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Original Article

Posterior Pole Asymmetry Analysis in the Children with Anisometropia

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Abstract

Objectives: The objectives of the study were to investigate the inter and intraocular differences in posterior pole asymmetry analysis (PPAA) with optical coherence tomography (OCT) in anisometropia, to examine the relationship between the presence of anisometropia and amblyopia and retinal thickness.

Methods: Patients between ages of 5 and 16 years with anisometropia who applied to our clinic were included in the study. Macular retinal thickness measurements were evaluated by PPAA using the posterior pole algorithm of the spectral domain-OCT device. Asymmetry was analyzed both as the difference between the right and left eyes and the difference between the superior, inferior, and mean retinal thicknesses of 64 separate quadrants in the same eye. Hemispheric and right-left eye asymmetry differences analyses were performed.

Results: 118 patients were included in the study(65 females and 53 males). Group 1 consisted of anisometropic patients (n=46), Group 2 consisted of anisometropic amblyopia patients (n=40), and Group 3 consisted of control group (n=32). The mean age of the patients was 9.72±5.6 years. The mean spherical equivalent difference between the two eyes of the patients was 1.7±0.6 D. When anisometropic eyes were compared with normal eyes, there was no significant difference between mean superior, inferior and total retinal thickness, and right-left eye asymmetry values (for all, $p>0.05$). In the asymmetry evaluation performed by counting the black boxes in the PPAA, a significant difference was found in the right-left asymmetry evaluation in anisometropic amblyopic eyes, in some quadrants and in the right-left asymmetry analysis ($p<0.05$).

Conclusion: While no difference was found between anisometropic and normal eyes in the PPAA, there was differences in some quadrants in the anisometropic amblyopic group compared to the control group suggesting that there is an involvement in the peripheral quadrants of the macula, especially in treatment resistant amblyopic patients.

Keywords: Anisometropia, childhood, optic coherence tomography, posterior pole analysis

Introduction

Optical coherence tomography (OCT) has been widely used for diagnosis and follow-up of optic nerve and retinal disorders in children. It allows objective measurements of the optic nerve head (ONH), retinal nerve fiber layer (RNFL), and macular thickness in a non-invasive manner (1-8). Certain tests may be difficult to perform in children and objective tests are required. Considering that children's compliance with tests is difficult and objective evaluation is limited, OCT has started to be used a lot in pediatric ophthalmology clinics as it is in adults (3-5). Apart from optic nerve and retinal diseases, it gives us valuable information for screening purposes and helps in diagnosis even in those with a history

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of preterm birth, neurological diseases or in the group of children we think is healthy. All the OCT devices have an integrated normative database, which includes only individuals 18 years of age and older. To evaluate changes in retinal measurements accurately, it is first necessary to determine the range in the normal population and to quantify the accuracy, reproducibility, and repeatability of measurements made by the system. For these reasons, it is very important to have normative OCT data in healthy children with different refractive values and to evaluate the test results in a healthy way in these age groups.

When we look at the recent literature, the posterior pole asymmetry analysis (PPAA) test has been a guide for us when it comes to early diagnosis in glaucoma cases and the question of whether the localized defects are really glaucoma or the difference in symmetry between the two eyes (3,5,9,10). Our curiosity about whether this method, which was investigated in adult healthy cases with suspected glaucomatous, is affected by anisometropic amblyopia or other high refractive values in childhood, led us to this study.

PPAA is a novel retinal imaging technique of the Spectral domain OCT (SD-OCT) device that at once maps the posterior pole retinal thickness and performs asymmetry analysis between eyes and between the hemispheres of each eye (11-14).

In 2011, Heidelberg Engineering (Spectralis, SD-OCT, Heidelberg, Germany) customized the most recent retinal thickness protocol to obtain retinal thickness measurements of the central 20° of the posterior pole. The posterior pole retinal thickness map is a color-coded map that provides a mean retinal thickness value of an 8 × 8 grid centered on the foveal pit. The grid is positioned symmetrically to the fovea-disc axis. Each cell of the grid represents a square area of 3 × 3° of the posterior pole. Concurrently, PPAA protocol was created (15). This protocol compares retinal thickness measurements of the corresponding cells in the retinal thickness map between the eyes and between two hemispheres within each eye. The asymmetry map is displayed as a gray scale depiction of difference in thickness from 0 to 30 µm.

A few studies detected inter- and intraocular retinal thickness asymmetry (RTA) in pre-perimetric glaucoma, and therefore concluded that RTA may be the first sign of glaucoma, and that the PPAA thus can be used in the early diagnosis and later follow-up of glaucoma (16-18).

At present, we have no data about PPAA regarding the anisometropia and anisometropic amblyopia in pediatric subjects. To determine any asymmetry that may exist, our study investigated children aged between 5 and 16 years, comparing all 64 cells of the asymmetry grid in the PPAA.

When we look at the previous studies, we come across a small number of studies on children, and these studies are generally determined to detect normal asymmetry between the two eyes in OCT data in healthy children (6,17-19). All these data will guide the research and the new diagnostic and following tests, to prevent late or unnecessary diagnosis. The database of OCT devices in cases under the age of eighteen is newly created, and it is intended to guide the studies on this subject and to ensure that high refractive disorders and especially anisometropia are considered in these tests as a corrective factor in future software of these devices.

In the literature, very limited data exist about childhood refractive status effect on the posterior asymmetry analysis, such as high refractive values, anisometropia or amblyopia. Only there are some studies regarding the normal asymmetry analysis in healthy pediatric subjects (6,19). To the best of our knowledge, this is the first study to present anisometropia for asymmetry using the entire PPAA-protocol.

Methods

This study was conducted by the Declaration of Helsinki and approved by the ethics committee of the Başkent University (Project No: KA 21/240). All participates involved in the study were required to sign written informed consent from legal guardian of each child.

The subjects underwent a full ophthalmic examination including best corrected visual acuity (BCVA) tested with age-appropriate charts, cycloplegic refraction with cyclopentolate 1% or tropicamide 1% eye drops, slit-lamb biomicroscopy, intraocular pressure measurements with air-puff non-contact tonometry if possible, fundus examination with indirect ophthalmoscopy, and orthoptic examination. All patient examinations were performed by same pediatric ophthalmologist (SAB), and all OCT measurements were done by the same expert technician.

Participants

This prospective, cross-sectional study conducted at Başkent University Hospital between May 2020 and April 2021. We recruited 118 children aged between 5 and 16 years among these patients.

Patients with anisometropia were classified as Group-1 (n=46), patients with anisometropic amblyopia were classified as Group-2 (n=40), and age-matched healthy patients were classified as Group-3 (n=32).

Subjects with a spherical equivalent (SE) between -1.00 and +1.00 diopters (D), and BCVA of 20/20 or better in both eyes were enrolled as the control (Group 3) group.

Care was taken to ensure that the refractive error was not above 1 D as a spherical value and not above 1.5 D as a SE in the children in the control group. There were no cases with anisometropia of 1.25 D and above in Group 3. All subjects had to complete a set of examinations including BCVA, auto- refraction, slit-lamp, and OCT measurement.

OCT Imaging Acquisition

The same examiner finished all OCT measurement (Heidelberg Engineering, Heidelberg, Germany) and PPAA were performed. Only images of good quality of OCT were used for further analysis. The PPAA screen showed the mean superior, inferior and total retinal thickness on posterior pole region (Fig. 1). The mean RTA was calculated for all cells of the posterior pole grid between superior and inferior hemispheres retinal thickness of the same eye. In this study, the central four cells of the whole 64 squares positioned around the fovea was named as the central macular area (called region 1), whereas the surrounding 16 square around the region 1 was named as the peri-central area (called region 2), the surrounding 20 square areas around the region 2 as the peri-macular area (called region 3), and the outer 28 square areas as the peripheral area (called region 4). The average thickness of each region was calculated as well. All images were acquired with the Spectralis SD-OCT (version 5.6.1) after pupillary dilation using eye tracking software (TruTrack; Heidelberg Engineering). Subjects were instructed to fixate on the internal fixation target prior to each scan. The instrument has a scan speed of 40.000 A-scans per second, with a 12° diameter scan circle around optic nerve. The scan circle diameter (mm) depends on the axial eye length of the eye, which is typically 3.5–3.6 mm. All scans had a quality score of >25. Images with artifacts or missing parts were excluded and repeated.

Inclusion criteria for all groups were: (1) BCVA of 20/30 or better, refractive error between -6.00 and +6.00 D SE; (2) cylinder correction within 3 D; and (3) clear ocular media to prevent poor-quality imaging of the optic disc and macula. Exclusion criteria for all groups were (1) severe myopic disc and fundus changes; (2) media opacities impaired imaging; (3) coexisting retinal or neurological disease could confound the results of spectral-domain OCT; (4) any manifest strabismus or microtropia; (5) nystagmus; (6) poor-quality OCT-scans (poor-signal strength <8, loss of fixation, asymmetric illumination, or motion artifacts); and (7) any intraocular surgery.

Spectral OCT

All patients were scanned using commercially available SD-OCT Spectralis HRA + OCT (Heidelberg Engineering). This instrument uses a wavelength of 820 nm in the near infrared spectrum in the SLO mode. The light source of the SD-OCT is a super luminescent diode with a wavelength 0f 870 nm. Infrared images and OCT scans (40.000 A-scans/s) of the dual laser scanning systems are acquired simultaneously. The macular thickness measurements were obtained using the posterior pole asymmetry scan protocol. This scan protocol was applied to targeted eyes in all subjects; the camera was centered on the fovea with even

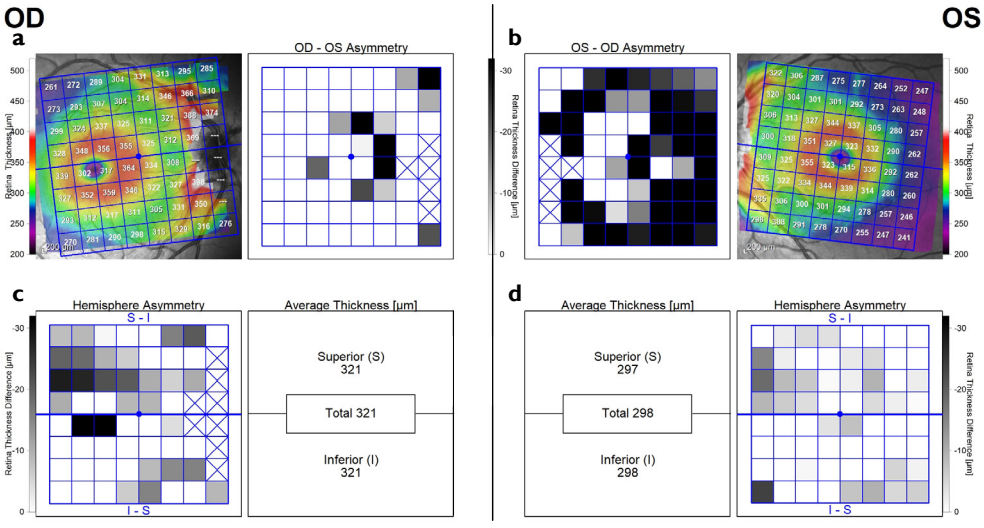

Figure 1. Posterior pole thickness asymmetry analysis of Spectralis optical coherence tomography. **(a)** Color-coded thickness map for each eye that represent retinal thickness patterns. **(b)** The mean macular thickness of total, superior, and inferior regions; **(c)** a gray-scale grid (labeled OS-OD asymmetry) represents inter eye thickness asymmetry. The middle pictures show the interocular asymmetry analysis (right eye-left eye/left eye-right eye) and the intraocular asymmetry analysis (S-I/I-S), respectively. The intraocular hemisphere asymmetry analysis displays the asymmetry between the superior and inferior hemisphere. The fovea-disc axis is the horizontal symmetry line. Asymmetry is graded in gray scale where darker gray indicates thinner retina and white indicates equal retinal thickness. The bottom pictures show the mean superior, total, and inferior retinal thickness. S: Superior hemisphere; I: Inferior hemisphere.

illumination within 6x6 mm area. The retinal thickness grid overlays a 24 × 24° retinal region centered on the measured area of 30 × 25°. This grid is composed of 64 cells; each cell represents the average measured retinal thickness of a 3 × 3° area. Asymmetry analysis of the posterior pole was evaluated with the map which compares the superior to inferior hemispheres for each eye. One hemisphere includes 32 cells, and each cell has an equivalent in the opposite hemisphere. The difference between the two equivalent cells is indicated with colors changing from the white to black (Fig. 1). A black cell means that the difference in retinal thickness is ≥30μm.

For calculating the superior-inferior (S-I) asymmetry, one eye was randomly chosen by a random number table and the inferior area values were subtracted from those of the superior. The differences were established in percentiles.

Statistical Analysis

SPSS software version 21.0 for Microsoft Windows was used for statistical analysis. All data were expressed as the mean ± standard deviation. Means and standard deviations of each zone asymmetry in anisometropic, anisometropic amblyopic, and control group were assessed. Independent sample t and Chi-square tests were used to determine significant differences between the groups, respectively. Results with $p<0.05$ were considered statistically significant. Multiple linear regression analysis was done to see the effect of age and refraction on the interocular as well as intraocular superior-inferior asymmetry of the OCT parameters.

Data Analysis

The area under the receiver operating characteristic curve (AUROC) was calculated to assess the ability of the overall numbers of black cells. Based on the AUROC analysis, criteria that might be clinically meaningful were selected, and the sensitivity and specificity of such criteria. To detect prominent thickness differences, black cells and dark-grey cells were included for interocular zonal comparison. Black cells indicate a mean thickness difference of >30 μm, whereas dark grey cells indicate a mean thickness difference of between 20 μm and 30 μm.

Results

A total 132 subjects were initially included. Fourteen subjects were unable to undergo a completed SD-OCT imaging or due to poor image quality were excluded from the study; finally, 118 subjects completed the study.

A total of 32 healthy, 46 anisometropic, and 40 anisometropic amblyopic eyes were included in the present study. There was 65 female (55%) and 53 male (44.9%) patients, and the mean age of participants was 9.72±5.6 years (range; 5–16). Mean BCVA was -0.01 logMAR (20/20 for Snellen chard) in the healthy control group (Group 3). The mean BCVA was 0.1 ± 0.02 logMAR in the right eye (RE) and 0.1±0.03 logMAR in the left eye at the Group 1 (anisometropic). The mean SE difference between the two eyes was 1.7±0.6 D (range: 1.50–3.75).

The mean BCVA was 0.2±0.02 logMAR in amblyopic eye at the Group 2 (anisometropic amblyopic). The refractive errors ranged from –6.00 to +6.00 D of SE. Strabismus and nystagmus were not included in this study groups. Table 1 shows mean refractive errors in both eyes and mean difference between two eyes, and the mean difference of OCT parameters between the right and the left eyes as well as between the superior and inferior areas of the same eye.

Figure 2a-c shows one sample case from each of the anisometropic, anisometropic amblyopic, and control groups (Fig. 2). Table 2 shows the mean posterior pole retinal thickness of total, superior, inferior, four sub-region fields, and the intraocular RTA. The percentile distribution of inter- and intraocular asymmetry of PPAA macular thickness parameters is shown in Table 3. The 2.5 and 9.75 percentiles of interocular difference tolerance limits for average total PPAA macu-

Table 1. Demographic characteristics of the participants

	All group (n=118)	Anisometropic Group-1 (n=46)	Anisometropic Amblyopia Group-2 (n=40)	Control Group-3 (n=32)	p*
Age (year)	9.72±5.6	9.65±4.8	10.2±5.3	9.12±4.4	0.74
Sex (n)					
Female	65	24	23	18	0.44
Male	53	21	18	14	0.65
SE difference in both eyes (D)	1.8±0.6 (0–5.50)	1.7±0.6 (1.50–5.50)	1.84±0.7 (1.50–5.50)	0.37±0.25 (0–1.25)	0.032
BCVA (LogMAR)	0.1±0.02 (0.0–0.4)	0.1±0.02 (0.0–0.2)	0.2±0.02 (0.1–0.4)	0.02±0.01 (0.0–0.1)	0.023 (1) 0.45 (2)
Axial length (mm)	22.34±0.68	22.56±0.65	22.75+ 0.63	22.24±0.58	0.12

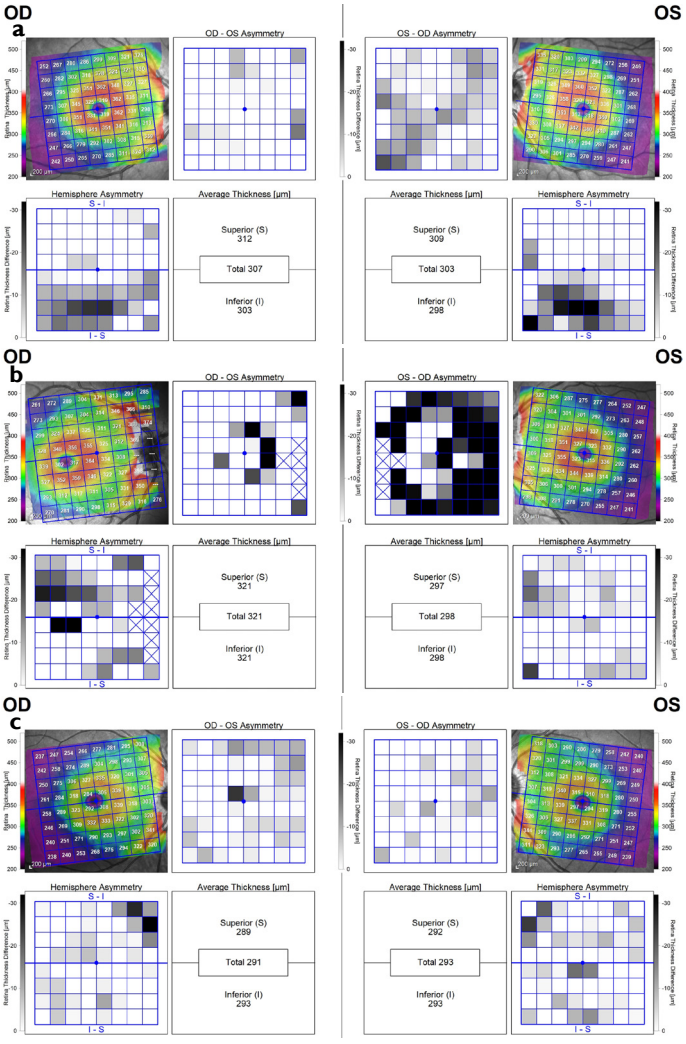

Figure 2. (a) Group 1. 10 year-old male had anisometropia in the right eye. **(b)** Group 2. 7 year-old female had anisometropic amblyopia in the right eye. **(c)** Group 3 (Control). 9 year-old female had no refractive error.

lar thickness and intraocular superior-inferior area difference for the PPAA macular thickness were –9–21 µm and –32–38 µm, respectively. The interocular correlations between the right and the left eye were significant for all OCT parameters as shown in Table 3.

Table 3. Asymmetry of the optical coherence tomography parameters between the right and the left eyes as well as between the superior and inferior areas of the same eye (2.5–97.5 confidence interval values)

	2.5	5	95	97.5
Total	–9.0	–6.5	8.0	9.5
Superior	–21.0	–19.0	14.5	17.8
Inferior	–19.0	–16.0	17.0	20.0
Temporal	–12.5	–10.0	16.0	21.0
Nasal	–13.0	–11.5	16.5	18.5

The 2.5th and 97.5th percentiles of interocular difference tolerance limits for central macular thickness were 17.60 µm and 23.30 µm, respectively. In the whole group, the interocular total macular thickness asymmetry limit was 23 µm and the difference between the intraocular superior-inferior hemispheres was 19 µm. In Group-1, the interocular macular asymmetry is 28±3.2 µm, and the intraocular S-I hemisphere difference is 22±4.1 µm. In Group-2, the interocular macular asymmetry was 33±5.6 µm, and the intraocular S-I hemisphere difference was 25±4.3 µm (Fig. 3).

In 95% of the children, interocular differences in macular parameters were up to 23.20 µm (macular thickness) and 0.64 mm^3 (macular volume). We have found the least difference between right and left eyes in parameters related to the optic disc, with 0.02 µm, 0.03 µm, and 0.01 µm for rim area, disc area, and cup-to-disc area ratio, respectively.

Discussion

There is a dire need for tools for objective assessment in the pediatric age groups, which are quick, reliable, reproducible, and less invasive. SD-OCT is one such diagnostic tool for assessing the macular thickness. Knowledge of normal interocular and intraocular asymmetry is, therefore, essential to avoid confusion with physiological variations.

Many pathological diseases are unilateral or asymmetrical in children. Changes in OCT measurements compared with

Table 2. Mean posterior pole retinal thickness of total, superior, inferior, four sub-region fields, and the intraocular RTA

	Group-1 Anisometropic	Group-2 Anisometropic Amblyopia	Group-3 Control	p*
Total macula thickness	293.7±11.2	289.7±10.3	287.7±12.4	0.25
Superior macula thickness	286.7±10.7	290.9±11.3	288.7±11.6	0.042
inferior macula thickness	282.4±11.1	288.4±11.2	291.5±10.7	0.034
Nasal macula thickness	301.3±12.5	298.9±11.4	305.8±12.6	0.38
Temporal macula thickness	297.4±10.2	287.6±11.5	297.8±10.5	0.041
Intraocular Asymmetry (RTA)	9.4±3.2	12.1±4.3	3.53±2.5	0.004

RTA: Retinal thickness asymmetry.

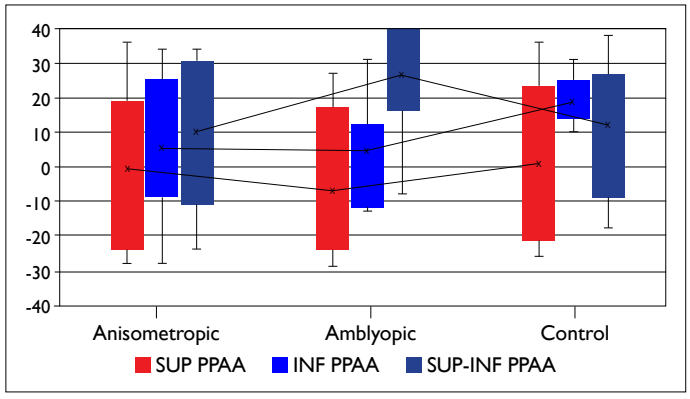

Figure 3. Box plot showing the inner- and interocular asymmetry for the optical coherence tomography parameters. SUP posterior pole asymmetry analysis (PPAA): Interocular superior area macular thickness difference of posterior pole asymmetry analysis. INF PPAA: Interocular inferior area macular thickness difference of posterior pole asymmetry analysis. SUP-INF PPAA: Intraocular superior-inferior area macular thickness difference of posterior pole asymmetry analysis.

the previous examinations or interocular asymmetry exceeding normal limits should be considered warning signs, and an indication for further examinations. Deviation from this difference may be deemed abnormal even if the absolute value appears to be within normal limits. There are several articles in the literature evaluating normal interocular asymmetry in children (3,6,19-24). Based on these articles, we conducted this study to understand whether high refractive values and refractive differences between two eyes influence the evaluation of OCT results in children with age of 5–16 years. In this article, we tried to investigate the criteria that we should consider as correction parameters in terms of the follow-up of retinal or optic disc-based diseases that may develop in the future, especially in anisometropic amblyopia cases.

The mechanism underlying interocular differences remains unclear. Because RNFL thickness is affected not only by the number of ganglion cell axons but also by glial and Müller cells, we cannot completely attribute the asymmetry to differences in a particular cell line. Huynh et al.(21) reported that 2.5–97.5 percentile limits of interocular asymmetry for their macular thickness parameters as –31–31 µm. In another study by Altemir et al.,(19) they reported their limits from –17.6 to –23.2 µm. They suggested that interocular differences in average RNFL and macular thickness of normal individuals should not exceed 13 µm and 23 µm, respectively, if measured with Cirrus HD-OCT (19). And differences greater than this value should be considered suggestive of pathology, such as pediatric glaucoma, optic nerve diseases, or macular diseases according to their study (19). Amblyopia can also affect OCT parameters, especially in patients with severe anisometropia and these group of patients may be followed by the changes on the PPAA.

In another study published by Altemir et al.(22) in the same year, one eye of 100 children was included in the study and they investigated the accuracy and reliability of repeated FD-OCT measurements in children. When inter-observer and intra-observer reproducibility were evaluated, it was found to have good repeatability in childhood (22). In the study made by Dave et al.,(6) they reported that the refractive error did not affect the OCT measurements in their study. They thought that this was because they did not include children with high refractive errors in their study group (6). They also stated that like as a few previous studies, refractive errors and axial length have been shown to have minimal effects on macular thickness measurements (6,23,24).

Dave et al.(6) stated that they did not look at the effect of anisometropia on OCT measurements, which is the weakness of their study. In addition, they mentioned that severe anisometropic cases were not included in their study group because they did not include amblyopia cases in the study (6). On the other hand, we evaluated the macular asymmetry measurements of anisometropia of 1.50 D and above, as well as the group of patients with anisometropia that we followed up for amblyopia, in our own study, which contributed additionally to all these studies.

Altemir et al.(19) discussed in their articles that one of the limitations of their study was that they did not consider the axial length of children with high refractive disorder. At the same time, none of these studies looked at the effect of anisometropia and high refractive values in both eyes, and the study groups were not homogeneously distributed. In a study published by Hwang et al.(25) in 2014 involving a wide age group (5–80 years), no statistically significant relationship was found between age and refractive error and macular thickness. Considering the study methodology, the refractive error ranges of this group, whose mean age was 36.4 years, were between –14.13 and +5.75 D and –14.50 and +5.75 D in the right and left eyes, separately (25). As a result of the study, the mean temporal equivalent of the RE was more myopic and the macular thickness in the RE was significantly thin in the superior quadrant ($r=0.160$, $p<0.001$), while it was thick in the temporal quadrant ($r=-0.236$, $p<0.001$), and there was no difference in the other quadrants ($p>0.05$) (25). In addition, it was observed that the difference in interocular nerve fiber layer thickness was not correlated with age or mean refractive disorder ($p>0.05$) (25). However, considering the study design, it was observed that the comparison was made over the absolute value and mean of the refractive error, and the refractive differences between the two eyes were not classified separately (25). In our study, we also evaluated whether the refractive difference between the two eyes influence the differences in interocular macular

thickness, and especially if there is amblyopia, whether there is a different effect in those cases.

Hwang et al. mentioned that in their previous studies, only adults or only children were included in the study, and in their study, it was superior to the study to look at the influence in a wide age group (25). In their study, it was mentioned that this asymmetry, which is considered normal up to a certain cutoff value between the two eyes, may be affected developmentally by the topographical location of retinal blood vessels, retinal ganglion cell axons and glial cell density, and cyclotorsions in the eye (25). Indeed, our observation is that asymmetry between the two eyes is evident in cases with cyclotorsion, and there may even be variability in these values after strabismus surgery.

Banc et al.,(20) in a review of OCT studies in the childhood, which compiled data from 74 very valuable studies that were newly published in 2021, the following common conclusions were highlighted: (1) Average RNFL thickness is not influenced by age, a gender, or eye laterality, (2) Macular thickness should be considered separately for children aged <5 and children aged >5, (3) central macular thickness has a tendency towards higher values in boys, (4) temporal RNFL sector is thicker in the RE, (5) superior RNFL sector is thicker in the left eye, (6) macular thickness is not significantly different between the right and the left eye, (7) the ISNT rule is not necessarily valid, (8) RNFL thickness increases as the SE of refractive error increases, (9) the ONH OCT parameters are not influenced by the refractive error, (10) ocular axial length can have an effect on the ocular magnification, and thus influence the lateral OCT measurements, and (11) handheld OCT devices are a good alternative for young or uncooperative children (20).

When we compared our results with all literature data, we came up with the following results: (1) The differences between the two eyes were determined by all these studies, the values above the cutoff limits should be reported to us by the test instruments, and the pediatric group should be considered as a separate entity. In this patient group data, new software suitable for age and refractive status should come to the fore, (2) Amblyopia cases should be followed up in terms of pre- and post-treatment changes between the two eyes, just as in other optic nerve or macula pathologies, and change indices in annual follow-ups, (3) If all the factors related to the increase in age from childhood and the development of refractive and axial length and cornea and lens are collected in a pool and age-appropriate nomograms are obtained, perhaps adult test data may also change.

One of the limitations or deficiencies of our study was that the high refractive errors could be classified as hyperopic, myopic, or astigmatic anisometropic and groups could be separated. We could not do this because it would not be statistically significant in this study due to the small number of people; but we included it in our further study plans. Our second limitation was that some of the amblyopia cases were naive, that is, they did not receive any treatment, and the other part had received occlusion treatment before. The changes during the months or years in the post-treatment follow-up of naive cases who have never received treatment are comparable; we considered this as another study plan.

In our study, we investigated the effect of these factors and for the first time investigated the effect of anisometropia and anisometropic amblyopia on PPAA in children. While no difference was found between anisometropic eyes and normal eyes in the PPAA, the difference in some quadrants in the anisometropic amblyopia group compared to the normal group suggests that there is involvement in the extra central quadrants of the macula, especially in amblyopes that are refractory to the occlusion.

Conclusion

PPAA is a new entity that allows us to recognize the differences between the two eyes in childhood and adulthood and can give us more objective data about the prognosis of optic disc and macula diseases that may occur later and are present. More useful results will be obtained in the future with more comprehensive studies.

Disclosures

Ethics Committee Approval: This study was conducted by the Declaration of Helsinki and approved by the ethics committee of the Başkent University (Project No: KA 21/240). All participates involved in the study were required to sign written informed consent from legal guardian of each child.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.A.B., A.S.S., S.O.; Design – S.A.B.; Supervision – S.A.B., S.O.; Materials – S.A.B.,A.S.S.; Data Collection and/or Processing – S.A.B., A.S.S., S.O.; Analysis and/or Interpretation – S.A.B., A.S.S.; Literature Search – S.A.B.,A.S.S.; Writing – S.A.B.; Critical Reviews – S.A.B., S.O.

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