healthy full-term children. While in healthy full-term children, the central foveal thickness was the thinnest part of the macula, with a mean thickness of 235.5 μm for children aged 5 to 9 years and 237.1 μm for children aged 10 to 13 years, in premature infants, it was thicker (313.7 μm for children aged 5 to 9 years and 320.9 μm for children aged 10 to 13 years). Normal data of Nigam et al. were consistent with reports by Eriksson et al, who also determined normal macular thickness values, assessed with OCT, in a population of full-term children [6]. The central foveal thickness of the retina, which in full-term infants is the thinnest part of the macula, in premature infants was comparable to the thickest part of the macula in full-term infants, namely the nasal inner segment (313.7 μm compared to 311.3 μm for children aged 5 to 9 years, 320.9 μm compared to 314.6 μm for children aged 10 to 13 years).

The mean central volume of the macula was 9.9 ± 0.6 mm3 in the group of full-term children [5], which was higher than the results reported by Eriksson et al. – 7.1 ± 0.4 mm^3 [6] and our findings in both age groups – 9.2 mm^3 for children aged 5 to 9 years and 9.1 mm^3 for children aged 10 to 13 years.

Literature data repeatedly confirm that prematurely born children have a thicker central macula than those born at term [1]. Akerblom et al. noted that irrespective of the severity of ROP, the degree of prematurity remains the primary risk factor for abnormal foveal development [1]. They also noted an absence of correlation between macular thickness and visual acuity or refraction. According to their findings, this lack of correlation could be attributed to a pause in the lateral migration of cells during the normal foveal development process. However, recent research indicates that the prevalence of foveal hypoplasia is significantly higher in individuals with lower gestational ages, with advanced stages of ROP requiring treatment associated with increased central foveal thickness. This suggests that while macular thickness alone may not predict visual acuity, the presence of foveal hypoplasia and its related complications can significantly impact visual function in adulthood [7].

Pétursdóttir et al. further supported this finding, showing that premature birth and previous treatment for ROP continue to affect macular and optic nerve morphology into adulthood, with central macular thickness remaining elevated in individuals aged 25-29 years. Thus, retinal sequelae persist into adulthood, highlighting the importance of monitoring the long-term effects in premature individuals [8].

In addition to prematurity, Molnar et al. observed that in children aged 6.5 years who were born extremely preterm, certain factors such as ROP and male gender appeared to influence increased macular thickness. Their study suggested a reduction in the macular thickness by 3.9 μm for each gestational week after adjusting for ROP and sex [9]. Ecsedy et al. considered that this subtle macular modification may be related mainly to ROP [10]. According to their conclusion, prematurity played only a marginally significant role [10]. Since in our study only children with previous severe ROP with laser treatment were included, no conclusion could be drawn about the effects of the ROP and its stage on the foveal thickness. Furthermore, since children with severe ROP are born extremely prematurely, it is very difficult to differentiate these two factors.

Typically, visual development progresses swiftly during the initial six months post-birth and persists throughout the initial ten years of life [11]. Visual system development proceeds at a more gradual pace after the age of six months. The process of myelination in the central visual pathways persists until approximately 4 years of age, while maturation of the visual cortex extends throughout the initial decade of life [11]. According to the literature data, the macular thickness in full-term children during 5-17 years increase with age, although the difference is not significant [5]. While comparing the OCT indicators from an age-related perspective, we also did not find any OCT indicator to be statistically significant. We attribute this to the fact that the retina anatomically of a premature baby after LPC due to ROP is typically fully developed by the age of 5 to 9 years.

According to our results, despite the structural features of the central region of the macula, absence of normal anatomical foveal depression and a shift in SE toward myopic refraction (-0.9 at the age of 5-9 years, -1.7 at the age of 10-13 years) in children with ROP who underwent laser treatment due to ROP, binocular vision was determined in 79.2% of children by 5-9 years and 87.5% by 10-13 years; high or normal stereovision was determined in 33.3% of children by 5-9 years and 45.8% by 10-13 years. This suggests that macular anatomy influences visual function, but visual function may differ in children with the same macular structure. Marmor et al. have confirmed this assumption [3]. Apparently, multiple factors can influence ocular functions. Kwinta et al. have concluded that the visual perceptual impairments observed in preterm children without significant sequelae of prematurity may be associated with subtle alterations in the brain microstructure, particularly affecting the corpus callosum [12].

In the structure of visual impairment among prematurely born children, ROP holds one of the leading positions, which is not always determined by the degree of residual changes after ROP.

In conclusion, we confirmed that there was no statistically significant difference in the central macular volume and macular thickness detected for both eyes for premature children who underwent retinal laser photocoagulation of avascular zones of the retina due to retinopathy of prematurity between the two time points, ($p>0.05$). In all age points for both eyes, it was established that the maximum thickness was observed in the inner macula, followed by the outer macula, with the nasal quadrant of the macula being the thickest, followed by the superior, inferior, and temporal quadrants in both the inner and outer macula. It was established that the central macula in all quadrants is thicker in prematurely born children who underwent retinal laser photocoagulation of avascular zones of the retina due to retinopathy of prematurity compared to healthy full-term children. The central foveal thickness of the retina, typically the thinnest part of the macula in full-term infants, was not the thinnest part in premature infants who underwent retinal laser photocoagulation of avascular zones of the retina due to retinopathy of prematurity, indicating the absence of normal anatomical foveal depression. Despite the anatomical peculiarities of the macula in premature children who underwent laser photocoagulation of the avascular zones of the retina due to retinopathy of prematurity, a significant number of children demonstrated normal binocular vision at both time points (79.2% at 5–9 years and 87.5% at 10–13 years) and high or normal stereovision at the second time point, aged 10–13 years (45,8% at 10-13 years compared to 33,3% at 5-9 years).

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