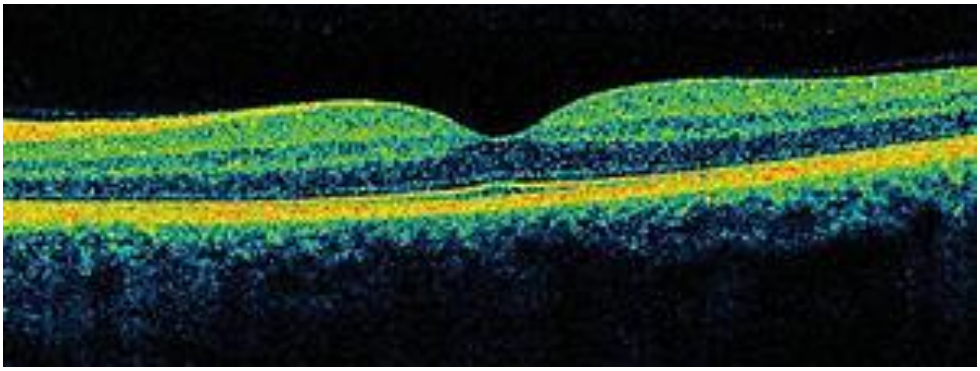
UNIVERSITAT POLITÈCNICA DE CATALUNYA
BARCELONATECH
Facultat d'Òptica i Optometria de Terrassa

MÀSTER UNIVERSITARI EN OPTOMETRIA I CIÈNCIES DE LA VISIÓ

TREBALL FINAL DE MÀSTER

MACULAR CHANGES IN CHILDREN WITH REFRACTIVE AMBLYOPIA



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CANVIS MACULARS EN NENS AMB AMBLIOPIA REFRACTIVA

RESUM

PROPÒSIT: Determinar si l'ambliopia està associada a canvis en l'espessor macular.
MÈTODES: Es va realitzar un estudi observacional, combinat amb elements retrospectius i prospectius. Vint-i-nou subjectes d'entre 4 i 12 anys diagnosticats d'ambliopia refractiva van ser seleccionats per l'estudi, i van dividir-se en dos grups: ambliopia refractiva anisometròpica o ambliopia refractiva isometròpica. A tots els pacients se'ls va realitzar un examen optomètric i oftalmològic complet, que incloïa agudesa visual sense correcció i amb la millor correcció, refracció, exàmens de binocularitat, dilatació pupil·lar i Tomografia de Coherència Òptica (3D OCT-1000; Topcon), a partir de la qual es va mesurar l'espessor macular (a diverses zones predeterminades) i el volum macular. Es van realitzar tres mesures: en la primera visita, al cap de tres mesos i al final del tractament.
RESULTATS: L'edat promig dels pacients va ser de 7.03 ± 2.83 anys. En aquest estudi s'han trobat diferències estadísticament significatives en la diferència inter-ocular (en valor absolut) en l'espessor macular central entre els pacients amb ambliopia refractiva anisometròpica i isometròpica (p=0.031), presentant major diferència inter-ocular els pacients amb ambliopia isometròpica. En el grup anisometròpic s'han trobat diferències estadísticament significatives entre l'ull ambliop i l'ull sa en el volum macular total (p=0.041) i en la zona superior de la primera anella (S1) (p=0.047), i gairebé diferències significatives en l'espessor macular central (p=0.062), en el centre (C1) (p=0.068) i a la zona temporal de la primera anella (T1) (p=0.055).
CONCLUSIONS: L'estudi de l'espessor macular en pacients amb anisometropia pot ser útil per entendre els canvis funcionals associats a aquesta condició. Per tant, la implementació de l'examen de fons d'ull mitjançant Tomografia de Coherència Òptica s'aconsella en pacients amb ambliopia.
PARAULES CLAU: ambiopia, espessor, màcula, refracció, nens

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CAMBIOS MACULARES EN NIÑOS CON AMBLIOPÍA REFRACTIVA

RESUMEN

PROPÓSITO: Determinar si la ambliopía está asociada a cambios en el espesor macular.
MÉTODOS: Se realizó un estudio observacional, combinado con elementos retrospectivos y prospectivos. Veintinueve sujetos de entre 4 y 12 años diagnosticados de ambliopía refractiva fueron seleccionados para el estudio, y se dividieron en dos grupos: ambliopía refractiva anisometrópica o ambliopía refractiva isometrópica. A todos los pacientes se les realizó un examen optométrico y oftalmológico completo, que incluía agudeza visual sin corrección y con la mejor corrección, refracción, exámenes de binocularidad, dilatación pupilar y Tomografía de Coherencia Óptica (3D OCT-1000; Topcon), a partir de la cual se midió el espesor macular (en varias zonas predeterminadas) y el volumen macular. Se realizaron tres medidas: en la primera visita, a los tres meses y al final del tratamiento.
RESULTADOS: La edad promedio de los pacientes fue de 7.03 ± 2.83 años. En este estudio se han encontrado diferencias estadísticamente significativas en la diferencia inter-ocular (en valor absoluto) en el espesor macular central entre los pacientes con ambliopía refractiva anisometrópica y isometrópica (p=0.031), presentando mayor diferencia inter-ocular los pacientes con ambliopía isometrópica. En el grupo anisometrópico se encontraron diferencias estadísticamente significativas entre el ojo ambliope y el ojo sano en el volumen macular total (p=0.041) y en la zona superior de la primera anilla (S1) (p=0.047), y casi diferencias significativas en el espesor macular central (p=0.062), en el centro (C1) (p=0.068) y en la zona temporal de la primera anilla (T1) (p=0.055).
CONCLUSIONES: El estudio del espesor macular en pacientes con anisometropía puede ser útil para entender los cambios funcionales asociados a esta condición. Por lo tanto, la implementación del examen de fondo de ojo mediante Tomografía de Coherencia Óptica se aconseja en pacientes con ambliopía.
PALABRAS CLAVE: ambliopía, espesor, macula, refracción, niños

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MACULAR CHANGES IN CHILDREN WITH REFRACTIVE AMBLYOPIA

ABSTRACT

PURPOSE: To determine whether amblyopia is associated with changes in retinal thickness.
METHODS: Study design was observational, combining retrospective and prospective elements. Twenty-nine subjects aged between 4 and 12 years and with a diagnosis of refractive amblyopia were eligible for the study, and were divided into two main groups: anisometropic refractive amblyopia or isometropic refractive amblyopia. All patients received a complete optometric and ophthalmologic examination, including uncorrected and best distance corrected visual acuity, refraction, binocular exams, pupil dilatation and Optical Coherence Tomography (3D OCT-1000; Topcon), which assessed macular thickness (in several predetermined areas) and macular volume. Three measurements were performed: the first visit, after three months and at the end of the treatment.
RESULTS: The mean age of the subjects was 7.03 ± 2.83 years. In this study, statistically significant differences were found in inter-ocular difference (in absolute values) for central macular thickness between patients with refractive anisometropic amblyopia and isometropic (p=0.031), in which the largest inter-ocular difference corresponded to the isometropic group. Statistically significant differences were found in the anisometropic group between amblyopic and fellow eyes, for total macular volume (p=0.041) and for superior ring 1 (S1) (p=0.047), and almost significant differences for central macular thickness (p=0.062), center (C1) (p=0.068) and temporal ring 1 (T1) (p=0.055).
CONCLUSIONS: The study of macular thickness in patients with anisometropic amblyopia may be useful to understand the functional changes associated with this condition. Therefore, the implementation of ocular fundus examination by Optical Coherence Tomography is recommended in patients with amblyopia.
KEYWORDS: amblyopia, thickness, macula, refraction, children

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Title: MACULAR CHANGES IN CHILDREN WITH REFRACTIVE AMBLYOPIA

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KEYWORDS: amblyopia, thickness, macula, refraction, children

INTRODUCTION

Amblyopia is defined by a reduced best corrected visual acuity in one or both eyes that occurs during the sensitive or critical period of vision development.[1,2,3,4,5,6,7,8] In addition, increased sensitivity to contour interaction effects, abnormal spatial distortions and uncertain, unsteady and inaccurate monocular fixation, poor eye tracking ability, reduced contrast sensitivity and an inaccurate accommodative response may be present.[9] Amblyopia is the most common cause of reduced vision in children. The prevalence of children with amblyopia within the population varies according to the country and its sociocultural development. However, most reports note values between 1.5% and 4% of the population.[3,4,5,8,10,11]

The causes of amblyopia are generally associated with high refractive error, strabismus or visual deprivation early in life.[3,4,9]

-High refractive error is when high and equal or nearly equal uncorrected refractive error is present in both eyes. In these cases, isometropic amblyopia occurs.

-Strabismus results in the foveas of both eyes not being stimulated by the same image, thus leading to the suppression of the image in the deviated eye and, consequently, to amblyopia in this eye due to an abnormal binocular interaction.[12] Strabismic amblyopia is commonly associated with a constant unilateral strabismus. Due to the absence of bifoveal fixation, the two eyes receive different images, originating confusion and diplopia. Therefore, the visual system makes an adaptation and suppresses the image from the deviated eye. These patients often have an eccentric fixation, with difficulty directing the fovea at the target. Patients with strabismic amblyopia have a wide range of visual acuity loss, from worse than 20/20 to 20/200. The average best corrected visual acuity is 20/94.

- Visual deprivation happens when the brain is deprived of the clear vision of the images due to an alteration in the transparency of the ocular media, for example, with congenital cataracts, corneal opacities, congenital ptosis, vitreous opacities, prolonged unilateral blepharospasm or prolonged uncontrolled patching in occlusion therapy. It may appear in one or both eyes.[4,9,12]

Amblyopia may be classified as organic or functional: Organic amblyopia or visual deprivation is defined by a reduced visual acuity due to pathological or structural anomalies that alter retinal or visual structure.[12] Functional amblyopia is defined by a reduced visual acuity in the absence of pathological or structural anomalies, that is, it may originate from an uncorrected refractive error

which did not allow good development of visual acuity. Von Noorden suggested a classification of functional amblyopia based on the clinical causes believed responsible for producing the condition.[13] The types of amblyopia are classified according to the refractive errors that cause the decrease in visual acuity, and may be either anisometropic or isometropic.

Refractive amblyopia results from uncorrected refractive errors. Isometropic amblyopia is an uncommon form of amblyopia caused by high but nearly equal uncorrected bilateral refractive error that creates a blurred image on each retina. Uncorrected astigmatism greater than 2.50 dioptres (D), hyperopia greater than 5.00 D and myopia greater than 8.00 D leads to isometropic amblyopia.[3,4,9,14] Patients have a wide range of visual acuity loss, from worse than 20/20 to 20/200, but the majority of patients have an initial best corrected visual acuity of 20/50 or better. On the other hand, anisometropic amblyopia is caused by an uncorrected refractive error in which the difference between both eyes is at least 1 D,[10] thus resulting in a blurred image in the eye with the greater refractive error. Anisometropic amblyopia may develop with differences larger than 1 D, 3.00 D and 1.5 D between eyes in myopia, hyperopia and astigmatism, respectively. Patients have a wide range of visual acuity loss, from worse than 20/20 to 20/200. The average best corrected visual acuity is 20/60.[9,12]

The visual prognosis of amblyopia depends on the aetiology of the condition, the age of onset and the period and the age when treatment begins. Therefore, an early detection of abnormal development of vision is important for children, and tests of visual acuity are useful for visual screening to detect refractive errors.[1] The most effective treatment for refractive amblyopia is the best correction of the refractive error by spectacles. However, there are other treatments such as patching, optical or pharmacological penalization and vision therapy. [1,4,8] In addition, it must be noted that the determination of the real magnitude of refractive error is only possible with cycloplegia, such as cyclopentolate, which paralyzes the ciliary muscle, thus preventing accommodation. Therefore, in those countries in which optometrists are not legally allowed to use cycloplegia, it is very important to refer all children for an ophthalmological examination, even in the absence of pathology, so that an early management of each case is possible, leading to better prognosis.

Optical coherence tomography (OCT) is a non invasive imaging technique that gives high resolution images of the retina in normal eyes and in pathological conditions. It has been used successfully in young children, although there is a current lack of normative database in the software of most devices for patients under 18 years.

Nowadays, several authors have investigated the retinal changes associated with amblyopia using OCT, but the results of these studies are contradictory. Thus, for instance, Andalib et al, 2013[6], used OCT to compare the macular and nerve fibre layer thickness in amblyopic and fellow eyes. They examined 25 children with monocular strabismic or anisometropic amblyopia. These authors found a significant increase in macular thickness in anisometropic amblyopic eyes, but the increase of macular thickness in strabismic amblyopic eyes was not significant. Similarly, Pang et al, 2011[7], used OCT to compare the macular thickness of the normal fellow eye to that of the amblyopic eye in children with unilateral high myopia. They examined 31 children and found thicker foveae and thinner inner and outer macular areas in the amblyopic eye compared to the fellow eye. Also, Wu et al, 2013[15], used OCT to compare the retinal nerve fibre layer thickness and macular thickness in the amblyopic eye in children with hyperopic anisometropic amblyopia. They examined 72 children, encountering increased thickness in the macular foveola and peripapillary retinal nerve fibre layer in the amblyopic than in the contralateral eye.

Interestingly, and in disagreement with the studies described above, Coella Mejías, 2007[16], used OCT to compare macular and retinal nerve fibre layer changes in amblyopic eyes with those of normal eyes. They examined 16 patients and found a decrease in parafoveal thickness and total macular volume in patients with strabismic and refractive amblyopia, as well as a decrease in the thickness of the retinal nerve fibre layer in patients with refractive amblyopia.

The purpose of our investigation was to determine whether amblyopia is associated with changes in retinal thickness as reported by previous authors and to contribute new findings to shed additional light to the ongoing debate. Therefore, optical coherence tomography (OCT) was employed to measure macular thickness in children with refractive amblyopia. For this purpose, patients with isometropic and anisometropic amblyopia were selected and retinal thickness was explored in the macular region at different, pre-defined areas. Comparisons were conducted according to type of amblyopia (isometropic *versus* anisometropic) and to type of refractive status (myopia, hyperopia or astigmatism).

METHODS

Study sample

Study design was observational, combining retrospective and prospective elements. Patients were selected from those attending an ophthalmic consultation, Inof- Centro de Investigación y Cirugía Ocular, in Centro Médico Teknon, Barcelona, between 2010 and 2017. Patients aged between 4 and 12 years and with a diagnosis of refractive amblyopia were eligible for the study. Informed consent was obtained from all parents or legal guardians of the children and the study was conducted in accordance with the Declaration of Helsinki tenets of 1975 (as revised in Tokyo in 2004).

Children under 4 years were excluded due to lack of collaboration during the diagnostic tests. Patients with a history of prior treatment with spectacles, patching or atropine were excluded from the study, as were those with any ocular pathology such as cataract, corneal opacity, strabismus or previous eye surgery. Only well-focused and good-quality scans with signal strength of 0.65 or over were considered for data analysis.

Patients were divided into 2 main groups: those with isometropic amblyopia and those with anisometropic amblyopia. Isometropic refractive amblyopia was defined as a bilateral refractive error greater than 5 D of hyperopia, 2.5 D of astigmatism or 8 D of myopia. On the other hand, anisometropic refractive amblyopia was diagnosed when patients presented refractive interocular differences larger than 1 D in hyperopia, 1.5 D of astigmatism or 3 D of myopia.

Procedure

All patients received a complete anamnesis, which included questions exploring ocular, general and family history, use of ocular or systemic drugs and presence of allergies. Next, an optometric and ophthalmological examination was performed, including uncorrected and best distance corrected monocular visual acuity, which was tested at 6 m using a Tumbling E chart (decimal notation), subjective refraction, Cover Test (with and without refractive correction) at distance and near, and ocular motility. Finally, cycloplegia was induced with 1% cyclopentolate (2 drops, one drop every 30 minutes) and cycloplegic autorefraction was determined with an Autorefractometer (Nidek ARK-710A) and then adjusted by cycloplegic retinoscopy. All patients underwent indirect ophthalmoscopy with a slit-lamp / lens attachment for anterior segment and fundus examination. Finally, for each case diagnosis was reached and treatment was decided. Initially, the best spectacle correction of refractive error was prescribed to all patients. In

successive visits, in 9 patients spectacles proved insufficient to improve visual acuity and it was decided to add patching to the ongoing treatment.

Both eyes of all participants were imaged in random order using a SD-OCT (3D OCT-1000; Topcon). The measurements of macular thickness were performed after pupil dilation and included information from each of the 9 map sectors, defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). A cube 6 mm x 6 mm in length fixed on the macular area was scanned with a resolution of 128-512 µm. The macular thickness map centered on the foveola, which divides the macula into nine regions, was used. Thus, the 6 mm diameter ring was divided into three areas, with the central ring corresponding to the fovea (1 mm in diameter), the middle ring corresponding to the perifovea (3 mm), and the outer ring to the parafovea (6 mm). For each ring, the software provided mean thickness values for each of the four quadrants: superior, inferior, nasal and temporal. Central macular thickness was defined as the average macular thickness in the central ring, whereas average macular thickness corresponded to the mean thicknesses of the nine regions, and macular volume to the summation of volumes of all nine regions.

Measurements were conducted in three occasions: the first visit (Visit 1) was at the time of diagnosis; the second (Visit 2) corresponded to 3 months after diagnosis; finally, the last one (Visit 3) was at the end of the treatment. Visual acuity without correction (UCVA) was measured during the first visit. Visual acuity with the best correction (BCVA) and refraction (spherical and cylindrical) were obtained during the second and third visits. The end of treatment was defined as the moment patients attained visual acuity values of approximately 1.0 (decimal) with their best correction. Retinal thickness measurements with the OCT were conducted at the end of treatment (or within 3 months of Visit 3). All measurements were conducted by two experienced optometrists and following exactly the same procedure.

Figure 1 shows a typical output of macular examination provided by the software of the OCT. The quality of the image and the date of the capture are shown at the top. Under this, the fundus photograph appears, with the selected area under study and the coordinates of the middle center point. Another fundus image displays the thickness of the selected area in a chromatic scale. Below the fundus photographs, the CUTS of the macula are provided, both horizontally and vertically, and the schematization of the average thickness at the different ETDRS areas. In addition, the output provides information of the average macular thickness, the thickness of the central point and the total macular volume in cubic millimeters. Finally, at the bottom there is a three-dimensional image of the internal limiting membrane and the retinal pigment epithelium, that is, the layers between which the retinal thickness is calculated. All thickness values are shown in micrometers.

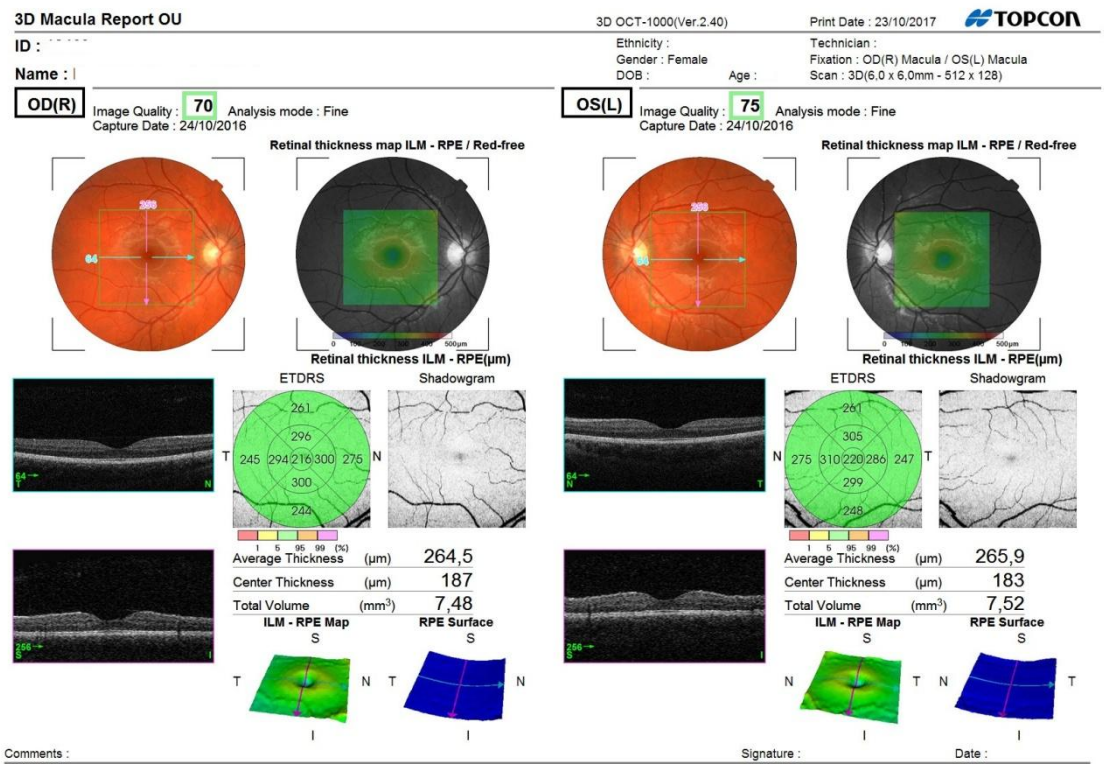

Figure 1: Typical output of macular examination provided by the software of the OCT

Data analysis

Statistical analysis was performed with the statistical software IBM SPSS v.21 for Windows (IBM Spain, Madrid). Data was imported to SPSS from an Excel file which collected medical history, date of birth, sex (male; female), type of refractive amblyopia (isometropic; anisometropic), age when treatment was started, period of treatment, UCVA (Visit 1) and BCVA (Visits 2 and 3) (for statistical purposes visual acuity was converted from decimal notation to logMAR values), refractive error (Visits 2 and 3), type of treatment (glasses; glasses and patch) and OCT values regarding center thickness (µm), average thickness (µm), total Volume (mm^3), and thickness at the 4 ETDRS quadrants (µm) and 2 annular areas (Visit 3 or within 3 months of Visit 3).

To facilitate the interpretation of the results, sectors were named N for nasal, T for temporal, S for superior and I for inferior, followed by the number 1 or 2, depending on the ring where measurements were conducted (**Figure 2**).

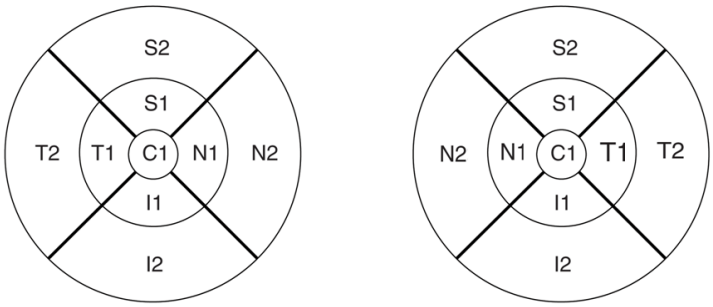

Figure 2. ETDRS map. Summary of the sectors examined in this study in the right and left eye.

Descriptive statistics is shown as mean ± standard deviation (SD). Given the reduced sample size and the dispersion of the results, when describing isometropic and anisometropic groups, results are presented as inter-ocular differences (in absolute value). It was our initial hypothesis that patients with anisometropic amblyopia would present larger inter-ocular differences in visual acuity, refractive error and retinal thickness than isometropic patients. Comparison between both amblyopic groups was conducted with the Student's t-test and the association between inter-ocular differences in refractive error and in retinal parameters was explored with a Pearson coefficient of correlation test.

In addition, anisometropic patients were further classified according to their main refractive status as myopic, hyperopic and astigmatic, and their inter-ocular differences in retinal thickness were explored at each quadrant under analysis. An ANOVA test was employed to determine the significance of differences between refractive status groups and, upon disclosing statistical significance, a *post-hoc* Bonferroni test was used for pair-wise analysis.

Throughout the statistical analysis, a p-value of 0.05 or less was defined to denote statistical significance.

RESULTS

Data was collected from 41 patients with refractive amblyopia. However, after considering the inclusion and exclusion criteria, only 29 subjects were finally included in the study (17 females and 12 males). The mean age of the subjects was 7.03 ± 2.83 years (mean ± SD), with a range from 4 to 12 years. Twenty-three (79.3%) subjects had anisometropic amblyopia and six (20.7%) subjects had isometropic amblyopia. According to the refractive error, 21 (72.4%) subjects had hyperopia, 3 (10.3%) subjects had myopia and 5 (17.2%) subjects had astigmatism. All subjects used spectacles to correct their refractive error and 9 of them also added patching to their spectacle correction. The mean period of treatment was 2.62 ± 1.83 years, with a range from 1 to 7 years.

Table 1 displays a summary of visual acuity and refractive error values corresponding to the first (UCVA) and second visit (BCVA and refractive data). Data from anisometropic and isometropic groups was pooled together. It may be observed that, in general, UCVA at Visit 1 was poor, with a mean value of approximately 0.500 logMAR.

	MINIMUM	MAXIMUM	MEAN ± SD
UCVA VISIT 1 OD (logMAR)	0.000	1.824	0.476 ± 0.533
UCVA VISIT 1 OS (logMAR)	0.000	1.824	0.500 ± 0.494
SPHERE VISIT 2 OD (D)	-5.00	9.50	1.57 ± 3.39
CYLINDER POWER VISIT 2 OD (D)	-3.50	0.00	-1.00 ± 1.08
BCVA VISIT 2 OD (logMAR)	0.000	1.000	0.144 ± 0.213
SPHERE VISIT 2 OS (D)	-4.50	8.00	2.44 ± 3.20
CYLINDER POWER VISIT 2 OS (D)	-3.50	0.00	-1.24 ± 1.14
BCVA VISIT 2 OS (logMAR)	0.000	1.00	0.143 ± 0.190

Table 1. Summary of visual acuity and refractive error values at Visit 1 and Visit 2. Data was pooled from both amblyopic groups. (UCVA: Uncorrected visual acuity; BCVA: best-corrected visual acuity; OD: right eye; OS: left eye).

For subsequent analysis, data was divided according to the type of amblyopia. **Table 2** displays a summary of the inter-ocular differences (in absolute values) in visual acuity and refractive error for both amblyopic groups. Statistically significant differences between isometropic and anisometropic were found for sphere and sum of sphere and cylinder at the second and last visit. Mean values show that the inter-ocular differences in all variables were greater in the anisometropic group (confirming our initial hypothesis).

	ISOMETROPIC (mean ± SD)	ANISOMETROPIC (mean ± SD)	t	p
SPHERE VISIT 2 (D)	0.21 ± 0.29	2.00 ± 1.36	-3.174	**0.004**
CYLINDER POWER VISIT 2 (D)	0.17 ± 0.20	0.69 ± 0.84	-1.507	0.143
BCVA VISIT 2 (logMAR)	0.054 ± 0.048	0.223 ± 0.284	-1.436	0.162
SPHERE VISIT 3 (D)	0.37 ± 0.47	2.38 ± 1.54	-3.120	**0.004**
CYLINDER POWER VISIT 3 (D)	0.25 ± 0.42	0.79 ± 0.96	-1.334	0.193
BCVA VISIT 3 (logMAR)	0.008 ± 0.019	0.036 ± 0.066	-1.021	0.316
SUM OF SHPERE AND CYLINDER POWER VISIT 2 (D)	0.37 ± 0.26	2.69 ± 1.77	-3.165	**0.004**
SUM OF SPHERE AND CYLINDER POWER VISIT 3 (D)	0.62 ± 0.82	3.17 ± 2.21	-2.747	**0.11**

Table 2. Summary of the inter-ocular differences (absolute values) for visual acuity and refractive error for the isometropic and anisometropic amblyopic groups at Visit 2 and Visit 3. P-values in bold denote statistical significance. (BCVA: best-corrected visual acuity).

Similarly, **Table 3** displays a summary of the inter-ocular differences (in absolute values) for each retinal parameter for the isometropic and anisometropic amblyopic groups. Statistically significant differences between isometropic and anisometropic were only found for center macular thickness (P-value=0.031), in which the largest inter-ocular difference corresponded to the isometropic group.

LOCATION	ISOMETROPIC (mean ± SD)	ANISOMETROPIC (mean ± SD)	t	p
Center macular thickness	40.17 ± 39.82	17.39 ± 14.93	2.279	**0.031**
Average macular thickness	6.28 ± 2.56	7.77 ± 7.04	-0.501	0.620
Total macular volume (mm^3)	0.18 ± 0.07	0.21 ± 0.18	-0.449	0.657
C1	18.17 ± 21.14	16.00 ± 12.58	0.325	0.748
N1	7.67 ± 8.52	17.09 ± 18.44	-1.206	0.238
T1	7.00 ± 6.03	10.65 ± 13.83	-0.625	0.537
S1	11.33 ± 13.06	11.33 ± 5.33	-0.631	0.634
I1	7.17 ± 8.86	17.61 ± 14.54	-1.667	0.107
N2	5.67 ± 3.78	13.74 ± 18.70	-1.038	0.308
T2	15.33 ± 10.42	14.17 ± 10.15	0.248	0.806
S2	8.83 ± 8.75	15.00 ± 21.02	-0.695	0.493
I2	17.33 ± 17.95	16.17 ± 20.02	0.129	0.899

Table 3. Inter-ocular differences (absolute values) in thickness for each retinal parameter for both amblyopic groups at Visit 3. (N: nasal; T: temporal; S: superior; I: inferior; 1: ring 1; 2: ring 2). P-values in bold denote statistical significance. All thickness values are in micrometers.

Upon exploring the possible associations between inter-ocular differences in refractive error and retinal parameters, Pearson correlation analysis failed to reveal any significant relationship, probably as a result of large data dispersion and reduced sample size. However, the association between the inter-ocular differences in sum of sphere and cylinder power and in central macular thickness almost reached significance, showing a possible trend worth exploring in future studies (r =-0.319; P-value = 0.091).

Despite the limitation of further decreasing our sample size, it was decided to reduce data dispersion by conducting a posterior analysis only of patients with anisometropic amblyopia (n=23). **Table 4** displays a summary of BCVA and retinal parameters for the anisometropic group, with eyes classified as amblyopic or non-amblyopic. The Student's t-test disclosed statistically significant differences between amblyopic and fellow eyes for BCVA at Visit 2 (P-value=0.001) and Visit 3 (P-value=0.016) and for total macular volume (P-value=0.041) and thickness at S1 (P-value=0.047). Mean values show that BCVA values were greater in the non-amblyopic eye and total macular volume and thickness at S1 values were greater in the amblyopic eye. Besides, almost statistically significant differences were observed in center macular thickness (P-value=0.062), C1 (P-value=0.068) and T1 (P-value=0.055).

	AMBLYOPIC EYE (mean ± SD)	FELLOW EYE (mean ± SD)	t	p
BCVA VISIT 2 (logMAR)	0.254 ± 0.270	0.031 ± 0.040	3.765	**0.001**
BCVA VISIT 3 (logMAR)	0.042 ± 0.066	0.006 ± 0.016	2.604	**0.016**
Center macular thickness	227.57 ± 50.94	218.78 ± 44.19	1.967	0.062
Average macular thickness	276.56 ± 14.00	273.10 ± 10.00	1.655	0.112
Total macular volume (mm^3)	7.82 ± 0.38	7.70 ± 0.29	2.169	**0.041**
C1	246.26 ± 37.13	238.61 ± 33.20	1.922	0.068
N1	307.48 ± 28.92	303.26 ± 10.71	0.808	0.428
T1	287.96 ± 13.99	281.13 ± 14.27	2.026	0.055
S1	307.35 ± 16.67	297.96 ± 15.43	2.108	**0.047**
I1	289.04 ± 27.75	283.43 ± 20.64	1.200	0.243
N2	284.57 ± 28.83	287.00 ± 13.48	-0.502	0.621
T2	258.22± 17.06	253.26 ± 12.68	1.402	0.175
S2	267.22±26.60	264.22 ± 10.38	0.557	0.583
I2	267.87± 23.25	272.04 ± 19.52	-0.782	0.443

Table 4. Summary of visual acuity and thickness for each retinal parameter for the anisometropic group. P-values in bold denote statistical significance. (BCVA: best-corrected visual acuity; N: nasal; T: temporal; S: superior; I: inferior; 1: ring 1; 2: ring 2). All thickness values are in micrometers.

Results are shown in **Table 5** for BCVA and for each retinal parameter with patients divided according to their refractive status in hyperopic, myopic and astigmatic. Statistical analysis was only conducted in the hyperopic group (n=18). A Student's t-test revealed significant statistical differences between the amblyopic and fellow eye in BCVA at Visit 2 (P-value= 0.002) and at Visit 3 (P-value=0.009), in total macular volume (P-value=0.042) and in retinal thickness at the T2 location (P-value=0.036). In agreement to the previous results, mean values show that BCVA values were greater in the fellow eye, whereas total macular volume and retinal thickness at T2 values were greater in amblyopic eye.

	REFRACTIVE ERROR					
	HYPERMETROPIA (n=18)		MYOPIA (n=3)		ASTIGMATISM (n=5)	
	AMBLYOPIC EYE (mean ± SD)	FELLOW EYE (mean ± SD)	AMBLYOPIC EYE (mean ± SD)	FELLOW EYE (mean ± SD)	AMBLYOPIC EYE (mean ± SD)	FELLOW EYE (mean ± SD)
BCVA VISIT 2 (logMAR)	0.244 ± 0.238	0.029 ± 0.041	0.417 ± 0.505	0.048 ± 0.048	0.097 ± 0.000	0.023 ± 0.032
BCVA VISIT 3 (logMAR)	0.029 ± 0.033	0.005 ± 0.015	0.133 ± 0.154	0.015 ± 0.026	0.023 ± 0.032	0.000 ± 0.000
Center macular thickness	237.11 ± 53.63	228.44 ± 45.20	196.33 ± 16.56	185.33 ± 15.53	188.50 ± 4.95	182.00 ± 2.83
Average macular thickness	276.81 ± 15.45	272.24 ± 10.76	277.37 ± 10.61	277.50 ± 8.73	273.05 ± 1.77	274.25 ± 2.33
Total Macular Volume (mm3)	7.82 ± 0.42	7.68 ± 0.32	7.84 ± 0.30	7.85 ± 0.25	7.72 ± 0.06	7.69 ± 0.03
C1	249.89 ± 41.21	241.50 ± 34.97	235.00 ± 13.00	218.33 ± 27.60	230.50 ± 2.12	243.00 ± 22.63
N1	307.06 ± 31.01	302.17 ± 11.73	320.67 ± 6.66	309.00 ± 4.36	291.50 ± 30.41	304.50 ± 4.95
T1	287.33 ± 15.43	280.17 ± 15.09	294.33 ± 5.77	284.00 ± 14.93	284.00 ± 5.66	285.50 ± 9.19
S1	306.67 ± 17.74	295.94 ± 16.72	312.67 ± 18.23	305.00 ± 8.72	305.50 ± 0.71	305.50 ± 0.71
I1	284.67 ± 29.56	278.94 ± 19.77	309.33 ± 2.08	304.67 ± 5.51	298.00 ± 18.38	292.00 ± 28.28
N2	281.56 ± 30.96	285.11 ± 14.28	298.67 ± 23.76	293.67 ± 10.69	290.50 ± 6.36	294.00 ± 2.83
T2	261.61 ± 17.11	253.06 ± 12.61	246.33 ± 14.29	258.67 ± 17.24	245.50 ± 7.78	247.00 ± 8.48
S2	266.17 ± 29.15	262.94 ± 9.17	271.67 ± 22.59	273.33 ± 18.04	270.00 ± 1.41	262.00 ± 1.41
I2	269.06 ± 25.99	273.11 ± 21.42	261.33 ± 9.02	265.33 ± 11.93	267.00 ± 9.90	272.50 ± 12.02

Table 5. Summary of visual acuity and thickness values for each retinal parameter for the anisometropic group and divided according to the refractive error, at Visit 3. (BCVA: best-corrected visual acuity; N: nasal; T: temporal; S: superior; I: inferior; 1: ring 1; 2: ring 2). All thickness values are in micrometers.

Table 6 displays a summary of the inter-ocular differences (in absolute values) in BCVA and sphere and cylinder for the hyperopic, myopic and astigmatic groups at Visit 3. An ANOVA test revealed statistically significant differences among refractive errors for sphere (P-value=0.004), cylinder power (P-value=0.013) and sum of sphere and cylinder power (P-value=0.009) at Visit 3. Further exploration with a matched pairs *post-hoc* Bonferroni test disclosed statistically significant differences between hyperopia and myopia in sphere (P-value= 0.012), cylinder (P-value = 0.034) and sum of sphere and cylinder (P-value = 0.008) and between myopia and astigmatism (P-value=0.007) in spherical inter-ocular differences.

	REFRACTIVE ERROR			F	p
	HYPERMETROPIA (mean ± SD)	MYOPIA (mean ± SD)	ASTIGMATISM (mean ± SD)		
SPHERE VISIT 3 (D)	2.18 ± 1.03	4.67 ± 2.47	0.75 ± 0.35	7.175	**0.004**
CYLINDER POWER VISIT 3 (D)	0.50 ± 0.68	1.92 ± 1.63	1.75 ± 0.35	5.390	**0.013**
BCVA VISIT 3 (logMAR)	0.023 ± 0.034	0.117 ± 0.161	0.023 ± 0.032	3.174	0.064
SUM OF SPHERE AND CYLINDER POWER VISIT 3 (D)	2.68 ± 1.44	6.58 ± 3.99	-	5.982	**0.009**

Table 6. Summary of inter-ocular differences (absolute values) for visual acuity and refractive error for anisometropic group at Visit 3 with results of the ANOVA analysis. P-values in bold denote statistical significance. (BCVA: best-corrected visual acuity).

Finally, **Table 7** presents a summary of the inter-ocular differences in retinal parameters at Visit 3 according to refractive status, in which no statistically significant difference was found among refractive status groups.

LOCATION	REFRACTIVE ERROR			F	p
	HYPERMETROPIA (mean ± SD)	MYOPIA (mean ± SD)	ASTIGMATISM (mean ± SD)		
Center macular thickness	19.67 ± 16.14	11.0 ± 3.00	6.50 ± 2.12	1.018	0.379
Average macular thickness	9.14 ± 7.38	2.73 ± 1.46	2.90 ± 1.70	1.690	0.210
Total Macular Volume (mm^3)	0.25 ± 0.18	0.08 ± 0 .042	0.03 ± 0.03	2.851	0.081
C1	16.06 ± 12.66	16.67 ± 14.84	14.50 ± 17.68	0.017	0.983
N1	17.00 ± 19.93	12.33 ± 9.81	25.00 ± 18.38	0.265	0.770
T1	11.61 ± 14.87	10.33 ± 12.10	2.50 ± 2.12	0.369	0.696
S1	17.89 ± 18.23	11.67 ± 4.93	-	1.098	0.353
I1	20.83 ± 14.72	5.33 ± 4.04	7.00 ± 8.48	2.282	0.128
N2	13.33 ± 19.82	21.00 ± 19.08	6.50 ± 4.95	0.358	0.704
T2	14.78 ± 9.97	12.33 ± 16.44	11.50 ± 2.12	0.139	0.871
S2	17.67 ± 23.11	3.67 ± 3.79	8.00 ± 2.83	0.671	0.522
I2	19.28 ± 21.57	4.67 ± 7.23	5.50 ± 2.12	0.996	0.387

Table 7. Summary of the inter-ocular differences (absolute values) in thickness for each retinal parameter for the anisometropic group at Visit 3. (N: nasal; T: temporal; S: superior; I: inferior; 1: ring 1; 2: ring 2). P-values in bold denote statistical significance. All thickness values are in micrometers.

DISCUSSION

In the present study, the results revealed greater inter-ocular difference in visual acuity, sphere and sum of sphere and cylinder in patients with anisometropic amblyopia than in patients with isometropic amblyopia. However, the isometropic group present larger inter-ocular differences in center macular thickness.

In our study, statistically significant differences between amblyopic and fellow eyes (only for the anisometropic group) were found for visual acuity at Visit 2 and Visit 3, and for total macular volume and thickness at S1. Mean values were greater in the amblyopic eye for total macular volume and thickness at S1. Besides, almost statistically significant differences were observed in center macular thickness, C1 and T1, also with larger values in the affected eye.

Our findings are in agreement with the study of Pang et al. [7], who reported that in 31 amblyopic children with high myopia, foveal minimum thickness and average foveal thickness were greater in the amblyopic eyes than in the normal fellow eyes. Similarly, Huynh et al. [17] found a slightly thicker central macular region and foveal minimum thickness in anisometropic (90.8%) and isometropic (9.2%) eyes, compared with normal eye. Kasem et al.[18] also found significant differences in macular thickness between the amblyopic eye and the normal fellow eye in patients with unilateral amblyopia. Finally, Wu et al.[15] used OCT to compare macular thickness in the amblyopic eye in 72 children with hyperopic anisometropic amblyopia, encountering increased thickness in the macular foveola in the amblyopic than in the contralateral eye.

However, research in this area still uncovers contradictory findings. Thus, for instance, Singh et al.[19] measured 101 subjects with anisometropic amblyopia and reported no statistically significant difference in central macular thickness between the amblyopic and the fellow eyes, albeit thickness values were in general larger in the amblyopic eye.

Our results show that for the anisometropic group with hyperopia there were significant statistical differences between the amblyopic and fellow eye in BCVA at Visit 2 and at Visit 3, in total macular volume and in retinal thickness at the T2 location. In agreement with the previous results, and as expected, mean values of BCVA were greater in the fellow eye, whereas total macular volume and retinal thickness at T2 values were greater in the amblyopic eye.

It is interesting to note that significant differences amongst refractive error types were found in the inter-ocular (absolute values of the difference between the amblyopic and fellow eye) differences in sphere, cylinder power and sum of sphere and cylinder power at Visit 3. These

findings were not evidenced in terms of inter-ocular differences in retinal parameters, in which no statistically significant difference was found among refractive status groups

The results of the present study support the hypothesis that anisometropic amblopyia may produce larger inter-ocular differences in visual acuity, refractive error and retinal thickness. Interestingly, previous authors reporting increased macular thickness in anisometropic amblyopia also observed no statistical differences in strabismic amblyiopia, thus suggesting different mechanisms leading to retinal changes depending on the type of amblyopia [6]. Thus, it has been proposed that an arrest in the normal postnatal changes in amblyopic eyes could affect the normal maturation of the macula, including the movement of Henle's fibers away from the foveola, and that would result in increased foveal thickness, as measured by OCT.[17]

It is interesting to note that Liu et al.[20] reported that some children with isometropic and anisometropic amblyopia who failed to achieve normal visual acuity after treatment showed a thicker macula on OCT examination. Therefore, it seems that the macular involvement in anisometropic amblyopia can lead to resistance to treatment.

Unfortunately, to further explore this association we would require a larger study sample including patients with successful and unsuccessful treatment outcomes and with better matched demographics, to allow statistically powerful results. Indeed, the main limitations of this study were the small number of patients examined and the great data dispersion of study sample.

In summary, statistically significant differences were found in inter-ocular differences (in absolute values) for center macular thickness between anisometropic and isometropic groups, in which the largest difference corresponded to the isometropic group. These findings may be of interest when investigating the functional changes associated with amblyopia and may open new paths to understand why some particular patients respond better to therapy than others.

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