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Longitudinal reproducibility of optical coherence tomography measurements in children

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Abstract

Purpose—To evaluate the longitudinal reproducibility of optical coherence tomography (OCT) measurements in normal and glaucomatous eyes of children.

Methods—In this two-setting prospective study, OCT-3 was used to obtain fast retinal nerve fiber layer (RNFL) and of macular thickness scans. In the first study setting, the normal eyes of healthy children were scanned on presentation, at 2 weeks, and 3 years, with axial length measured at the first and last examinations. In the second setting, OCT scans of patients in the pediatric glaucoma clinic were performed over 4 years as clinically indicated. Eyes were classified as “normal,” (normal eyes and those with physiologic cupping but normal intraocular pressure (IOP)); “mild glaucoma” (elevated IOP and a normal optic nerve appearance); or “advanced glaucoma,”(severe cupping or progressive glaucoma). Intraclass correlation coefficients (ICC) were used to evaluate the reproducibility of measurements on the same day and over time.

Results—In the first setting, 8 normal eyes were included. Axial length increased 0.11 ± 0.04 mm/year over an average of 3.3 years ($P = 0.03$); there was no statistically significant change in RNFL thickness ($P = 0.30$). In our second setting, 27 normal eyes and 37 eyes with glaucoma were included. ICCs across the three visits for total macular volume were 0.80–0.91 and for average RNFL were 0.73–0.95.

Conclusions—Global OCT measurements in children were reproducible over years and were not affected by normal increase in axial length. OCT shows promise as an objective tool for longitudinal assessment of children.

Monitoring children with known or suspected glaucoma often poses a challenge to the clinician due to the difficulty of obtaining reliable visual fields and other objective measures of disease progression or stability. Optical coherence tomography (OCT) is a fast, noninvasive imaging technology that can measure the retinal nerve fiber layer (RNFL)

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thickness and macular thickness. In adults, OCT has been shown to be reproducible[1,2] and has been used to detect early RNFL loss in patients with glaucoma[3,4]; however, few studies describe the use of OCT in children with glaucoma.

OCT measurements of RNFL and macular thickness differ in normal and glaucomatous eyes of children.[5] OCT measurements of both RNFL and macular thickness have also been shown to correlate negatively with increasing grade of glaucomatous damage seen on optic nerve head stereophotographs.[6] In order for OCT to be useful in monitoring children with glaucoma for disease progression, it must be reproducible over time despite normal axial length growth. Previous studies have shown that in healthy eyes of children, OCT measurements of macular and RNFL thickness are reproducible within the same day[7]; however, average RNFL has also been correlated with axial length.[8] To our knowledge, the reproducibility profile of OCT over years in children has not been previously studied. The purpose of this study was to prospectively evaluate the longitudinal reproducibility of OCT measurements in children in two settings: (1) in normal eyes of healthy children over 3 years (given that axial length may increase with normal eye growth); and (2) in children with known or suspected glaucoma who presented to a pediatric glaucoma clinic.

Methods and Materials

This study was approved by the Duke Health System Institutional Review Board and complied with the requirements of the Health Insurance Portability and Accountability Act. Written informed consent was obtained for each subject from the legal guardian. Verbal assent was obtained from all subjects. Additional written assent was obtained from each child who was at least 12 years of age.

The Stratus OCT (Carl Zeiss, Dublin, CA) was used to obtain fast-mode macular and fast RNFL 3.4 thickness protocols.[8] All scans used an internal fixation target and a default eye length of 24.46 mm. Only children <18 years of age at initial OCT scan were enrolled. Axial length was measured via a noncontact partial coherence interferometer (IOLMaster; Carl Zeiss, Dublin, CA). Unreliable axial length scans were deleted and repeated until a total of three reliable scans were obtained; the average of these values was recorded.

This study was designed in two settings. In the first, healthy children underwent a complete eye examination by a fellowship-trained pediatric ophthalmologist (MAE), and axial length was measured. OCT scanning was performed three times on each eye after dilation. OCT scanning was performed again three times by the same operator (MAE), on the same machine, 1–4 weeks later. Three years later the children were again examined, with axial length and OCT measurements performed in a similar fashion to the first visit.

In the second setting, subjects were selected from the pediatric glaucoma clinic at the Duke Eye Center; OCT measurements were obtained as part of standard clinical care. Each eye was classified into one of three groups: the “normal” group included normal eyes with cup/disk ratios <0.5 (including those in the first study setting) and those with physiologic cupping (cup/disk ratio ≤0.6, cup/disk asymmetry <0.2) and repeatedly documented normal intraocular pressure (IOP). The “mild glaucoma” group included eyes with documented elevated IOP (>21 mm Hg) and a normal optic nerve appearance (cup/disk ratio <0.5 and cup/disk asymmetry <0.2) on clinical examination as well as eyes of children with known mild glaucoma. The “advanced glaucoma” group included eyes with severe (advanced cupping and visual field changes) or progressive glaucoma (ie, IOP above target, worsening reliable visual field, worsening optic nerve appearance, or need for surgical intervention).

OCT of each eye was obtained once after pupillary dilation. Follow-up OCT scans were not necessarily performed by the same operator or on the same machine. OCT scans were

reviewed for quality, and scans with signal strength <6 or those with plotting errors were excluded. Subjects who had fewer than three visits with reliable OCT scans were excluded. Before data analysis, a single glaucoma-trained pediatric ophthalmologist (SFF) reviewed clinical data on each child and classified each eye into one of the three groups. If the two eyes belonged in different clinical groups (n = 10), then both eyes were included, each analyzed in its respective group. If both eyes belonged to the same clinical group, the right eyes were included, unless there were fewer than three reliable scans available for the right eye and at least three reliable scans available for the left eye with signal strength of ≥6, in which case the left eye was the study eye. Exclusion from either the fast macular thickness or fast RNFL (3.4) thickness portion of the analysis did not preclude the eye's being included in the other portion of the analysis.

SAS 9.3 (SAS Institute Inc, Cary, NC) was used for all statistical analysis. All values are reported as mean plus or minus standard deviation unless otherwise indicated. OCT measurements from the normal, mild glaucoma, and advanced glaucoma groups were compared using unpaired *t* tests. Reproducibility was evaluated using coefficient of variation (CoV) and intraclass correlation coefficients (ICC). A mixed linear regression model with random effects for within-visit error ("machine" error), inter-visit (within-subject) error, and between-subject error was used to investigate linear association between outcomes and age, as appropriate. Outcomes included axial length, average retinal thicknesses, total macular volume and average RNFL thickness. ICC was calculated as the ratio of the sum of model-estimated inter-visit variance and inter-subject variance to the total variance (within-visit ICC), or the ratio of the model-estimated inter-subject variance to the total variance (inter-visit ICC), as appropriate.

ICC ≥ 0.8 was considered very good correlation; 0.6 ≤ ICC < 0.8, good correlation; 0.4 ≤ ICC < 0.6, fair correlation; and ≤0.4, poor correlation. For each subject-visit combination (or subject), CoV was calculated as the ratio of standard error of observations within subject-visit (or subject across visits) to the mean of observations within subject-visit (or subject) for those with multiple (or a single) measurement(s) taken at each study visit. CoV was multiplied by 100 to be presented as a percentage.

Results

The first study setting included 8 normal eyes of 8 children. The average age at initial examination was 9.1 ± 2.3 years. The average time between the first and second visits was 0.2 years; between the first and third visits, 3.3 years. The ICC for total macular volume and average RNFL within visits showed very good reproducibility (0.91–0.98, Tables 1 and 2).

At the initial visit, the average axial length was 23.5 mm (range, 22.3–24.1), the average total macular volume was 7.0 mm^3 (95% CI, 6.2–7.8; Table 1), and the average RNFL thickness was 108 μm (95% CI, 90–126; Table 2). Among normal eyes, over an average of 3.3 years (range, 3.1–3.6), the axial length increased by 0.11 mm/year (SE = 0.04, $P = 0.03$), and there was no significant change in the average RNFL thickness with time ($P = 0.30$). The CoV for average macular volume and RNFL thickness are reported in Table 3.

The second study setting included 64 eyes of 54 children: normal group, 27 eyes of 27 children; mild glaucoma group, 23 eyes of 23 children; advanced glaucoma group, 14 eyes of 14 children. The average age at initial examination for the normal group was 9.4 ± 2.5 years; mild glaucoma group, 9.3 ± 3.4 years; and advanced glaucoma group, 11.0 ± 3.7 years. The average time between the first and third visits was 3.4 years for the normal group, 3.8 for the mild glaucoma group, and 4.2 for the advanced glaucoma group.

At initial examination, the average MV was sequentially lower for the normal (7.1 ± 0.3 mm^3), mild glaucoma (7.0 ± 0.6 mm^3), and advanced glaucoma groups (6.4 ± 0.7 mm^3). Similarly, the average RNFL thickness was sequentially thinner for the normal (110 ± 11 μm), mild glaucoma (108 ± 12 μm), and advanced glaucoma groups (73 ± 31 μm), with $P < 0.05$ for the advanced glaucoma group versus both the normal and mild glaucoma groups. The ICC for total macular volume and average RNFL across the three visits for the normal, mild glaucoma and advanced glaucoma groups showed good to very good reproducibility (0.73–0.95, Tables 4 and 5). The CoV for average macular volume and RNFL thickness for all groups are reported in Table 6.

Of the 12 eyes with advanced glaucoma included in this study, 11 did not show progression of disease during the study period by visual field or optic nerve appearance (e-Supplement 1, available at jaapos.org). One subject (case 12) with uncontrolled IOP and no notable optic nerve damage underwent trabeculectomy with mitomycin C during the study period. Only one subject (case 10, bilateral congenital glaucoma) showed disease progression by optic nerve appearance and underwent trabeculectomy with mitomycin C after the study period. After surgery, this eye had reversal of cupping and optic nerve pallor as well as overall decrease in OCT measurements (average RNFL dropped from 97.8 μm to 48.4 μm; macular volume, from 6.81 mm^3 to 6.19 mm^3), while the OCT measurements of the contralateral eye remained stable (within 5 μm for average RNFL and 0.2 mm^3 for macular volume). Of note, a child with Sturge-Weber–associated glaucoma (patient 9), developed a serous retinal detachment from a choroidal hemangioma during the study period and was treated with photodynamic therapy. We excluded OCTs during the time period that the serous detachment was visible on the OCT scans.

Discussion

Among children with normal eyes as well as those with suspected or known glaucoma global Stratus OCT measurements of total macular volume and average RNFL thickness were reproducible over several years. Among normal eyes, over an average of 3 years, there was a statistically significant increase in average axial length measurements; however, the change in average RNFL thickness as average axial length increased was not statistically significant. While previous cross-sectional studies have found a negative correlation between average RNFL and axial length[9] in white,[8,10] East Asian,[10] and Hong Kong Chinese children,[11] our longitudinal study found that this correlation did not significantly affect the reproducibility of OCT measurements. A previous cross-sectional OCT study in normal children showed that the average RNFL decreased by an average of 2.2 μm for each 1 mm increase in axial length.[8] In the present study, the normal eyes of children measured over a 3.3-year interval showed a mean axial length increase of 0.46 mm. This axial length increment would theoretically engender only a 1.01 μm decrease in average RNFL, a decline not detectable given the present study's variance of 9.3 μm for average RNFL. In order to power a study to detect a 1.01 μm change in average RNFL as statistically significant ($\alpha = 0.05$), 585 normal subjects would have to be scanned with OCT at least twice at an interval of 3 years. The change however, would not be clinically significant. As a matter of fact, although an emmetropic human eye is expected to grow by less than 3 mm from the ages of 3 to 21 years,[12] larger axial length changes may occur in myopic or pseudophakic children's eyes.[13–15] In any event, axial length growth would still likely be <1.0 mm over the course of 3 to 4 years; the average RNFL decline of 2.2 μm attributable an axial length growth of 1.0 mm would still fall within the variance of 9.3 μm^2 for this variable in the present study and other adult published studies.[4]

In a clinical setting, children who have mild glaucoma or advanced (largely stable) glaucoma showed high reproducibility for OCT measurements of total macular volume and

average RNFL thickness over three measurements spanning an average of 4.3 years. Just as one study in an adult population found that longitudinal variability in OCT measures did not change with the severity of glaucoma,[16] we found that in children OCT measurements were reproducible for those with a history of elevated IOP. High reproducibility in our sample of children with a history of elevated IOP may be attributable to the fact that only 1 patient (who was in the advanced glaucoma group) had progression in their disease during the study period.

Our study has several limitations, including relatively small sample size and limited longitudinal follow-up time. Because children with suspected or known glaucoma in this study had OCT scans performed only as part of standard clinical care, axial length was not measured and the scanning interval was not possible to control as well as might have been possible in subjects scanned solely for inclusion in a study. Because only a single patient with advanced glaucoma experienced disease progression during the study period, we are unable to evaluate whether total macular volume or average RNFL thickness is a more useful measure in progressive glaucoma cases. Also, because we did not note any reversal in optic nerve cupping in any of our patients during the study period, we do not know whether surgical intervention to lower the IOP can increase OCT measurements of macular volume or RNFL thickness due to cupping reversal. In addition, our sample of patients with advanced glaucoma was not homogeneous, which may have resulted in overestimated ICC values. However, the fact that those in the advanced glaucoma group also had an average CoV <10% suggests that this patient population truly had acceptable reproducibility. Our study was also limited to the relatively older technology of time domain OCT, which has a standard error of approximately 10 μm for average RNFL thickness, rendering RNFL loss in very mild glaucoma cases below the threshold of detection.[4] The more recent spectral domain OCT technology has higher resolution and its ability to track eye movements probably offers better reproducibility measures in adults.[17]

In conclusion, the findings of this study suggest that OCT could be used as an objective tool for following children with a history of elevated IOP or glaucoma. OCT measurements seem to be reproducible over time despite normal changes in axial length. Just as repeated serial visual fields are used to monitor disease progression in adult glaucoma patients,[18] it is likely that repeated serial OCT measurements will need to be performed in order to monitor disease progression in children. Further larger, longitudinal studies of OCT in children with known or suspected glaucoma, including those with clinically worsening glaucomatous optic nerve and visual field damage using newer technologies are warranted.

Literature Search

The authors searched PubMed (MEDLINE) for English-language only articles for the period 1946 to 2012, using combinations of the following search terms: pediatric glaucoma, *OCT* OR *optical coherence tomography*, *reproducible* OR *reproducibility*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Reproducibility of optical coherence tomography macular measurements (fast macular thickness map scan) among children with normal eyes (N = 8)

Parameter	Visit 1[a]	Within-visit variance ("machine" error)	ICC[b]
	Mean (SD)		
Average retinal thickness, μm			
Outer superior macula	245 (12)	5.2 μm^2	0.96
Inner superior macula	278 (10)	6.4 μm^2	0.94
Outer nasal macula	261 (16)	9.5 μm^2	0.96
Inner nasal macula	271 (22)	12.2 μm^2	0.94
Outer inferior macula	238 (13)	12.9 μm^2	0.95
Inner inferior macula	275 (10)	12.0 μm^2	0.91
Outer temporal macula	224 (19)	12.5 μm^2	0.95
Inner temporal macula	260 (16)	5.4 μm^2	0.96
Fovea	167 (14)	77.4 μm^2	0.63
Total macular volume (mm^3)	**7.0 (0.4)**	**0.003 $(mm^3)^2$**	**0.98**

ICC, intraclass correlation coefficient; *SD*, standard deviation.

[a] Average age (SD) in years at visit 1, 9.1 (2.3).

[b] ICC within-visit calculated over multiple visits.

Table 2

Reproducibility of optical coherence tomography measurement of RNFL thickness (Fast RNFL 3.4 scan) among children with normal eyes (N = 8)

Parameter	Visit 1[a] Mean (SD)	Within-visit variance ("machine" error), μm^2	ICC[†]
RNFL thickness (μm)			
Superior quadrant	142 (16)	73.7	0.76
Temporal quadrant	80 (17)	79.3	0.85
Inferior quadrant	125 (14)	56.8	0.77
Nasal quadrant	84 (7)	82.9	0.26
Average	**108 (9)**	**9.3**	**0.91**

SD, standard deviation; *ICC*, intraclass correlation coefficient.

[a] Average age in years at was 9.1 ± 2.3.

[b] Within-visit ICC calculated over multiple visits.

Table 3

CoV of average total MV and average RNFL thickness measurements by OCT among children with normal eyes (N = 8)

Visit (time in years from Visit 1)	Mean age (SD), years	CoV ± SD (MV),[a] %	CoV ± SD (RNFL),[b] %
Visit 1 (0)	9.1 (2.3)	0.5 ± 0.3	1.4 ± 1.1
Visit 2 (0.2)	9.3 (2.3)	0.8 ± 0.4	3.3 ± 2.3
Visit 3 (3.3)	12.4 (2.4)	0.5 ± 0.3	2.8 ± 2.1
Among the 3 visits		0.6 ± 0.3	2.3 ± 1.6

CoV, average coefficient of variation; *OCT*, optical coherence tomography; *MV*, macular volume; *RNFL*, retinal nerve fiber layer; *SD*, standard deviation.

[a] Average MV (SD) at Visit 1, 7.0 (0.4) mm^3.

[b] Average RNFL thickness (SD) at Visit 1, 107.8 (8.5) μm.

Table 4

Reproducibility of OCT macular measurements (Fast Macular Thickness Map scan) among Children

Group Parameters	Normal[a] (n = 27)		Mild glaucoma[b] (n = 22)		Advanced glaucoma[c] (n =12)	
	Visit 1	Visit 1–3 T = 3.4 yrs	Visit 1	Visits 1–3 T = 3.9 yrs	Visit 1	Visits 1–3 T = 4.2 yrs
	Mean	ICC^	Mean	ICC^	Mean	ICC^
Age at Visit 1, years (SD)	9.4 (2.5)		9.3 (3.5)		11.0 (3.7)	
RE at Visit 1, SE (range)	0.0185 (−3.13 to +3.13)		−0.903 (−6.00 to +3.50)		−1.36 (−5.00 to +1.38)	
Average retinal thickness, μm (SD)						
Outer superior macula	248 (12)	0.75	245 (26)	0.88	226 (26)	0.66
Inner superior macula	277 (15)	0.72	275 (26)	0.89	259 (30)	0.71
Outer nasal macula	263 (15)	0.85	259 (25)	0.87	237 (34)	0.67
Inner nasal macula	274 (19)	0.67	275 (27)	0.82	256 (29)	0.61
Outer inferior macula	239 (13)	0.83	234 (22)	0.88	216 (35)	0.78
Inner inferior macula	275 (15)	0.79	272 (25)	0.83	245 (26)	0.82
Outer temporal macula	227 (15)	0.68	225 (24)	0.83	207 (24)	0.49
Inner temporal macula	263 (15)	0.74	260 (25)	0.86	244 (24)	0.65
Fovea	160 (16)	0.58	170 (29)	0.48	181 (28)	0.52
Total macular volume, mm^3 (SD)	**7.1 (0.3)**	**0.83**	**7.0 (0.6)**	**0.91**	**6.4 (0.7)**	**0.80**

OCT, optical coherence tomography; *ICC^*, intraclass correlation coefficient (over multiple visits); *RE,* refractive error; *SD*, standard deviation; *t*, average time after Visit 1.

[a]Including normal eyes with cup/disk ratios <0.5 (including those in part one of the study) and those with physiologic cupping (cup/disk ratio ≤0.6 and cup/disk asymmetry <0.2) and repeatedly documented normal intraocular pressure (IOP).

[b]Including eyes with documented elevated IOP (>21 mm Hg) and a normal optic nerve appearance (cup/disk ratio <0.5 and cup/disk asymmetry <0.2) on clinical examination as well as eyes of children with known mild glaucoma.

[c]Including eyes with severe (advanced cupping and visual field changes) or progressive glaucoma (ie, IOP above target, worsening reliable visual field, worsening optic nerve appearance, or need for surgical intervention).

Table 5

Reproducibility of OCT measurement of RNFL thickness (Fast RNFL 3.4 scan) among children

Group Parameter	Normal[a] (n = 20)		Mild glaucoma[b] (n = 16)		Advanced glaucoma[c] (n = 10)	
	Visit 1	Visit 1–3 T = 3.5 yrs	Visit 1	Visit 1–3 T = 3.6 yrs	Visit 1	Visit 1–3 T = 3.6 yrs
	Mean (SD)	ICC^	Mean (SD)	ICC^	Mean (SD)	ICC^
Age at Visit 1, years RNFL, µm	9.2 (2.2)		10.0 (4.1)		11.5 (4.3)	
Superior quadrant	141 (20)	0.66	131 (23)	0.61	85 (43)	0.78
Temporal quadrant	78 (15)	0.76	88 (22)	0.62	64 (26)	0.71
Inferior quadrant	134 (17)	0.68	131 (14)	0.76	80 (41)	0.92
Nasal quadrant	87 (15)	0.51	83 (24)	0.62	63 (27)	0.69
Average	**110 (11)**	**0.79**	**108 (12)**	**0.73**	**73 (31)**	**0.95**

OCT, optical coherence tomography; *ICC^*, intraclass correlation coefficient (over multiple visits); *RNFL*, retinal nerve fiber layer; *SD*, standard deviation; *T*, average time after Visit 1.

[a]Including normal eyes with cup/disk ratios<0.5 (including those in part one of the study) and those with physiologic cupping (cup/disk ratio≤0.6 and cup/disk asymmetry <0.2) and repeatedly documented normal intraocular pressure (IOP).

[b]Including eyes with documented elevated IOP (>21 mm Hg) and a normal optic nerve appearance (cup/disk ratio <0.5 and cup/disk asymmetry <0.2) on clinical examination, as well as eyes of children with known, mild glaucoma.

[c]Including eyes with severe (advanced cupping and visual field changes) or progressive glaucoma (ie, IOP above target, worsening reliable visual field, worsening optic nerve appearance, or need for surgical intervention).

Table 6

CoV of average total MV and average RNFL thickness measurements by OCT among children

Subject Group	Total MV at Visit 1, mm^3 (SD)	CoV ± SD over 3 visits for total MV, %	RNFL thickness at Visit 1, μm (SD)	CoV ± SD over 3 visits for RNFL thickness, %
Normal[a]	7.1 (0.3)	2.3 ± 1.7	119.7 (10.6)	3.9 ± 2.6
Mild Glaucoma[b]	7.0 (0.6)	2.7 ± 2.3	108.3 (12.2)	4.8 ± 2.7
Advanced glaucoma[c]	6.4 (0.7)	3.3 ± 2.7	73.1 (30.7)	9.4 ± 5.6

CoV, average coefficient of variation; *MV*, macular volume; OCT, optical coherence tomography; *RNFL*, retinal nerve fiber layer; *SD*, standard deviation.

[a]Including normal eyes with cup/disk ratios <0.5 (including those in part one of the study) and those with physiologic cupping (cup/disk ratio ≤0.6 and cup/disk asymmetry <0.2) and repeatedly documented normal intraocular pressure (IOP).

[b]Including eyes with documented elevated IOP (>21 mm Hg) and a normal optic nerve appearance (cup/disk ratio <0.5 and cup/disk asymmetry <0.2) on clinical examination as well as eyes of children with known mild glaucoma.

[c]Including eyes with severe (advanced cupping and visual field changes) or progressive glaucoma (ie, IOP above target, worsening reliable visual field, worsening optic nerve appearance, or need for surgical intervention).