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Multicenter Spanish study of spectral-domain optical coherence tomography in normal children

Jesús Barrio-Barrio,[1] Susana Noval,[2] Marta Galdós,[3,4] Miguel Ruiz-Canela,[5] Elvira Bonet,[1] María Capote[2] and Maialen Lopez[3]

[1]Department of Ophthalmology, Clínica Universidad de Navarra, University of Navarra, Pamplona, Spain
[2]Department of Ophthalmology, Hospital Universitario La Paz, Autonomous University, IdiPaz, Madrid, Spain
[3]Department of Ophthalmology, Hospital de Cruces, Bilbao, Spain
[4]Instituto Clínico Quirúrgico Oftalmológico (ICQO), Bilbao, Spain
[5]Department of Biomedical Humanities, University of Navarra Pamplona, Spain

ABSTRACT.

Purpose: **To compile a multicenter normative database of retinal nerve fibre layer (RNFL) and macular thicknesses and macular volume values in healthy Caucasian children 4–17 years using spectral-domain optical coherence tomography (SD-OCT). To analyse variations in the OCT measurements as a function of age, sex, refraction, and axial length (AL).**

Methods: **An observational, multicenter and cross-sectional study among 301 healthy Caucasian children recruited at three Spanish centres was performed. To compile the database, each child underwent a dilated eye examination and a cycloplegic refraction, five AL measurements (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), five OCT scans with Cirrus OCT: three peripapillary RNFL scans (Optic Disc Cube 200X200 protocol) and two macular scans (Macular Cube 512X128 protocol). One eye of each subject was selected randomly for analysis.**

Results: **Two hundred eighty-three children (117 boys, 41.34%; 166 girls, 58.66%) were included in this study. The mean age of the children was 9.58 ± 3.12 years (range, 4–17). The mean SE was +0.63 ± 1.65 D; (range, −4.88 to +5.25). The mean AL was 22.94 ± 1.10 mm (range, 20.10–26.27). The mean global RNFL thickness was 97.40 ± 9.0 μm (range, 77–121.7 μm). Multivariate analysis showed a positive correlation between the RNFL and spherical equivalent (SE) ($p = 0.014$). The mean central macular thickness was 253.85 ± 19.76 μm, the average thickness 283.62 ± 14.08 μm, and the mean macular volume 10.22 ± 0.49 μm^3. Multivariate analysis showed a positive correlation between central macular thickness and age ($p < 0.001$). Boys had a significantly thicker central macula than girls ($p < 0.001$).**

Conclusions: **Normative paediatric SD-OCT data might facilitate use of SD-OCT for assessing childhood ophthalmic diseases. This study provides a multicenter paediatric normative database of SD-OCT peripapillary RNFL and macular data.**

Key words: database – macular thickness – optical coherence tomography – retinal nerve fibre layer

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Introduction

Optical coherence tomography (OCT) is an essential ancillary test for both macular and optic nerve diseases. It is a non-invasive technology that uses laser light to acquire in vivo high-resolution images and measurements of the central retina and the retinal nerve fibre layer (RNFL). The third-generation instrument, Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA), relies on time-domain technology (TD-OCT) (Knight et al. 2009). This technology recently was superseded by new instruments that use spectral-domain technology (SD-OCT), such as Cirrus OCT (Carl Zeiss Meditec) providing about twice the axial resolution and 43–100 times the scanning speed (Hirasawa et al. 2010). Spectral-domain optical coherence tomography significantly increases the amount of data acquired during each session; the motion artefacts are significantly reduced; and better repeatability and reproducibility and an increased signal-to-noise ratio are achieved compared with TD-OCT (Kiernan et al. 2010; Menke et al. 2011; Eriksson et al. 2012). The data obtained with different OCT devices correlate with each other; however, they are not exchangeable (Hirasawa et al. 2010).

The diagnosis and follow-up of children with an ocular disease is more difficult than that of adults because of the challenge in obtaining reliable and reproducible visual examinations. Important diagnostic tools used in adults, such as visual fields, require their cooperation. For children, such tools are often impractical because the results are unreliable, and hence difficult to interpret (Salchow et al. 2006; Larsson et al. 2011). However, OCT provides objective measurements of the affected structures. Generally, children older than 3 or 4 years of age can cooperate sufficiently. Macular measurements are even easier to obtain than those of the optic nerve, making OCT particularly suitable for use with uncooperative children or those with poor fixation.

Macular and RNFL measurements provided by OCT are useful at any age for long-term follow-up because they allow direct comparison with previous values of the same patient. However, no commercially available machines include an age-normalized database for individuals younger than 18 years, which limits application in a paediatric population. Several studies have been conducted to provide a normative paediatric database of RNFL and macular thickness values using TD-OCT (Ahn et al. 2005; Hess et al. 2005; Huynh et al. 2006a,b, 2008; El-Dairi et al. 2009; Eriksson et al. 2009; Gire et al. 2010; Leung et al. 2010; Qian et al. 2010). These studies included patients from different countries and ethnic groups. To our knowledge, this is the first multicenter study using a SD-OCT technique in European Caucasian children that provides a normative database of peripapillary RNFL and macular thickness values.

The primary purpose of the current study was to compile a normative database of data collected from children that includes the RNFL and macular thickness values obtained using SD-OCT. The secondary aim was to analyse variations in the RNFL thickness and macular thickness as a function of age, sex, refraction and axial length (AL).

Subjects and Methods

Healthy children aged 4–17 years were invited to participate in this study at three Spanish hospitals: Clínica Universidad de Navarra, Pamplona; Hospital Universitario La Paz, Madrid; and Hospital Cruces, Bilbao. We established three groups based on age: 4–7, 8–12 and 13–17 years. The inclusion criteria included a best-corrected visual acuity (BCVA) of at least 0.7 (on the Snellen visual acuity scale) in the 4–7-year-olds and 0.8 in the older groups; a maximal difference of one line of vision between the VA (visual acuity) of both eyes; and no ocular problems other than low or medium refractive errors. The exclusion criteria were a high refractive error, defined as a SE exceeding ± 5.5 dioptres (D) or astigmatism exceeding 3 D, and ocular conditions, such as strabismus, amblyopia or any retinal or optic disc anomaly as determined by mydriatic fundus examination. Intraocular pressure (IOP) was determined in cases of high C/D ratio (≥0.5) or C/D ratio asymmetry (≥0.3) by Goldman or Perkins tonometry. Children were excluded when the IOP was >21 mm Hg. Children with systemic diseases were also excluded.

All procedures were performed in accordance with the Declaration of Helsinki. All caregivers received detailed information about the nature of the investigation and provided written informed consent before study enrolment. Each of the local ethics committee of the participating centres approved the study.

Study protocol

All subjects underwent an initial ophthalmic examination including measurement of the BCVA, assessment of ocular motility and alignment, and assessment of the anterior and posterior poles.

The AL was measured in the three centres using the IOLMaster (Carl Zeiss Meditec) before cycloplegia. The average of five non-contact measurements was recorded. Poor signal values and values that differed by more than 0.1 mm were rejected, and the measurement was repeated. The pupils were dilated with three drops of cyclopentolate 1% at intervals of 5 min, and the cycloplegic autorefraction was assessed 25–30 min after the last drop was instilled.

Before the fundus examination, SD-OCT was performed through dilated pupils using Cirrus-HD Model 4000 (software version 4.5; Carl Zeiss Meditec). The three centres used the same device model. A superluminescent diode laser with an 840-nm wavelength, acquisition rate of 27 000 A-scans per second and resolution of 5 μm are the main features of this high-definition SD-OCT. An internal fixation target was used in all examinations. To evaluate the RNFL thickness, the optic disc cube 200 × 200protocol was used. Three scans of each eye of each subject were performed. This protocol is based on a three-dimensional scan of a 6×6-mm^2 area centred on the optic disc where information from a 1024 (depth) 200×200-point parallelepiped is collected. A 3.46-mm-diameter circular scan is placed around the optic disc, and the information about the peripapillary RNFL thickness is obtained (Leite et al. 2011). To evaluate the macular thickness, two scans of each eye of every subject were performed using the macular cube 512×128 protocol. This protocol is based on a 128 horizontal line raster with 512 A-scans each, within a 6×6-mm^2 area centred on the fovea. The instrument calculates the retinal thickness and summarizes the thickness results according to the nine areas corresponding to the Early Treatment Diabetic Retinopathy Study (ETDRS) (ETDRS Research Group 1985). Early Treatment Diabetic Retinopathy Study areas include a central 1-mm disc, representing the foveal area, and the inner and outer rings of 3 and 6 mm, respectively. The inner and outer rings are divided into four quadrants: superior, nasal, inferior and temporal. Central foveal thickness, the average retinal thickness and the total macular volume in the 6-mm ETDRS ring are also calculated (Garcia-Martin et al. 2011).

The first eye to be examined in each patient was chosen randomly. A specific order in which to perform the scans was followed to ensure that the alignment system was re-established for each measurement. Retinal nerve fibre layer and a macular scan were performed in the first eye and then the fellow eye, and this sequence was repeated three times. In the third step, only the optic disc cube scan was repeated, so we ultimately obtained three optic disc cube scans and two

macular cubes per eye of each child. The sequence was adjusted in uncooperative children, and just one macular scan was performed in some of the youngest children.

The same operator in each centre performed all OCT scans. The scans were only accepted if they were completed, well centred, had signal strength of at least 7 and had no motion or blinking artefacts. An independent investigator (MRC) examined all measurements acquired in the three centres to identify any outliers and excluded them just in case they were attributed to acquisition errors.

Statistical analysis

One eye of each subject was selected randomly, and the average of the three RNFL and the two macular scans was used in the statistical analyses. The other eye was included in the study in cases in which the randomized eye had a coefficient of variation (CV) exceeding 6% among the three RNFL measurements. Outlier measurements were reviewed and excluded in cases because of misalignments or artefacts. The intrasession CV was calculated by dividing each standard deviation of the repeated measurements by its mean. Analysis of variance was used to compare the mean RNFL values by age group. Normal macular thickness values were compared among the quadrants using the paired *t*-test. All p values were adjusted by the Bonferroni factor. Univariate and multivariate regression analyses were used to analyse the effects of age, gender, AL and SE on the RNFL and macular measurements. $p < 0.05$ (two-sided) was considered significant. All statistical analyses were performed using the SPSS package version 15 (SPSS Inc., Chicago, IL, USA).

Results

Demographics

Three hundred and one children were examined. In 15 cases, reliable optic nerve measurements could not be obtained owing to lack of cooperation among the youngest children. Another two children (4 years old) had important artefacts in all optic nerve measurements and had to be excluded. One 13-year-old child had outlier measurements in all RNFL measurements (not owing to artefacts), and he was excluded because he also had a mild mental disorder.

Two hundred eighty-three children (117 boys, 41.34%; 166 girls, 58.66%) were finally included in this study. The distribution of children enrolled from the three hospitals is as follows: Clínica Universidad de Navarra (Pamplona): 92 children (39 boys, 53 girls) with a mean age of 9.63 ± 3.13 years; Hospital Universitario La Paz (Madrid): 107 children (44 boys, 63 girls) with a mean age of 8.81 ± 3.1 years; and Hospital Cruces (Bilbao): 84 children (34 boys, 50 girls) with a mean age of 10.49 ± 2.96 years. The mean age of the 283 children included was 9.58 ± 3.12 years (range, 4–17). After randomization, 145 right eyes and 138 left eyes were included. The mean SE was +0.63 ± 1.65 D; (range, −4.88 to +5.25). The mean AL was 22.94 ± 1.10 mm (range, 20.10–26.27). Table 1 shows the characteristics of the children and the randomized eye for each age group.

Retinal nerve fibre layer thickness measurements

All outlier OCT measurements were reviewed, and 16 (4 RNFL and 11 macular measurements) of 12 children were excluded because misalignments or other artefacts. The mean age of these children was 8 ± 2.82 years. The remainder of the measurements of these children was used in the analysis.

The CV among the RNFL measurements of each eye was ≤3% in 82.8% of the eyes. A CV higher than 6% was found in 26 of the eyes: the mean age of these children was 6.73 ± 2.86 years and the mode was 4 years. The fellow eye was included in the analysis in these cases.

The mean signal strength of the included eyes was 8.4 ± 0.9, and there were no significant differences among the three age groups. The mean global RNFL thickness was 97.40 ± 9.0 μm (range, 77–121.7).

Table 1. Characteristics of the children and the randomized eye by age group.

			Spherical equivalent		Axial length	
Age group (years)	No. subjects	Sex (girls, %)	Mean (SD)	Range	Mean (SD)	Range
4–7	80	45 (56.3)	+1.49 (1.12)	(−2.00 to +5.25)	22.22 (0.85)	20.10–24.09
8–12	147	90 (61.2)	+0.46 (1.60)	(−4.88 to +5.13)	23.06 (1.01)	20.41–26.09
13–17	56	31 (55.4)	−0.17 (1.92)	(−4.63 to +4.50)	23.66 (1.05)	21.14–26.27

Table 2. Distribution of retinal nerve fibre layer (RNFL) using Cirrus HD-optical coherence tomography in eyes of normal children.

Age groups	Total (n = 283)				4–7 years (n = 80)				8–12 years (n = 147)				13–17 years (n = 56)			
		Percentile				Percentile				Percentile				Percentile		
RNFL	Mean	1st	5th	95th	Mean	1st	5th	95th	Mean	1st	5th	95th	Mean	1st	5th	95th
Average (μm)	97.4	78.6	82.4	113.3	99.0	79.3	83.8	115.3	97.2	78.3	81.6	113.2	95.7	77.0	82.5	113.5
Superior (μm)	124.7	89.0	98.4	152.0	126.9	90.7	96.1	154.2	125.0	83.2	99.3	152.3	120.6	90.0	94.3	153.3
Temporal (μm)	67.4	48.4	51.8	83.3	69.2	49.7	52.4	85.6	66.5	47.4	52.6	81.5	67.1	48.0	49.8	84.8
Inferior (μm)	128.0	89.3	103.5	154.7	131.2	101.0	103.7	164.9	128.2	88.6	106.0	153.9	122.8	95.7	98.5	146.5
Nasal (μm)	69.7	43.3	52.0	89.0	69.8	35.0	51.1	98.0	69.1	44.6	54.2	88.0	71.4	44.0	47.2	99.4

Table 2 shows the averages of the three scans performed to obtain the mean RNFL and the mean for each quadrant by age. There were no differences in the mean RNFL among any of the age groups (p = 0.10, ANOVA test). The mean inferior quadrant was significantly (p = 0.008, Bonferroni adjusted ANOVA test) thicker in the 4–7-year-olds compared to the 13–17-year-olds. The RNFL was thicker inferiorly than superiorly or nasally, and the temporal quadrant was the thinnest, although there was no difference between the nasal and temporal quadrants (p = 0.06, paired *t*-test).

Univariate regression analysis did not find any correlations between sex, age and RFNL thickness. The SE had a significant effect on the RNFL thickness ($p < 0.001$; $R^2 = 0.087$); the equation for the regression line (Fig. 1) was $y = (1.59 \times SE) + 96.56$ [95% confidence interval (CI) for the coefficient, 0.98–2.20]. The AL also had a significant effect on the RNFL thickness ($p < 0.001$; $R^2 = 0.082$); the equation for the regression line (Fig. 2) was $y = (-2.33 \times AL) + 151.1$ (95% CI for the coefficient, −3.26 to −1.40).

A significant association between the RNFL and the spherical equivalent was found after adjusting for age, sex and AL. The regression coefficient (*b*) was 1.05 (CI 95% 0.22–1.89, p = 0.014). The AL showed a tendency towards significance (p = 0.06). The multivariate analysis did not show correlations between sex and age with the RNFL.

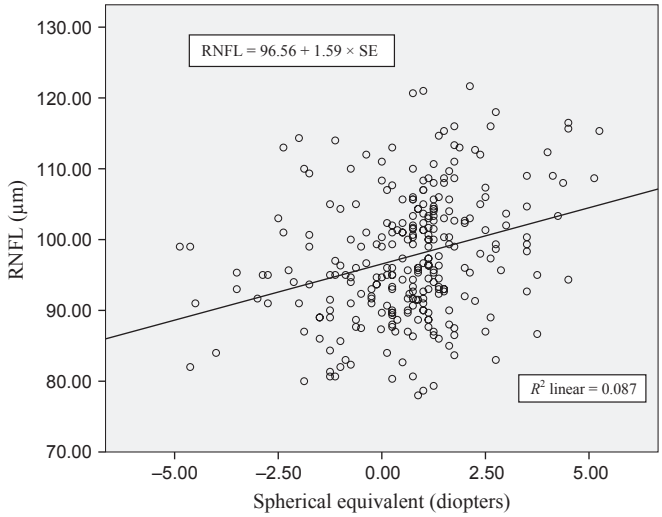

Fig. 1. The mean global retinal nerve fibre layer (RNFL) thickness in normal children as a function of spherical equivalent (dioptres). SE = spherical equivalent; R^2 linear = R^2 (linear regression).

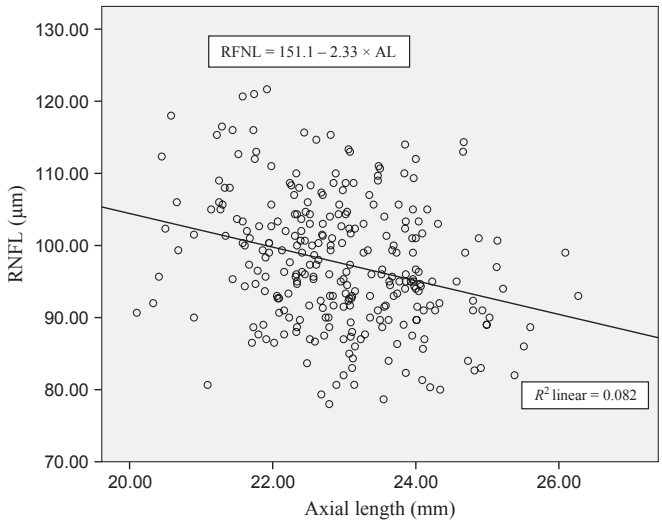

Fig. 2. The mean global retinal nerve fibre layer (RNFL) thickness in normal children as a function of axial length (mm). AL = axial length; R^2 linear = R^2 (linear regression).

Macular thickness measurements

Table 3 shows the normal macular thickness values (the mean of two measurements), assessed using the OCT macular cube 512 × 128 protocol, by age groups. The mean retinal thickness of the nine ETDRS subfields, the macular volume and the average retinal thickness also are given. The mean thickness was 253.85 ± 19.76 µm for the central macula, 283.62 ± 14.08 µm for the average thickness and 10.22 ± 0.49 μm^3 for the macular volume. The central macula was the thinnest of the nine areas. The inner macular circle was thicker than the outer area (average values, 318.24 ± 16.27 and 285.06 ± 14.82 µm, respectively) ($p < 0.001$, paired *t*-test). The temporal areas were significantly thinner than the nasal areas in both circles ($p < 0.001$, paired *t*-test). In the inner circle, no significant differences were found between the superior and the inferior areas. In the outer circle, all the areas differed significantly ($p < 0.001$, paired *t*-test).

Univariate regression analysis showed that boys had significantly ($p < 0.001$) thicker central macula than girls. Age ($p < 0.001$; $R^2 = 0.075$), SE (p = 0.011; $R^2 = 0.023$) and AL ($p < 0.001$; $R^2 = 0.073$) had significant effects on the central macular thickness.

A multivariate-adjusted model revealed a significant association between sex and the central macular thickness. Boys had a significantly thicker central macula than girls ($b = -10.394$, CI 95% −14.829 to −5.959, $p < 0.001$). The model also showed a positive association between age and central macular thickness ($b = 1.708$, CI 95% 1.007–2.409, $p < 0.001$). However, no association was observed for SE and AL with the central macular thickness.

Multivariate analyses also revealed that both the average macular thickness and macular volume were positively associated with age ($p < 0.001$),

Table 3. Distribution of macular values using Cirrus HD-optical coherence tomography in eyes of normal children.

	Total (n = 281)				4–7 years (n = 80)				8–12 years (n = 146)				13–17 years (n = 55)			
		Percentile				Percentile				Percentile				Percentile		
Age groups	Mean	1st	5th	95th	Mean	1st	5th	95th	Mean	1st	5th	95th	Mean	1st	5th	95th
Central macular thickness	253.8	206.0	220.1	287.4	246.3	202.0	209.3	273.0	255.5	209.4	224.5	291.7	260.5	226.5	229.0	286.7
Average macular thickness	283.6	235.3	260.1	308.0	281.5	229.0	253.0	304.0	284.1	243.2	260.0	309.7	285.4	263.0	264.9	310.0
Macular volume (μm^3)	10.2	9.1	9.4	11.1	10.2	8.3	9.2	10.9	10.2	9.2	9.4	11.1	10.3	9.5	9.6	11.2
Inferior outer macula	278.2	243.0	252.5	308.0	281.0	228.0	252.6	313.6	278.1	246.2	252.2	307.3	274.6	246.0	250.4	321.2
Nasal outer macula	302.5	256.6	275.0	331.0	302.0	242.0	269.2	327.9	302.0	226.9	272.9	335.4	304.8	273.0	277.2	335.4
Superior outer macula	291.7	238.6	263.0	323.0	295.7	209.0	262.1	334.0	290.3	215.0	260.1	321.6	289.2	263.5	265.4	318.1
Temporal outer macula	268.0	233.9	243.0	294.1	269.3	231.0	243.0	305.8	267.7	234.6	243.5	291.9	266.6	234.0	241.5	298.2
Inferior inner macula	319.3	263.9	290.1	347.0	313.9	262.5	279.2	342.0	321.1	277.2	295.0	349.3	322.7	290.5	294.9	353.2
Nasal inner macula	324.8	280.7	298.1	354.0	320.0	277.0	287.1	347.9	325.9	285.0	302.2	354.7	329.0	261.5	301.3	362.8
Superior inner macula	317.6	257.9	279.1	351.8	311.6	259.0	273.6	344.0	319.0	259.1	284.0	354.2	322.8	251.5	283.8	356.6
Temporal inner macula	311.0	274.3	284.6	338.0	307.9	267.0	278.1	337.0	311.9	279.9	287.5	339.5	313.3	279.0	282.2	346.2

The thickness measurements are expressed in μm.

but neither of them were associated with sex. Positive associations were found between the average macular thickness and SE ($p = 0.016$) and macular volume and SE ($p = 0.011$). The AL showed a trend towards significance with the average macular thickness ($p = 0.06$) and macular volume ($p = 0.07$).

Discussion

Optical coherence tomography is a diagnostic tool that is useful in children because it is safe, easy and fast to perform. Examination of the posterior pole by funduscopy or biomicroscopy is still the primary diagnostic method; however, it may be difficult to observe details in children who cannot maintain fixation for a long time. Optical coherence tomography provides images and measurements of the macula and the optic nerve without using an intense light source. Optical coherence tomography is especially useful for assessing children with macula diseases, allowing early diagnosis and follow-up in pars planitis, retinal dystrophies, postsurgical changes and intraocular tumours (Shields et al. 2004). Besides, OCT is used in optic neuropathies in childhood to detect early papilledema in CNS tumours, or initial atrophy in optic nerve gliomas, to follow up children with pseudotumor cerebri (Sánchez-Tocino et al. 2006), as well as to asses genetic diseases such as dominant optic atrophy or Wolfram syndrome.

Several studies have compared measurements obtained using Stratus TD-OCT and Cirrus SD-OCT in adults (Bengtsson et al. 2012). The SD-OCT instrument typically provides a higher central subfield macular thickness because the instrument uses a different posterior reference line within the hyper-reflective band of the outer retina (Abedi et al. 2011; Krebs et al. 2011). In contrast, Cirrus obtains thinner RNFL measurements in eyes of healthy subjects and those with optic nerve atrophy (Seibold et al. 2010; Hong et al. 2011; Lee et al. 2011; Rebolleda et al. 2011). Therefore, although the Cirrus OCT and Stratus OCT RNFL thickness measurements are well correlated, the RNFL measurements are not interchangeable (Seibold et al. 2010; Hong et al. 2011; Rebolleda et al. 2011). Direct comparisons of RNFL thickness measurements among OCT instruments may be misleading, because there are substantial differences among devices (Lee et al. 2011; Larsson et al. 2011).

The current study reported normative values for Cirrus OCT measurements of the peripapillary RNFL thickness, macular thickness and macular volume in 283 Caucasian children. We also determined the effects of age, sex, refraction and AL in these measurements. We conducted a multicenter study to provide a wider range of measurements and to make the conclusions of the current study applicable to different populations.

Only two multicenter studies have been conducted in healthy adults to determine a normative database of OCT measurements with SD-OCT technology: the Cirrus OCT normative database study group (Mwanza et al. 2011a) and another among adults in Japan (Hirasawa et al. 2010).

However, several studies have reported OCT measurements in normal children using TD-OCT (Ahn et al. 2005; Hess et al. 2005; El-Dairi et al. 2009; Eriksson et al. 2009; Gire et al. 2010; Leung et al. 2010; Qian et al. 2010; Larsson et al. 2011). All these studies had been carried out in one institution. Population-based studies by Huynh et al. (2006a,b, 2008) were performed in many different schools although using the same OCT device.

A study to determine the normative values of the RNFL and macular data in healthy Turkish children using SD-OCT was published recently (Turk et al. 2011). Several characteristics in the design differed from the current study, the primary difference being that they used the Spectralis OCT device (Heidelberg Engineering) for the OCT assessment. The study included 107 children between 6 and 16 years of age, excluding the youngest and oldest ages of the current series, which ranged from 4 to 17 years. Besides, all children were recruited from the same centre. Another recent study, focused exclusively on the optic nerve measurements, has been performed in Spain using SD technology. Several differences in the design and methodology from the current study can be remarked, such as the range of age, the exclusion criteria and the limited number of variables collected to be included in the analysis (Elía et al. 2012).

SD technology offers faster scanning than TD-based tomography, so more information is obtained in the same amount of time. Besides, the methods of RNFL measurement may differ between TD-OCT and SD-OCT. For example, in Stratus OCT, the examiner manually centres the measurement ring around the optic disc; in Cirrus OCT, the examiner obtains a cube of scans and the Cirrus device automatically places the measurement ring around the optic disc. This advantage of Cirrus OCT may explain why small ocular movements in Cirrus OCT have less effect than in Stratus OCT (Moreno-Montañés et al. 2011). Moreover, there is a significant variability between RNFL measurements performed with two different Stratus OCT instruments, while the interinstrument variability of measurements obtained with Cirrus OCT is non-significant (Mwanza et al. 2011b), an important issue when dealing with multicentric studies. Theoretically, the faster the device works, the easier it is for the children to cooperate and the more reliable the measurements will be. More than 80% of the RNFL measurements obtained in the current study had a CV ≤3%. Movement artefacts and uncentred scans are frequent in adults and even more so in children. In the current study, we reviewed each outlier for movement artefacts; they occurred more frequent in younger children: 17 children had to be excluded because were unable to cooperate or had important artefacts; 16 measurements (of another 12 children with a mean age of 8 years) had to be excluded owing to artefacts; 26 of the eyes (of 26 children with a mean age of 6.73 years) had a CV higher than 6% in the RNFL measurements, and therefore, the fellow eye had to be included in the analysis. Strict criteria were applied to achieve reliable measurements. The RNFL measurements were more difficult to acquire than the macular measurements, because they needed more patient cooperation.

Peripapillary retinal nerve thickness

In the current study, the mean RNFL thickness in the study population was 97.40 ± 9.0 μm. Compared with adults, the average RNFL thickness in the current population was comparable to but slightly higher than that reported in the Cirrus normative database, which included 284 adults 18–84 years of age with an average RNFL thickness of 93.09 ± 9.33 μm in the right eye and 92.57 ± 9.86 μm in the left eye (Mwanza et al. 2011a).

Several studies have been published in which Stratus OCT was used in normal children. Comparisons among these studies are difficult not only because different tomography devices and methodologies have been used but also because of differences in the population epidemiology. Almost all studies using Stratus OCT in children reported a thicker RNFL than the current study independent of race: 107 ± 11.1 μm (Salchow et al. 2006), 105.53 ± 10.53 μm (Ahn et al. 2005), 103.7 ± 11.4 μm (Huynh et al. 2006b), 103.6 ± 10.6 μm (Huynh et al. 2008), 108.27 ± 9.8 μm (El-Dairi et al. 2009), 104.33 ± 10.22 μm (Gire et al. 2010), 113.5 ± 9.8 μm (Leung et al. 2010), and 112.36 ± 9.21 μm (Qian et al. 2010). Only Larsson et al. (2011), in a study of Caucasian children aged 5–16 years, reported an average RNFL thickness of 98.4 ± 7.88 μm, similar to that in the current study. The Turkish study performed using SD-OCT technology (Spectralis) obtained a mean RNFL thickness of 106.45 ± 9.47 μm, which was consistent with the previous findings (Turk et al. 2011). However, they did not agree with the published reports in which the Stratus and Cirrus devices were compared (Knight et al. 2009; Leite et al. 2011). Seibold et al. (2010) compared several SD-OCT machines with TD-OCT in normal adults and concluded that each SD-OCT had a unique and independent relationship with Stratus. Measurements on Spectralis and Cirrus were thinner than Stratus but to markedly different degrees: 3.4 and 11.3 μm, respectively. This difference agrees with the current findings compared to the other paediatric studies carried out with Stratus OCT. Elía et al. (2012), using Cirrus OCT technology in children, obtained an average RNFL thickness of 98.46 ± 10.79 μm which is similar to our results.

In accordance with previously published studies of adults and children (Salchow et al. 2006; Larsson et al. 2011), the inferior quadrant was the thickest followed by the superior quadrant. The temporal quadrant was the thinnest, but there was no significant difference between the nasal and the temporal quadrants.

A high variation in global RNFL thickness among normal children has already been reported in other studies with Stratus OCT (Huynh et al. 2006b, 2008; Salchow et al. 2006; Larsson et al. 2011). We found a range of 77–121.7 μm, with 95% of the values between 80.7 and 115.7 μm (95% central range).

The RNFL thickness has been considered dependent on factors such as race, age, AL and, in some cases, refraction. Several authors have reported that the RNFL thickness decreases with age in adults in contrast to most paediatric studies, including the current study, and have not found any correlation between age and RNFL thickness (Ahn et al. 2005; Huynh et al. 2006b, 2008; Salchow et al. 2006; El-Dairi et al. 2009; Larsson et al. 2011; Turk et al. 2011). The progressive decrease in the RNFL thickness seems to not reach significance until the fifth decade of age (Parikh et al. 2007; El-Dairi et al. 2009).

In the current study, only refraction entered the final multivariate model, implying an independent effect of this factor on the RNFL thickness regardless of the age or sex of the child. The RNFL thickness increased an average 1.05 μm per D. Other authors have reported similar findings in children: a thicker RNFL in hyperopic children and a thinner RNFL in myopic children (Huynh et al. 2006b; Salchow et al. 2006). Although other authors have reported a significant association between AL and RNFL in children (Huynh et al. 2006b; El-Dairi et al. 2009; Tariq et al. 2010), in the current study, multivariate analysis showed that the AL had only a borderline statistical association ($p = 0.06$) with the RNFL. It is possible that these results might have been different if the current study included more children.

Macular thickness

The inner fixation localizes the fovea in the centre of macular map, and therefore, the central macula thickness (referred to as the central subfield thickness by the Cirrus OCT software)

is the thinnest of the nine areas. We obtained a mean central macular thickness of 253.85 ± 19.76 μm, which seems to be slightly thinner than the results observed in adults using the same OCT device (range, 257.6–277 μm) (Wolf-Schnurrbusch et al. 2009; Sull et al. 2010; Garcia-Martin et al. 2011; Hagen et al. 2011; Liu et al. 2011). However, our result was just slightly lower than the value obtained in the Turkish study using a different SD-OCT device (mean, 258.6 ± 17.2 μm) (Turk et al. 2011). The current outcome can be explained by multivariate analysis, which identified a positive correlation between the central macular thickness and age. Huynh et al. (2008) found that the year-1 students (age range, 11.1–14.4 years) had slightly thinner central, inner and outer macular regions than did the year-7 students. The minimal foveal thickness in the year-1 students was significantly thinner than in the year-7 students. El-Dairi et al. (2009) also reported an approximate 1.7-μm increase for every 1-year increase in age, although only in black children, which was exactly what we obtained in Caucasian children. Huynh et al. (2008) suggested that the minimal foveal thickness remains unchanged, although the macular thickness increases until early adulthood.

The values that we obtained for the mean average thickness (283.62 ± 14.08 μm) and the mean macular volume (10.22 ± 0.49 μm^3) were similar to those obtained in studies of adults using the Cirrus OCT (Garcia-Martin et al. 2011; Hagen et al. 2011; Liu et al. 2011). Contrary to our paediatric series, in adults, both the mean average thickness and the mean macular volume declined with age (Liu et al. 2011). Sex also might affect the central macular thickness. In the current study, in accordance with the Turkish series (Turk et al. 2011), boys had a significantly thicker central macula than girls by 10.39 μm. Huynh et al. (2008) reported similar results in children and Liu et al. (2011) in adults. Furthermore, in adults, the central subfield thickness was thicker in men compared to women as were the mean average macular thickness and the macular volume.

In the current study, multivariate analyses did not find correlations between the SE and AL and the central macular thickness.

Around the thinnest central macula subfield, the inner macular circle was significantly thicker than the outer area as other studies reported in children (El-Dairi et al. 2009; Eriksson et al. 2009) and adults (Garcia-Martin et al. 2011). The temporal areas were significantly thinner than the nasal areas in both circles. The nasal area of the outer circle was the thickest because of the convergence of the retinal nerve fibres in the optic disc (Huynh et al. 2008; El-Dairi et al. 2009; Eriksson et al. 2009; Garcia-Martin et al. 2011).

A small number of subjects and the exclusion of eyes with high refractive error might have limited our ability to identify additional relationships between the RNFL thickness and the macular thickness and AL. Although we followed the same strict protocol in the three centres and used the same devices and software, differences related to the different observers may have affected the results. However, we used several methods to reassess the quality of the data, an important issue when working with children. The same experienced investigator acquired all the measurements in each centre. We excluded OCT images with a signal strength lower than 7 or images with artefacts. Moreover, the same investigator analysed all the measurements acquired in the three centres to find any outliers, identify the cause of that measurement and exclude them in cases of misalignments or decentred OCT images. When different measurements of the same eye had a high CV, the other eye was included in the analysis. To the best of our knowledge, this is the first multicenter study to provide normative database of the RNFL and macular thicknesses and macular volumes using Cirrus OCT from the eyes of healthy Caucasian children. This information should facilitate the assessment of optic neuropathies and macular conditions in children.

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Correspondence:
Jesús Barrio-Barrio, PhD
Clínica Universidad de Navarra
University of Navarra
Avenida Pío XII, 36
31008 Pamplona
Spain
Tel: +34 948 255 400
Fax: +34 948 296 500
Email: jbarrio@unav.es