

Reliability of Handheld Optical Coherence Tomography in Children Younger Than Three Years of Age Undergoing Vigabatrin Treatment for Childhood Epilepsy

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Purpose: Vigabatrin-associated retinal toxicity manifests as reduction in the clinical electroretinogram and retinal nerve fiber layer (RNFL) thinning. This observational investigation of RNFL thickness in young vigabatrin-treated children was to identify intravisit and intervisit reliabilities of peripapillary RNFL thickness measurements performed with Envisu (optical coherence tomography) OCT. Secondly, a longitudinal assessment investigated the presence and extent of RNFL thinning.

Methods: We measured the handheld OCT in sedated children to evaluate the RNFL thickness using segmentation software. Intraclass correlation coefficient (ICC) statistics identified intravisit and intervisit reliabilities for RNFL thickness.

Results: Twenty-nine children (10.1 ± 6.0 months old) underwent handheld optical coherence tomography (OCT). Fourteen of these completed follow-up assessments. Intravisit reliability was good for the right eye (ICCs = 0.82–0.98) and the left eye (ICCs = 0.75–0.89) for each of the 4 retinal quadrants. Inter-visit ICCs for each of the 4 retinal quadrants were good (ICC = 0.82–0.98). There was no consistent change in RNFL thickness longitudinally.

Conclusions: In this pediatric cohort, RNFL thickness measures using handheld OCT provided good reliability within a single visit and between consecutive visits supporting its use as an adjunctive tool in the clinical setting. Further long-term follow-up is required to understand RNFL thickness changes in this specific population and its association with vigabatrin toxicity.

Translational Relevance: The findings of good reliability and clinical feasibility would provide an opportunity for the handheld OCT to monitor reliably for vigabatrin-associated retinal toxicity in children who often show noncompliance to traditional testing approaches.

Background

Infantile spasms (IS) is a childhood seizure disorder with very poor prognosis. IS affects 2–4 children

per 10,000.^{1–7} Vigabatrin (γ -vinyl GABA; Sabril; Lundbeck, Deerfield, IL) is an effective antiepileptic medication and is used in Canada as first-line monotherapy in children ≤ 2 years of age with IS.^{8,9} Vigabatrin is a competitive and irreversible

pharmacologic inhibitor of the GABA-transaminase enzyme and functions by increasing GABA (γ -aminobutyric acid) concentrations in the central nervous system.^{10,11} Vigabatrin is associated with irreversible bilateral peripheral visual field deficits.^{12,13} These visual field complications are associated with reduction of the light-adapted (LA) 30 Hz flicker electroretinogram (ERG)¹⁴. The peripapillary retinal nerve fiber layer (RNFL) thickness, measured with optical coherence tomography (OCT), is likewise reduced.^{15–19} In older children and adolescents treated with vigabatrin in early childhood, there is thinning of RNFL thickness in nasal, superior, and inferior quadrants in those with previously-diagnosed toxicity based on ERG.²⁰ The temporal quadrant is unaffected. Because of these vigabatrin-associated retinal complications, it is recommended by the drug manufacturer that patients treated with vigabatrin undergo regular retinal assessments (Sabril; Lundbeck, Deerfield, IL, USA; <https://www.sabril.net>). Early detection of vigabatrin-related vision loss in children might allow physicians and guardians to reach earlier informed decision regarding the course of treatment.

Monitoring children younger than 3 years of age for vision loss using traditional techniques is profoundly difficult²¹ because of poor compliance with adult-oriented procedures such as the Goldmann visual field perimetry and table-top OCT,^{22–28} which require stable upright postures for a prolonged period of time. When vigabatrin is required for those under the age of 3 years, assessment is limited to fundus examination, confrontational visual fields and in some centres, ERGs. To the best of our knowledge, there has been no previous study of spectral-domain OCT (SDOCT) for assessment of RNFL evaluations in vigabatrin treated children younger than 3 years of age.

Envisu (Leica Microsystems, NC, USA) is a handheld SDOCT system with a maneuverable eyepiece allowing young children to be tested in a supine position.²⁹ Envisu OCT acquires volumetric scans of the optic nerve head (ONH) and is effective as a structural biomarker for various retinal conditions.^{25,30–32} Notably, Avery and colleagues demonstrated high intra- and inter-visit reliabilities in evaluating RNFL thickness in children with optic pathway glioma and neurofibromatosis type I (age range, 0.8–13 years).³² We propose that Envisu OCT is a suitable technique for monitoring vigabatrin related retinal changes in young children. In this prospective observational study, we assessed the intra- and inter-visit reliabilities of the Envisu OCT peripapillary RNFL thickness in children undergoing vigabatrin treatment. Secondarily, using longitudinal study design, we assessed the presence and extent of RNFL thinning.

Methods

Research Ethics

The Research Ethics Board at the Hospital for Sick Children (SickKids) gave approval for this study; the study followed the tenets of the Declaration of Helsinki for clinical research. Informed consents were obtained from parents or guardians of children after thorough explanation of the study.

Recruitment

Inclusion Criteria

Children ≤ 3 years of age diagnosed with IS by the Neurologists at SickKids Hospital. These children were undergoing vigabatrin treatment either as a monotherapy or alongside other medications. Sedation for the clinical ERG (standard of care to monitor for vigabatrin-associated retinal toxicity) occurred before assessment with the handheld OCT. Rothman and colleagues³³ reported on the possible racial differences in RNFL thickness in healthy, full-term neonates (aged 37–42 weeks) undergoing handheld SDOCT assessments. Toronto is a multicultural city; because the current study population included children from diverse cultural backgrounds, the ethnicity was not deemed to be a factor and was not recorded during the study.

Exclusion Criteria

Children with other known retinal conditions or had been taking medications that affected the retina. Sex was not a determining factor for inclusion in this study.

Intake Evaluation

Patients, whose parents or guardians provided written approval, were first tested for visual acuity and identification for the presence of strabismus or nystagmus as part of their pre-sedation procedure by an orthoptist. Following this, pupils were dilated with mydriatic eye drops of 1% tropicamide (Mydriacyl; Alcon Laboratories Inc, Fort Worth, TX, USA) and 2.5% phenylephrine (Mydrin; Alcon Laboratories Inc).

Sedation

The child was sedated (chloral hydrate 80 mg/kg up to 1g maximum) for standard clinical ERG assessment.³⁴

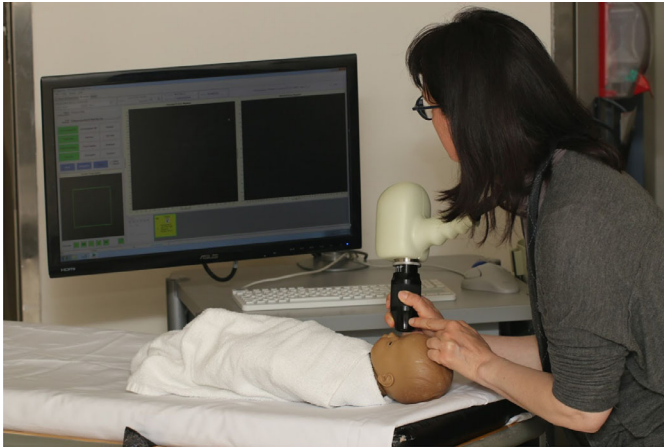


Figure 1. Imaging specialist operating the handheld Envisu OCT on an infant under sedation. The eye-piece connected to the fiberoptic cable allows flexibility because children can be imaged in a supine position. Real-time optic disc images can be displayed on the on-board computer screen for instant appraisal of quality and location of scan.

Handheld Envisu OCT Assessment

With the child under sedation, the imaging specialist acquired ONH scans with the Envisu C2300 handheld SDOCT with a 36,000 A-scans per second acquisition rate, a 3.5- μm tissue resolution and a 2.45-mm scan depth.³⁵ The image acquisition process resembled previous published studies.^{25,32,35,36} The adjustable eye-piece (camera probe) attached to the main computer via a 1.3-m fiberoptic cable allowing flexibility (Fig. 1). To account for differences in axial length, the reference arm length was adjusted before imaging such that it was shortened to accommodate for the decrease in axial length in the neonatal eye.³⁶ The axial length increases linearly during the neonatal period and slowly plateaus with age.³⁷ Refractive error was compensated for by adjusting the eyepiece focus. While positioning the camera over the eye, the pupil was revealed by holding the eyelids open with the index finger. A foot pedal initiated the ONH scan, and 2 repeated measurements for both right (OD) and left (OS) eyes were completed in less than 3 minutes during the same visit. The right eye was always imaged first followed by the left eye. The Envisu OCT system does not measure signal strength of each scan; consequently the experienced imaging specialist examined each scan and determined the image quality. Scans were noted to be subpar when dark shadows were observed over the peripapillary region; these likely arose from head or eye movements, and these scans were repeated. The scans covered an area of 12 mm \times 12 mm at a depth of 2.45 mm to ensure maximum coverage around the ONH.

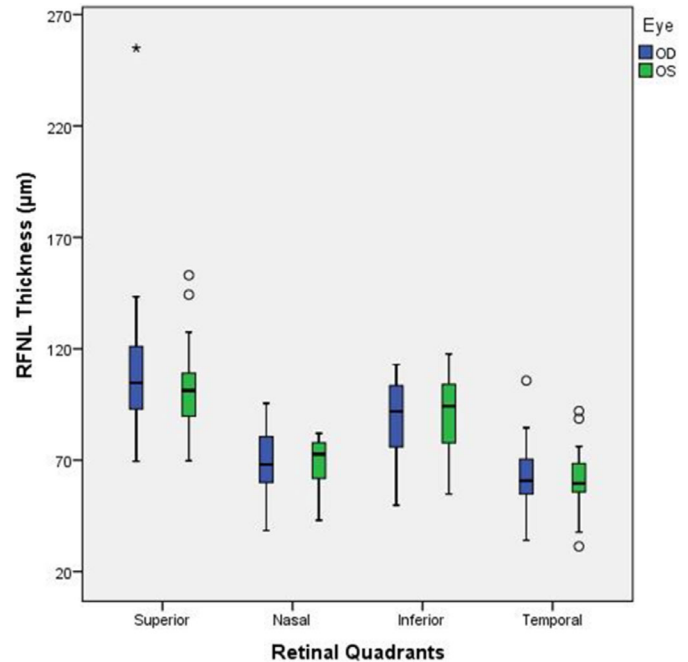


Figure 2. Boxplot of peripapillary RNFL thickness across four 90-degree retinal quadrants in both eyes (n = 28 for OD; n = 25 for OS) measured during the first visit. The median and percentiles are shown. Hollow-circles (°) and asterisk (*) refer to the outliers and extreme outliers respectively of each quadrant. The asterisk represents an extreme outlier in the OD superior quadrant RNFL thickness of participant ID 021 with the presence of tuber in the retina (etiology of TSC).

Using the non-isotropic 1000 A-scans \times 100 B-scans sampling method, each ONH scan was imaged in a few seconds. The real-time horizontal and vertical B-scans of the ONH displayed on the on-board computer software (InVivoVue 2.4 OCT Management Software) allowed an instant appraisal of image quality. After imaging completion, horizontal B-scans along with an en-face fundus-like image allowed qualitative examination for motion and other artifacts.

OCT Segmentation

The raw files (.OCT) were exported from the InVivoVue 2.4 software for RNFL thickness analysis. The OCT Explorer Iowa Reference Algorithms software (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging, Iowa City, IA, USA) was user-friendly and was accessible for investigational use, which allowed segmentation to determine the peripapillary RNFL thickness in the superior, nasal, inferior and temporal quadrants around the ONH. In the event of subpar image quality, the software's automatic segmentation mechanism was insufficient and manual tracing was conducted under guidance of an experienced neuro-ophthalmologists. The ONH was masked

Table. Demographic and Clinical 30 Hz Flicker ERG Information for N = 29 Participants Tested on the Handheld OCT

Sub ID	Age at testing (months)	Sex (M/F)	Cause	Other medications	Current daily dose (body weight)	Clinical 30 Hz ERG findings
001	6 (1 st visit) 11 (2 nd visit)	M	Unknown	None	1200 mg (9.8 kg @ visit 2)	Visit 1 – slightly reduced amplitude in OD in comparison to normal limits Visit 2 - WNL, increase from visit 1
002	4 (1 st visit) 14 (2 nd visit)	M	TSC	1. Phenobarbitol 2. Vitamin D	1000 mg (12.8 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, no change
003	17	F	Focal cortical dysplasia	None	1200 mg (10 kg)	WNL
004	23	F	TSC	1. Oxcarbazepine 2. Topiramate	1600 mg (16.7 kg)	WNL
005	7	M	Periventricular Leukomalacia and Hypoglycemia at Birth	Clobazam	1250 mg (10 kg)	WNL
006	9 (1 st visit) 16 (2 nd visit)	F	Intra-parenchymal Hemorrhage with Ventricular Extension	1. Vitamin D 2. Phenobarbitol	1200 mg (8.77 kg @ visit 1) Discontinued following visit 1	Visit 1 - WNL Visit 2- WNL, no change
007	9 (1 st visit) 18 (2 nd visit)	F	Left Middle Cerebral Artery Infarction	Keppra	1000 mg (10.5 kg @ visit 2)	Visit 1 - WNL Visit 2- WNL, no change
008	9 (1 st visit) 13 (2 nd visit)	M	Unknown	Vitamin D	1200 mg (9.5 kg @ visit 2)	Visit 1 - WNL Visit 2- WNL, 23.7% decline in OD from Visit 1
009	6 (1 st visit) 14 (2 nd visit)	F	Unknown	None	1000 mg (9.9 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, 40.2% decline in OD from Visit 1
010	6	M	Neonatal Hypoxic-ischemic Encephalopathy	Keppra	900 mg (7 kg)	WNL
011	11	M	Unknown	1. Phenobarbitol 2. Vitamind D	Discontinued	WNL

Table. Continued

Sub ID	Age at testing (months)	Sex (M/F)	Cause	Other medications	Current daily dose (body weight)	Clinical 30 Hz ERG findings
012	27 (1 st visit) 34 (2 nd visit)	F	TSC	1. Oxcarbazepine 2. Keppra	1500 mg (15 kg @ visit 2)	Visit 1 – slightly reduced amplitude in OD in comparison to normal limits Visit 2 - WNL, increase from visit 1
013	9 (1 st visit) 15 (2 nd visit)	M	Unknown	None	1000 mg (10.3 kg @ visit 2)	Visit 1' - WNL Visit 2 - normal, no change
014	8 (1 st visit) 12 (2 nd visit)	F	Periventricular Leukomalacia	Pyridoxine	1800 mg (12 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, 26.2% decline in OD from Visit 1
015	7	M	Unknown	None	1000 mg (8.3 kg)	WNL
016	9 (1 st visit) 13 (2 nd visit)	M	Unknown	1. Iron 2. Vitamin D 3. Probiotics	1000 mg (8.8 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, no change
017	10 (1 st visit) 13 (2 nd visit)	F	Periventricular leukomalacia	1. Prednisolone 2. Vitamin D	900 mg (7.8 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, no change Visit 3 - WNL, no change
018	5 (1 st visit) 9 (2 nd visit)	F	Mutation of TUBBB2A gene	1. Prednisolone 2. Topiramate 3. Vitamin D	1000 mg (10.3 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, 21% decline in OD from Visit 1
019	7 (1 st visit) 11 (2 nd visit)	F	Trisomy 21	None	300 mg (9.1 kg @ visit 2)	Visit 1 - WNL Visit 2 - WNL, 38.5% decline in OS from Visit 1
020	22	M	Right posterior cerebral infarction	1. Keppra 2. Clobazam	1500 mg (10.8 kg)	WNL
021	4	M	TSC	ACTH	1000 mg (8.7 kg)	WNL
022	16	F	Unknown	1. Keppra 2. ACTH	1400 mg (12.4 kg)	WNL
023	13	F	Unknown	None	1500 mg (9.6 kg)	WNL

Table. Continued

Sub ID	Age at testing (months)	Sex (M/F)	Cause	Other medications	Current daily dose (body weight)	Clinical 30 Hz ERG findings
024	5	F	Polymicrogyria in the left frontal lobe	1. Phenobarbitone 2. Clobazam 3. Topiramate 4. Keppra	1500 mg (9.8 kg)	WNL
025	8	M	Right schizencephaly	1. Keppra 2. Prednisolone	1000 mg (<i>not available</i>)	WNL
026	12	F	Unknown	None	1300 mg (10.2 kg)	WNL
027	5	F	Unknown	None	1000 mg (8.2 kg)	Slightly reduced amplitudes in OD in comparison to normal limits
028	1	M	Right parietal occipital focal cortical dysplasia	Phenobarbital	700 mg (5.4 kg)	WNL
029	8 (1 st visit) 13 (2 nd visit)	F	TSC	Pyridoxine	1000 mg (9.5 kg)	Visit 1—WNL; Visit 2—WNL, no change

*WNL (within normal limits) clinical 30 Hz flicker ERG response is based on comparisons to age-expected normative range. N/A refers to participants without follow-up testing on the handheld OCT. Weight information is not available in one child (ID025). Vigabatrin was discontinued at the time of most recent handheld OCT testing in 2 children (ID006, ID011). TSC represents tuberous sclerosis complex and ACTH represents adrenocorticotrophic hormone.

with a 3.4-mm diameter circle, 256 A-scans from the 3.4-mm annulus surrounding the ONH were analyzed, and each retinal quadrants contained 64 A-scans.

values across two longitudinal visits for each of the 4 retinal quadrants. Probability values < 0.05 were considered significant.

Statistical Analysis

Intravisit reliability and intervisit reliability represented correlations between 2 repeated ONH scans within a single testing session and the correlations between 2 scans across repeated study visits of the same participant, respectively using the intraclass correlation coefficient (ICC) statistics (Statistical Package for Social Studies software (SPSS, IBM, Chicago, IL)). Bland-Atman test evaluated the presence of bias between RNFL measurements of the two repeated trials for both intravisit and intervisit assessments. The median and percentiles were calculated for both intra-visit and inter-visit assessments. Paired-sample *t*-test tested for the difference between the mean RNFL

Longitudinal Assessments

Longitudinal changes were assessed across two OCT scans of the same eye, 1 from the first visit, and another from the follow-up visit. RNFL thickness from the first visit served as each child's baseline measurements. Because the youngest children would still be in the period of ocular development, the current study aimed at identifying reductions in RNFL thickness.

Results

Twenty-nine children (10.1 ± 6.0 months old; range, 4–27 months) with IS undergoing vigabatrin

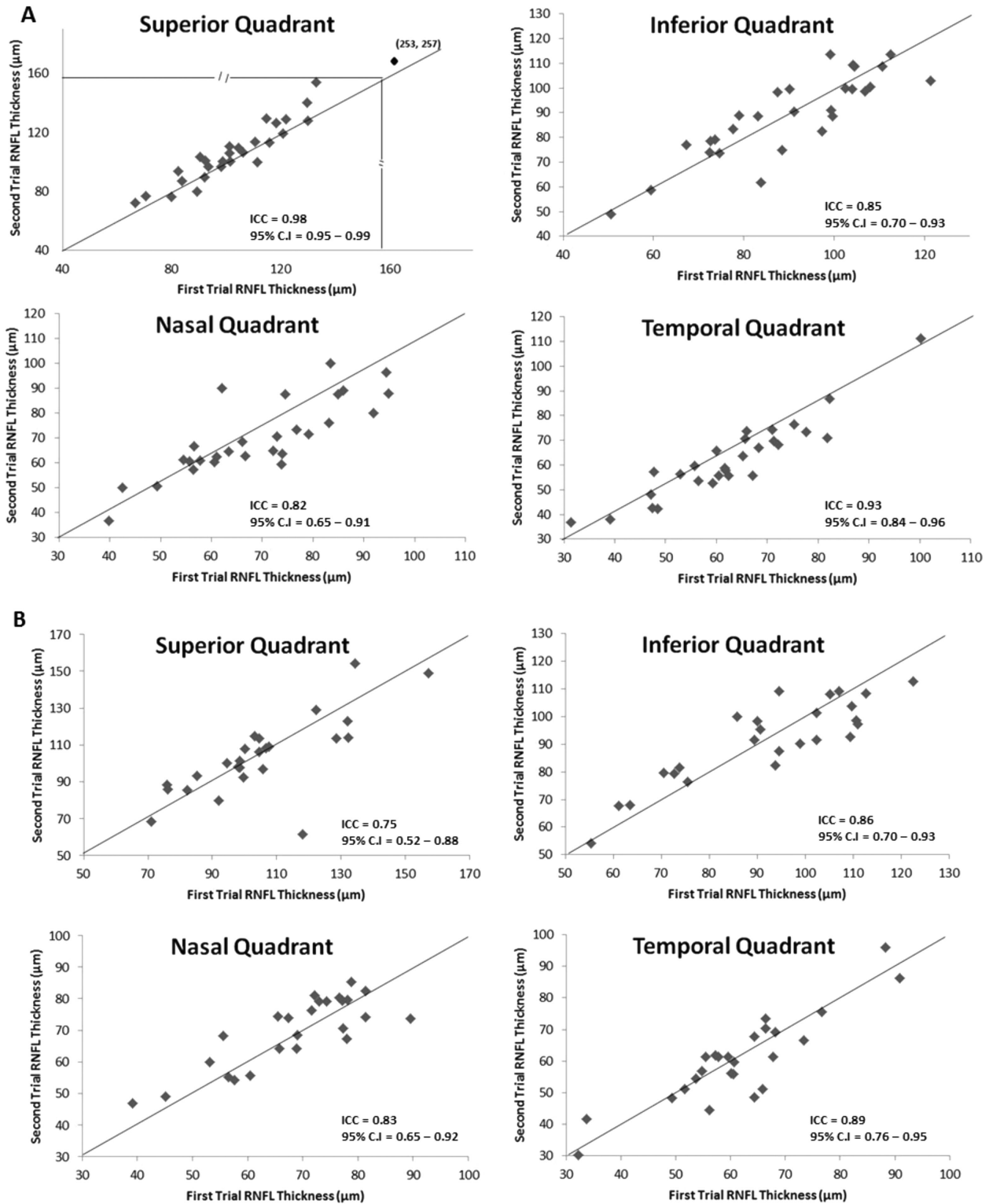


Figure 3. Intravital reliability expressed as plots of second trial RNFL thickness against first trial RNFL thickness for all four 90-degree retinal quadrants of OD (A) and OS (B). The line of perfect agreement between the 2 trials is used as reference. The ICCs and 95% confidence intervals (C.I) are shown.

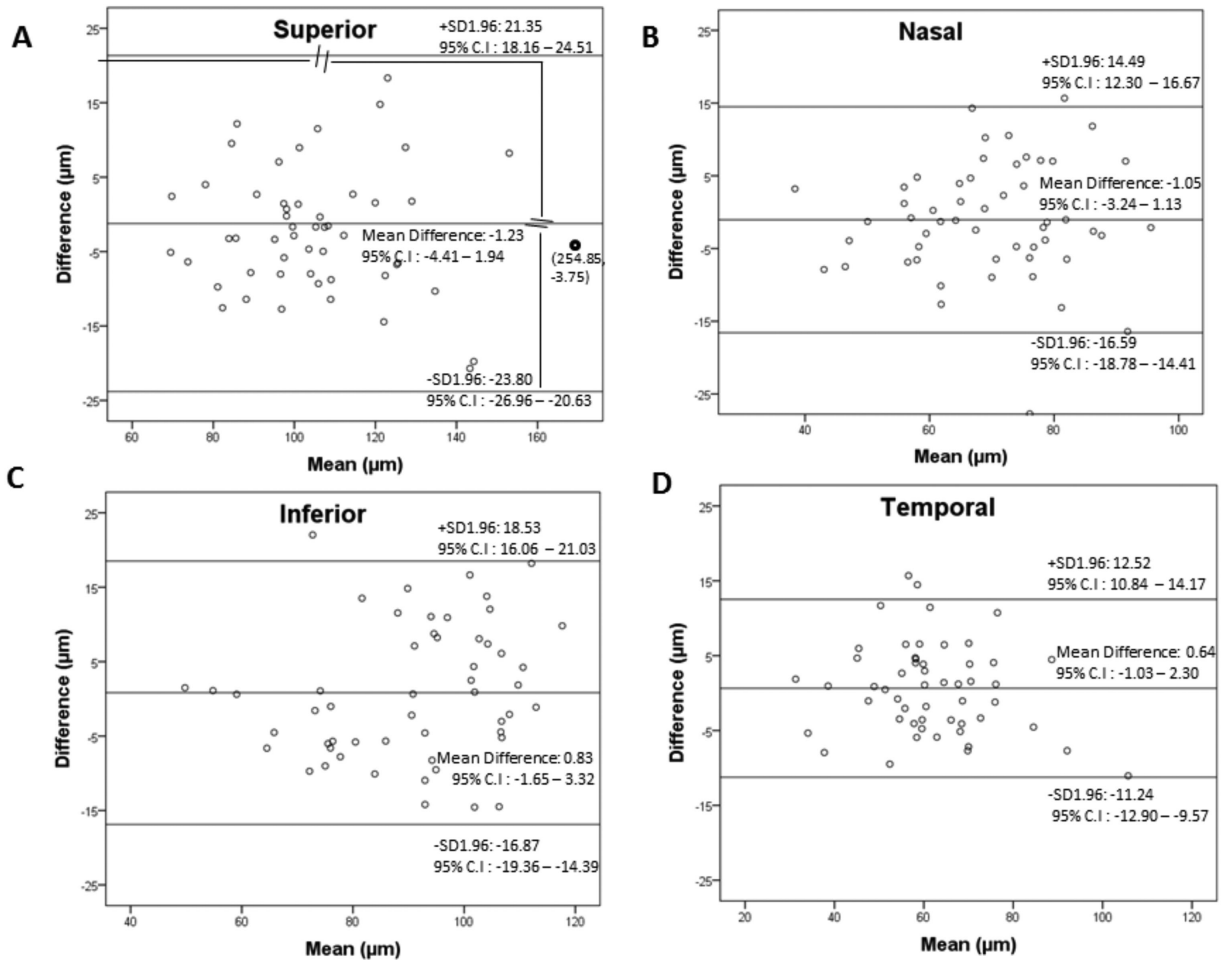


Figure 4. Bland-Altman plot of RNFL thickness (μm) for all retinal quadrants recorded from 2 trials on the Envisu handheld OCT. The middle line represents the mean difference between the 2 trials, and the top and bottom lines represent the upper ($\pm\text{SD } 1.96$ in μm), and lower ($\pm\text{SD } 1.96$ in μm) limits of agreement within which 95% of the differences lie. There is no bias between the mean differences in RNFL measurements of the 2 trials. The repeatability coefficient (test-retest reliability) for the 4 quadrants are: 22.58(superior), 15.54(nasal), 17.70(inferior), and 11.88(temporal).

therapy were recruited during their scheduled clinical ERG appointment at the SickKids Ophthalmology clinic. All children ($N = 29$) completed the handheld OCT testing in 1 or both eyes. Fourteen children completed 1 follow-up session with the handheld OCT (14.7 ± 5.8 months old at second visit, range 9–34 months). The Table lists the demographics information for all participants. The median and percentiles of RNFL thickness across each of the four 90-degree retinal quadrants (superior, nasal, inferior and temporal) was calculated for both right and left eyes (Fig. 2).

Intravisit Reliability

Twenty-nine children imaged with the handheld OCT contributed 28 right eyes ($n = 28$) and 25 left eyes ($n = 25$) for the intravisit reliability calculation. The intravisit ICCs for peripapillary RNFL thickness

for right eyes ranged from 0.82–0.98, and for left eyes ranged from 0.75–0.89. Data are plotted as second trial against first trial RNFL thickness values (Fig. 3). Bland-Altman plots show no clear bias in the mean RNFL thickness difference of the 2 repeated trials for both right and left eyes (Fig. 4). There is some evidence of heteroscedasticity particularly affecting the nasal and inferior quadrants.

Intervisit Reliability

Fourteen children ($n = 14$) who completed 1 follow-up visit on the handheld OCT contributed 1 eye for intervisit reliability analysis. Ten of the 14 eyes tested were from the right eye, and the remaining 4 eyes were left eyes. The intervisit ICCs for the superior, nasal, inferior and temporal quadrants were 0.90, 0.82, 0.86, and 0.98, respectively. Figure 5 shows the intervisit

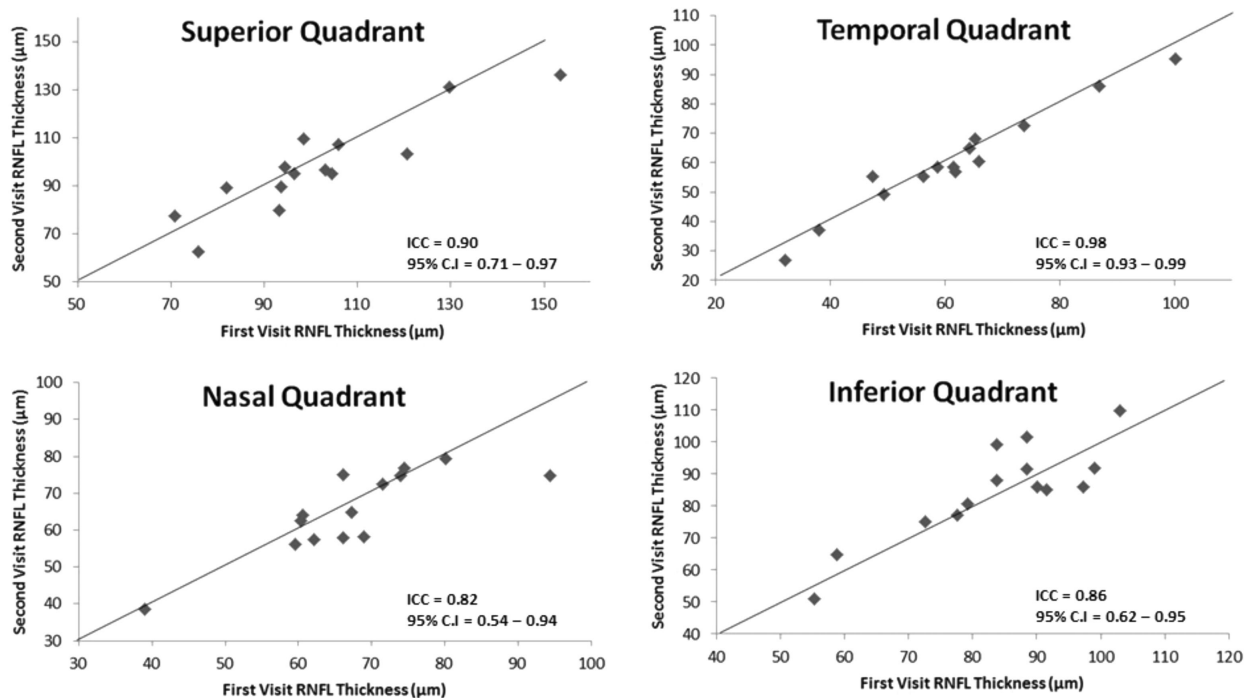


Figure 5. Intervisit reliability expressed as plots of second visit RNFL thickness against first visit RNFL thickness for all four 90-degree retinal quadrants. A total of 14 children ($n = 14$) have completed 2 consecutive visits on the handheld OCT. Four eyes (4/14) were from analyzed OS, and the remaining eyes (10/14) were from OD. The line of perfect agreement across 2 visits is used as a reference. The ICCs and 95% confidence intervals (C.I.) are shown.

reliability for all 4 retinal quadrants expressed as plots of second visit against first visit RNFL thickness. Bland-Altman plot shows no clear bias between the RNFL thickness measurements of 2 consecutive visits for all retinal quadrants (Fig. 6), again there is some evidence of heteroscedasticity.

Longitudinal Assessment

Fourteen children ($n = 14$) completed 1 follow-up visit with handheld OCT testing at a mean interval of 5.7 months (range, 3–10 months) after the first visit. The median RNFL thicknesses across all quadrants were not different between the 2 visits (Fig. 7), and the mean RNFL thicknesses were not significantly different. It was of particular interest to determine whether there were reductions in RNFL in the nasal, superior, and inferior quadrants of individual children.²⁰ There were no such changes; within the superior and nasal quadrants (Fig. 8), 6 children showed more than 10% decline in RNFL thickness from baseline, and 4 children showed an equivalent increase.

Discussion

To the best of our knowledge, this was the first study to assess the reliability of handheld OCT in

young children (<3 years old) undergoing vigabatrin therapy. Previous studies incorporating the SDOCT to investigate vigabatrin-associated retinal toxicity were mostly restricted to adults and older children who could tolerate table-mounted OCT imaging protocols. Studies of younger children on vigabatrin have involved electrophysiological testing using the LA 30 Hz flicker ERG,^{38,39} table-top OCT, and visual fields testing after drug discontinuation during adolescence.²⁰ RNFL thickness attenuation is associated with vigabatrin toxicity; therefore reliable retinal monitoring should occur regularly. Given issues of testing compliance, the use of SDOCT for ONH assessment in infants are currently limited. In the present study, oral sedation had been given for evaluation of a standard clinical ERG; the children remained under sedation for the handheld OCT assessment, thus imaging without sedation in children was not attempted.

Reliability

In previous studies using conventional table-top SDOCT, intra-visit reliability was excellent (ICCs > 0.9) in evaluating central macular thickness⁴⁰ and peripapillary RNFL thickness for each of the four 90 degree retinal quadrants.⁴¹ The present study

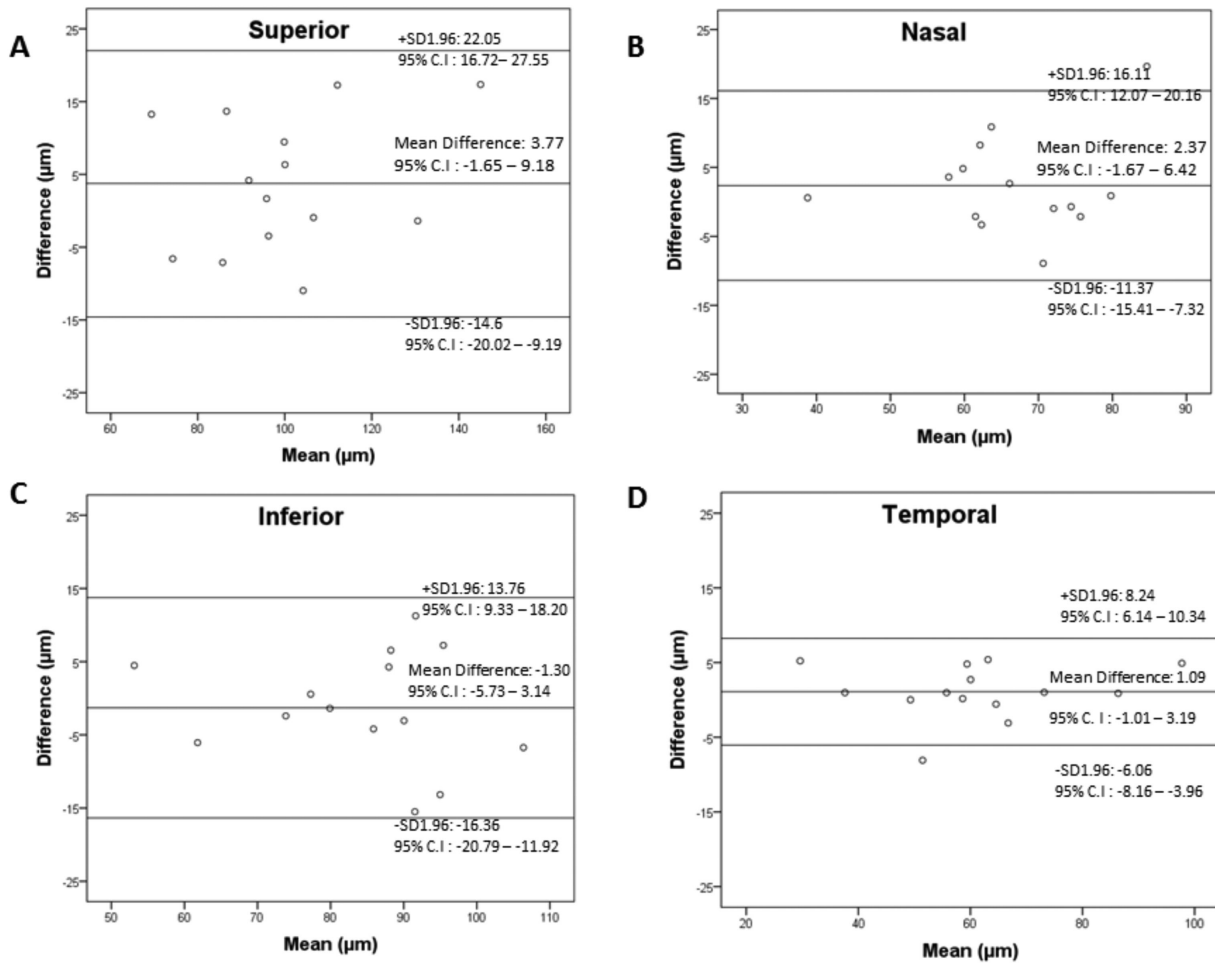


Figure 6. Bland-Altman plot of RNFL thickness (μm) for all retinal quadrants recorded from 2 consecutive visits on the Envisu handheld OCT. The mean difference between the 2 visits and the upper (+SD 1.96 in μm), and lower (–SD 1.96 in μm) limits of agreement within which 95% of the differences lie are shown. There is no bias between the mean differences in RNFL measurements of the 2 visits. The repeatability coefficient (test-retest reliability) for the 4 quadrants are: 18.28 (superior), 13.74 (nasal), 15.06 (inferior), and 7.15 (temporal).

demonstrated good intra-visit as well as inter-visit reliabilities, suggesting that RNFL assessments with handheld OCT are reproducible within a single session and between consecutive sessions in infants (1-34 months) undergoing vigabatrin treatment. The Bland-Altman plot showed no clear bias between the 2 intravisit and 2 intervisit repeated measurements of all retinal quadrants. Of note, there is a suggestion of changes in the variance with increasing means (heteroscedasticity). A future study with a larger sample size and more repeated measurements is required to ensure that reliability does not vary across the range of retinal thicknesses. The findings from the Bland-Altman test add to the suggestion of good intravisit and intervisit reliabilities. ICCs calculated from this study may not be applicable to infants younger than 3 years of age with other retinal conditions affecting the RNFL, because ICCs are

population-specific and the mechanisms of RNFL attenuations are not always universal.³²

The intravisit and intervisit ICCs in the current study are comparable to the values published by Avery and colleagues³² in children (mean age 5.1 years; range, 0.8–13 years) with optic pathway glioma or neurofibromatosis type 1 who had normal vision. For both intravisit and intervisit testing, the ICCs in the current study are slightly lower across all quadrants in comparison to the aforementioned study. The slight reduction in reliability measures may have resulted from the differences in the mean age of participants between the Avery study and the current study. The current study focused on a much younger cohort (mean age 0.84 years compared with 5.1 years). The smaller head and eye dimensions in the infant cohort affects the space available for the eyepiece, which might create additional motion artifacts affecting the

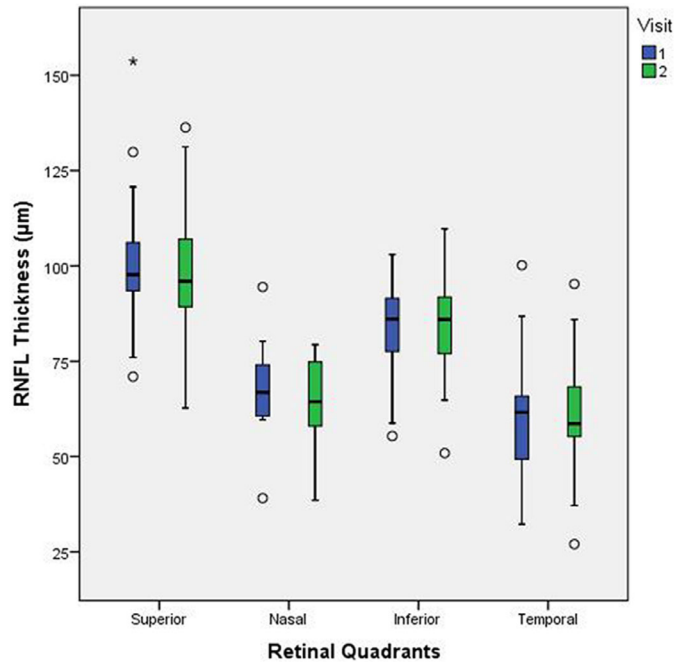


Figure 7. Longitudinal RNFL thickness assessments across two visits (visit 1 = baseline, visit 2 = first follow-up) for all 4 retinal quadrants. The median and percentiles are shown. Paired-sample *t*-tests (two-tailed) showed that the differences in mean RNFL thickness between baseline and the first follow-up visit were not statistically significant. *P* values for the superior, nasal, inferior, and temporal quadrants were 0.16, 0.23, 0.54, and 0.29, respectively.

signal-to-noise ratio and overall quality of the ONH scan. The intervisit ICCs in the current study will be influenced by difference in age between the 2 visits of up to 5 months and the possible reductions in RNFL thickness in some children as a result of vigabatrin treatment.

Longitudinal Assessment

The ability to assess longitudinal changes in peripapillary RNFL thickness would be beneficial for infants taking vigabatrin for IS, as scheduled monitoring may detect structural biomarkers of retinal toxicity which could then affect the course of treatment. In the current study, it was not expected that vigabatrin related changes would be marked as the investigative period was short with most children receiving vigabatrin for less than 6 months. However, we conducted the longitudinal assessment to determine the likelihood of early vigabatrin related changes in the superior, nasal or inferior quadrants. As an age-matched normative range for healthy children was not established, each child's first visit on the handheld OCT served as his/her baseline result for comparison with follow-up testing sessions. For the 14 children who completed 1

follow-up handheld OCT evaluation, the mean RNFL thickness in each of the 3 quadrants at risk was not significantly different between the 2 visits. In this study, any significant quadrant-specific changes in RNFL thickness between consecutive visits may be attributed to noise. Further long-term follow-up studies are required to better understand RNFL thickness reductions and their associations with vigabatrin toxicity.

Patel and colleagues investigated normal RNFL development in children ($N = 352$; aged 1 day–13 years) and described a marked decline of 35% in temporal thickness between birth and 12 months of age followed by an increase of 22% between 12 months and 13 years.⁴² In the current study no association was found between age and temporal RNFL; this is not surprising because there was a limited age range of children (aged 4–34 months), a limited sample size ($N = 29$), and there may have been early changes caused by vigabatrin in this study.

Limitations

Because of recruitment specificities, the relatively small sample size in this study may restrict the generalizability and the power of our results. The longitudinal assessment revealed no significant findings; if it had been possible to monitor the children for longer with additional visits, the results would have been more conclusive. This did not happen; some children were weaned off vigabatrin, and follow-up ERG was not required; at other times the sedation was canceled, or the OCT was unavailable. Variability in vigabatrin status occurred because the first handheld OCT assessment sometimes occurred during one of the follow-up clinical ERG visits when the child was receiving vigabatrin as opposed to the baseline pre-vigabatrin visit. To ensure the smooth and efficient patient flow in the Ophthalmology clinic, there were strict time limits to complete all OCT assessments, thus only 1 eye may have been imaged. In these follow-up OCTs if data from 1 eye were collected, then follow-up was always compared with the same eye from the first visit. Although no participants in this study were identified as having development of retinal toxicity, it is possible vigabatrin associated retinal changes occurred in some participants, which would lead to overestimation of the amount of intervisit variation.

Conclusions

To the best of our knowledge, this is the first study to assess the reliability of the handheld OCT and use

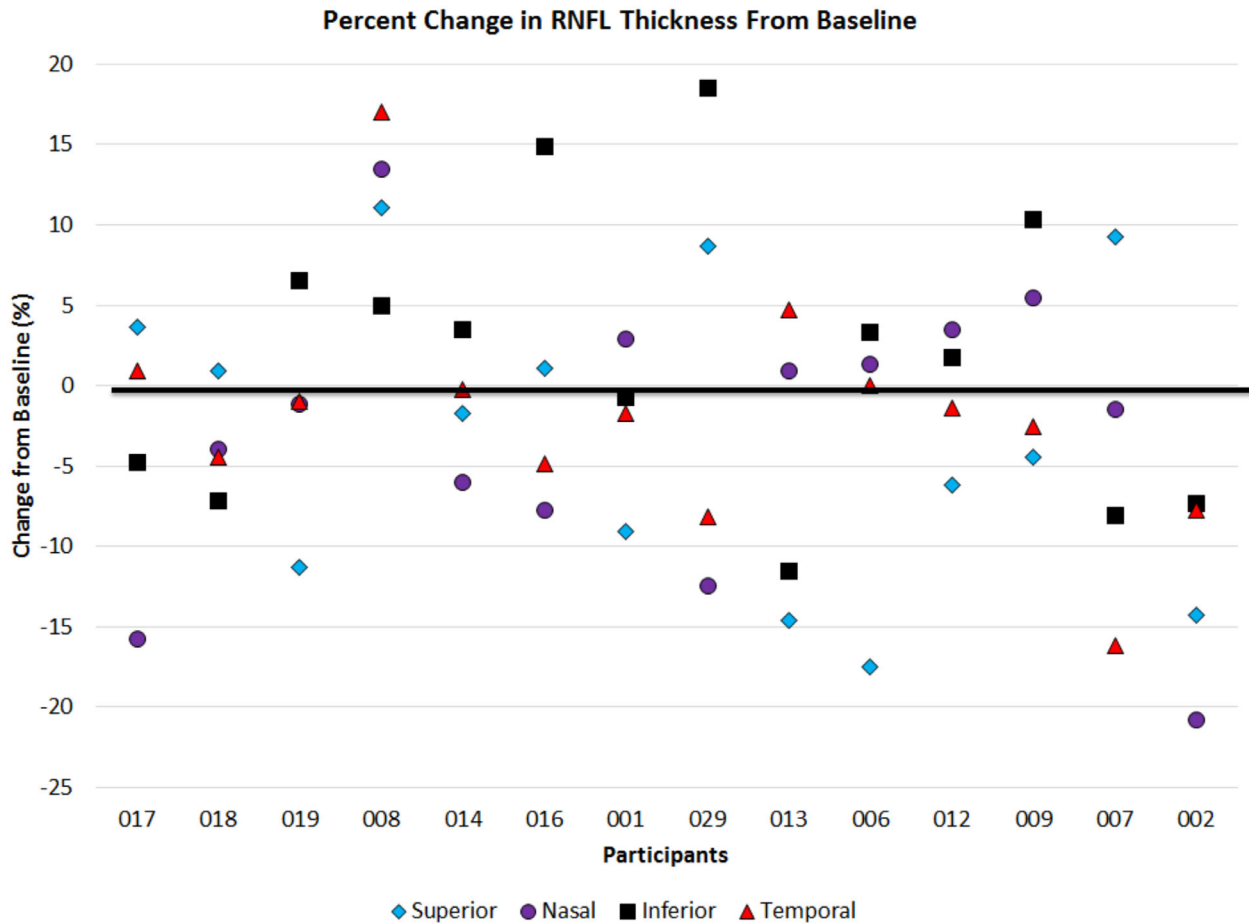


Figure 8. Percent change from baseline during visit 2 for n = 14 children who have completed 1 follow-up test on the handheld OCT. All 4 peripapillary quadrants are shown by separate colors. Black reference line represents no change from baseline in the respective retinal quadrant. Participants are arranged from shortest to longest duration between 2 consecutive visits.

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a longitudinal design measuring RNFL thickness in infants younger than 3 years of age with IS undergoing vigabatrin treatment. RNFL thickness measures using the handheld OCT provided good reliability within a single visit and between consecutive visits. Further long-term follow-up is required to gain a better understanding of RNFL thickness reductions in this specific population and its association with vigabatrin toxicity.

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