Ganglion Cell Layer–Inner Plexiform Layer Thickness and Vision Loss in Young Children With Optic Pathway Gliomas

Sherry Gu,¹ Natalie Glaug,² Avital Cnaan,^{2,3} Roger J. Packer,^{2,4,5} and Robert A. Avery^{2,4}

¹George Washington University School of Medicine, Washington, DC

²Gilbert Family Neurofibromatosis Institute, Children's National Medical Center, Washington, DC

³Division of Biostatistics and Study Methodology, Children's National Medical Center, Washington, DC

⁴Center for Neuroscience and Behavior, Children's National Medical Center, Washington, DC

⁵The Brain Tumor Institute, Children's National Medical Center, Washington, DC

Correspondence: Robert A. Avery, Neuro-Ophthalmology Service, Department of Neurology, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010; ravery@childrensnational.org.

Submitted: August 22, 2013

Accepted: January 21, 2014

Citation: Gu S, Glaug N, Cnaan A, Packer RJ, Avery RA. Ganglion cell layer–inner plexiform layer thickness and vision loss in young children with optic pathway gliomas. *Invest Ophthalmol Vis Sci*. 2014;55:1402–1408. DOI:10.1167/iovs.13-13119

PURPOSE. To determine if measures of macular ganglion cell layer–inner plexiform layer (GCL–IPL) thickness can discriminate between children with and without vision loss (visual acuity or field) from their optic pathway glioma (OPG) using spectral-domain optical coherence tomography (SD-OCT).

METHODS. Children with OPGs (sporadic or secondary to neurofibromatosis type 1) enrolled in a prospective study of SD-OCT were included if they were cooperative for vision testing and macular SD-OCT images were acquired. Manual segmentation of the macular GCL–IPL and macular retinal nerve fiber layer (RNFL) was performed using elliptical annuli with diameters of 1.5, 3.0, and 4.5 mm. Logistic regression assessed the ability of GCL–IPL and RNFL thickness measures (micrometers) to differentiate between the normal and abnormal vision groups.

RESULTS. Forty-seven study eyes (normal vision = 31, abnormal vision = 16) from 26 children with OPGs were included. Median age was 5.3 years (range, 2.5–12.8). Thickness of all GCL–IPL and RNFL quadrants differed between the normal and abnormal vision groups ($P < 0.01$). All GCL–IPL measures demonstrated excellent discrimination between groups (area under the curve [AUC] > 0.90 for all diameters). Using the lower fifth percentile threshold, the number of abnormal GCL–IPL inner macula (3.0 mm) quadrants achieved the highest AUC (0.989) and was greater than the macula RNFL AUCs ($P < 0.05$).

CONCLUSIONS. Decreased GCL–IPL thickness ($<$ fifth percentile) can discriminate between children with and without vision loss from their OPG. Ganglion cell layer–inner plexiform layer thickness could be used as a surrogate marker of vision in children with OPGs.

Keywords: OCT, optic pathway glioma, pediatric, ganglion cell, neurofibromatosis type 1

The ophthalmologic examination and monitoring of children with optic pathway gliomas (OPGs), low-grade gliomas of the anterior visual pathway, is challenging for a number of reasons. Most children with OPGs typically present between the ages of 1 and 8 years old—a time when the reliability and accuracy of their vision examination may be compromised by their young age and/or poor cooperation.^{1,2} Furthermore, children with OPGs secondary to neurofibromatosis type 1 (NF1) have a high incidence of cognitive delay and behavioral problems.^{3,4} Even children with OPGs not related to NF1, termed sporadic OPGs, typically perform recognition visual acuity (VA) tasks at an older age than otherwise healthy children.⁵ Younger children also have difficulty reliably performing visual field (VF) testing that can detect subtle changes indicative of OPG progression.

Most commonly, treatment of OPGs with chemotherapy is initiated only after the child has experienced a decline in their vision (VA and or VF).⁶ Waiting until a child experiences vision loss before treatment is initiated likely contributes to a worse visual outcome, although it avoids unnecessarily treating children who would have never experienced vision loss. Not

surprisingly, the presence of optic nerve pallor at treatment onset was associated with poorer visual outcomes and treatment response in children with NF1-related OPG.⁶ Furthermore, the study by Fisher et al.⁶ demonstrated that young age (< 2 years old) at treatment initiation was significantly associated with a poor visual outcome and decreased treatment response. These factors highlight the need for a surrogate marker of vision that would ideally detect which children are at risk for impending vision loss, thereby permitting early treatment before vision loss occurs. Also, for the young children who are at high risk of vision loss, but are also at the age when they are least cooperative with the ophthalmologic exam,⁵ a surrogate marker could confirm the presence or absence of damage to the afferent visual system.

Optical coherence tomography (OCT) has been established as a reliable noninvasive measure of anterior visual pathway integrity in a variety of conditions including glaucoma, multiple sclerosis, and optic neuropathy.^{7–16} While a majority of the research in these conditions has focused on measuring the peripapillary retinal nerve fiber layer (pRNFL), recent data suggest the ganglion cell layer–inner plexiform layer (GCL–IPL)

of the macula may be a more accurate and reliable biomarker of vision.^{17,18} Accurate and reliable pRNFL measurements are known to be hampered by axonal swelling, axonal atrophy, blood vessel artifact within the pRNFL, and between-subject variation in the mapping of RNFL bundle to corresponding VF.^{18–20} On the other hand, measures of the macular GCL-IPL thickness may demonstrate a more accurate relationship with VA/VF since it is typically unaffected by acute optic nerve swelling, lacks large retinal vessels that could confound measurements, has less between-subject variability, is unaffected by refractive error, and identifies the exact location of the ganglion cell rather than the accumulation of axons in the pRNFL.¹⁸

The association between pRNFL thickness and vision in children with OPGs has been previously reported.^{21,22} To our knowledge, no studies have specifically examined the relationship between GCL-IPL thickness and vision loss in young children with OPGs. The primary aim of this study was to determine if GCL-IPL measures differed between children with and without vision loss from their OPG, and if these differences could discriminate between these groups.

MATERIALS AND METHODS

Subjects

Children between 1 and 18 years of age with OPGs (sporadic or secondary to NF1) were recruited through the neuro-ophthalmology clinic at the Children's National Medical Center (Washington, DC) as part of an ongoing visual outcomes and OCT imaging protocol. Subjects were recruited between June 2011 and July 2012, and they were included in this cross-sectional convenience sample if they had a diagnosis of an OPG, were willing to have mydriatic eye drops instilled, and could reliably cooperate with quantitative VA testing. Requiring the ability to cooperate with VA testing was needed to assess the relationship between structure (GCL-IPL) and function (VA). All subjects underwent a comprehensive neuro-ophthalmologic examination including assessment of intraocular pressure and optic nerve cupping by the same pediatric neuro-ophthalmologist (RAA). Exclusion criteria, identical to previously published criteria,²¹ were any non-OPG-related ophthalmologic or neurologic disease that could currently or have previously affected their VA or VF (e.g., amblyopia, cataracts, history of papilledema or glaucoma). This study was approved by the Children's National Medical Center IRB and was in accordance with HIPAA regulations. The research adhered to the tenets of the Declaration of Helsinki, and written consent for the study was obtained from the patients and/or their legal guardian prior study participation. All subjects received a \$10 gift card for their participation.

Demographic and clinical information was abstracted onto a standardized form and included: age, sex, race, ethnicity, treatment history, diagnosis (NF1 or sporadic OPG), and location of OPG. Optic pathway glioma location was determined using contrast-enhanced magnetic resonance imaging (MRI) and defined as either isolated optic nerve, optic chiasm with or without optic nerve involvement, or optic tracts with or without optic nerve or chiasm involvement.

VF Testing

All subjects underwent monocular VA testing with an age-appropriate method using their updated corrective eyewear. Subjects unable to complete recognition acuity tasks were tested with Teller grating acuity using an established protocol and the results converted to logarithm of the minimal angle of

resolution (logMAR) units.²³ Recognition VA results were recorded in logMAR. Magnitude of vision loss was calculated by subtracting the subjects' VA from their age-based norm. Children with a VA of ≥ 0.2 logMAR below age-based norms were labeled as having abnormal VA. Visual field testing was performed by confrontation or kinetic or static perimetry based on the child's age and cognitive abilities. Visual field results were considered abnormal if a defect existed in any quadrant and was not related to testing ability. Given the young age of our subjects, high rate of behavioral problems and cognitive delays, a standardized or quantitative VF protocol was not feasible for all subjects.^{3,4} In order to compare specific OCT measures, subjects were categorized as "normal" vision (i.e., normal VA and VF) or "abnormal" vision (abnormal VA, VF, or both).

Optical Coherence Tomography

All subjects underwent OCT imaging using a handheld spectral domain (HH-OCT; Bioptigen, Durham, NC). Thirty to 60 minutes prior to OCT imaging, mydriatic eye drops were instilled. All subjects were imaged in the supine position. Older children able to cooperate with OCT imaging were instructed to lie in the supine position on an exam table. The room was dimly lit and subjects fixated on target projected on the ceiling. Younger children unable to cooperate were imaged while sedated for their clinically indicated MRI scan.

All images were acquired with the HH-OCT operator (RA) positioned at the head of the bed. The HH-OCT reference arm length was adjusted according to the patient's age and axial length.²⁴ Once the patient achieved adequate fixation or was sedated, the noncontact HH-OCT probe was positioned until the foveola was clearly displayed in the center of the live horizontal and vertical B-scan image. Image quality, vignetting, and clipping could be optimized in real time by adjusting the reference arm and while adjusting the HH-OCT probe for refractive error. Once optimal image quality was achieved, a 6-mm $\times$ 6-mm image was acquired with 1000 A-scans per 100 B-scans (60- μ m distance between B-scans). Due to an evolving imaging protocol, three subjects had macula images acquired at 300 A-scans per 300 B-scans (20- μ m distance between B-scans). Adequate scan quality was determined if the following criteria were met: uniform signal intensity across the entire image, the foveola was centered, and movement artifact was isolated to areas outside those being analyzed. During acquisition, the operator could instantly review the image quality and acquire additional images if needed. If multiple images were obtained in the same patient, the highest quality image was segmented.

Macular Segmentation and Measurement

After identifying the foveola, an annular grid was manually placed over the foveola with annuli corresponding to the outer (diameter = 4.5 mm), inner (radius = 3.0 mm), and central (radius = 1.5) macula. Superior, nasal, inferior, and temporal quadrants were established for each annulus. Prior to segmentation, image contrast, and quality was adjusted. Using manufacturer-supplied software, individual B-scan images were manually segmented by first labeling the border between the inner limiting membrane and the inner border of the macular nerve fiber layer (termed RNFL). Ganglion cell layer-inner plexiform layer was then manually labeled from the innermost border of the RNFL to the innermost border of the IPL. Average RNFL and GCL-IPL thickness (micrometers) was calculated from 120 separate samples across all four anatomic quadrants of each annulus. Pilot testing of this protocol compared the analysis of 240 vs. 120 samples and found no significant qualitative difference when measuring more samples because

most adjacent samples were identical or within the range of device's axial resolution. A single investigator (SG), blinded to all patient information, performed all of manual segmentation. A second investigator (NG) independently segmented 20 subjects to determine reproducibility of the method.

Statistical Analysis

Demographic and clinical characteristics were summarized by standard descriptive statistics (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as sex). Intraclass correlation coefficients (ICC) determined the interrater reproducibility for each anatomic layer and quadrant and classified as good (≥ 0.75), fair (0.7–0.50), and weak (0.49–0.25). Patients were then grouped by the absence (normal VA and VF) or presence (abnormal VA, VF, or both) of vision loss. Wilcoxon rank-sum test was used to compare the RNFL and GCL-IPL thickness between subjects with and without vision loss. The lower fifth and lower first percentile of RNFL and GCL-IPL measures from each anatomic quadrant was determined in the normal vision group. Using logistic regression, receiver operating characteristic curves and the area under the curve (AUC) were calculated for discriminating between those with and without vision loss based on both the lower fifth and first percentile in each quadrant. Positive predictive value and negative predictive values were determined comparing the normal vision group to the abnormal group.

To evaluate the relationship between VA and GCL-IPL measures, a generalized estimating equation (GEE) approach to variance estimation was used.²⁵ The GEE model can account for the correlation between eyes of patients and determine the unadjusted and adjusted associations of GCL-IPL thickness, diagnosis (NF1 or sporadic OPG), location of OPG, and history of chemotherapy treatment with VA (logMAR below normal for age). Sample size was calculated to detect a 20% change in GCL-IPL thickness between subjects with and without vision loss. Setting the alpha value to 0.01 (based on multiple comparisons) to achieve a power of 0.9 to detect the GCL-IPL change required a total of 32 subjects eyes (16 with normal vision and 16 with abnormal vision). Data were analyzed using commercially available software (STATA, version 11; StataCorp, College Station, TX).

RESULTS

Twenty-six subjects met inclusion criteria. Five subjects contributed only one study eye due to cooperation, technical error, or poor image quality; resulting in 47 total study eyes (see Table 1 for clinical and demographic characteristics). Nineteen subjects with normal vision contributed 31 study eyes (both eyes in 12 subjects, one eye in seven subjects). Eleven subjects with abnormal vision contributed 16 study eyes (both eyes in five subjects, one eye in six subjects). Three of these subjects had one eye with normal vision and one eye with abnormal vision. Two subjects were imaged with HH-OCT while awake and 24 during sedation for their clinically indicated MRI scan. Three subjects needed corrective eyewear due to relatively mild refractive error (sphere range, -1.25 to $+2.50$). Interrater reliability for manual segmentation was classified as good for GCL-IPL and RNFL measures (ICC > 0.75 , all quadrants). Table 2 lists the RNFL and GCL-IPL thickness measures by anatomic quadrant for those with normal and abnormal vision. All comparisons differed between the groups ($P < 0.001$ for all comparisons) except the inner (3.0 mm) and center (1.5 mm) temporal RNFL ($P = 0.001$ and $P = 0.008$, respectively).

TABLE 1. Demographic and Clinical Characteristics of Children With OPGs

	Normal VA/VF, N = 31‡	Abnormal VA/VF, N = 16‡
Age*	5.3/5.2	6.1/4.3
Range	2.5–12.6	2.6–12.8
Female sex, n (%)†	10/19 (53)	5/11 (45)
Race, n (%)†		
White/Caucasian	17/19 (90)	10/11 (91)
Black/African American	1/19 (5)	—
Asian	—	1/11 (9)
Multiple races	1/19 (5)	—
Ethnicity, n (%)†		
Non-Hispanic	18/19 (95)	11/11 (100)
Hispanic	1/19 (5)	—
Diagnosis, n (%)†		
NF1 with OPG	16/19 (84)	4/11 (36)
Sporadic OPG	3/19 (16)	7/11 (67)
Location of optic pathway glioma, n (%)		
Optic nerve only	8/31 (26)	1/16 (6)
Optic chiasm and anterior	15/31 (48)	11/16 (69)
Optic tract and anterior	8/31 (26)	4/16 (25)
Category of vision loss, n (%)		
Normal VA/normal VF	31/31 (100)	—
Abnormal VA/normal VF	—	3/16 (19)
Normal VA/abnormal VF	—	6/16 (38)
Abnormal VA/abnormal VF	—	7/16 (43)

* In years mean/median and range.

† Individual subjects, not subject eyes.

‡ Subject eyes.

Logistic regression, receiver operating characteristic curves, positive predictive values, and negative predictive values were analyzed for the normal and abnormal vision groups (see Table 3). The AUC was highest for the fifth percentile GCL-IPL of inner macula (3.0 mm). Using this location and AUC as the gold standard, all other AUCs were not statistically different except for the fifth percentile RNFL outer macula (4.5 mm), fifth percentile RNFL inner macula (3.0 mm), and the first and fifth percentile RNFL center macula (1.5 mm; $P < 0.05$ for all comparisons, Bonferroni correction for multiple comparisons). Two subjects classified as having normal vision were found to have multiple GCL-IPL and RNFL values below the fifth percentile (i.e., false positives). Both subjects had OPGs located in the bilateral optic tracts and had experienced vision loss in their contralateral eye.

Table 4 lists the unadjusted and adjusted multiple regression analysis (GEE model) of the effect of GCL-IPL (inner macula 3.0 mm) thickness, diagnosis (presence or absence of NF1), treatment history, and OPG location on VA. Decreased GCL-IPL thickness and diagnosis of a sporadic (non-NF1) OPG were significantly associated with a worse VA in both unadjusted and adjusted regression models. Optic pathway gliomas isolated to the optic nerve and treatment with chemotherapy were not independently associated with poor VA but did reach significance in the adjusted analysis ($P < 0.05$ for both).

DISCUSSION

Our study demonstrated that GCL-IPL thickness has potential to be a meaningful surrogate marker of vision loss in children

TABLE 2. Retinal Nerve Fiber Layer and GCL-IPL Thickness Measures in Children With OPGs

Location	Normal Vision,* N = 31†		Abnormal Vision,‡ N = 16†
	Mean (SD)	Fifth/First Percentile	Mean (SD)
Outer, 4.5 mm			
Superior			
RNFL	36.5 (5.1)	29.4/19.4	19.1 (8.6)
GCL-IPL	70.0 (8.7)	52.0/50.5	52.1 (7.1)
Nasal			
RNFL	40.9 (8.1)	23.9/14.6	19.9 (8.2)
GCL-IPL	70.9 (9.5)	47.9/46.9	47.5 (4.8)
Inferior			
RNFL	39.6 (6.7)	23.4/19.7	20.3 (10.2)
GCL-IPL	72.2 (9.5)	51.6/49.7	52.3 (6.7)
Temporal			
RNFL	19.9 (3.7)	12.1/11.6	12.9 (5.2)
GCL-IPL	73.2 (6.3)	58.7/57.5	56.0 (8.1)
Average			
RNFL	34.3 (5.3)	22.6/16.5	18.1 (7.2)
GCL-IPL	71.6 (7.9)	52.2/51.9	52.2 (5.0)
Inner, 3.0 mm			
Superior			
RNFL	30.8 (5.0)	22.2/18.1	17.8 (7.1)
GCL-IPL	90.5 (10.5)	70.2/64.0	60.8 (6.4)
Nasal			
RNFL	28.6 (4.7)	20.6/15.9	15.5 (5.9)
GCL-IPL	92.3 (12.0)	59.8/55.7	55.9 (10.7)
Inferior			
RNFL	32.1 (4.5)	25.9/21.5	19.4 (6.4)
GCL-IPL	93.8 (9.3)	64.3/63.3	69.8 (9.0)
Temporal			
RNFL	19.5 (3.8)	11.2/10.5	14.2 (5.4)
GCL-IPL	91.8 (6.7)	76.0/73.2	63.4 (15.3)
Average			
RNFL	27.7 (4.1)	21.3/16.5	16.7 (5.3)
GCL-IPL	92.1 (9.1)	67.4/64.3	60.0 (7.9)
Center, 1.5 mm			
Superior			
RNFL	14.4 (2.6)	9.0/8.3	9.8 (2.6)
GCL-IPL	76.6 (10.6)	60.7/45.5	45.5 (12.5)
Nasal			
RNFL	13.3 (2.4)	10.0/8.3	9.4 (2.5)
GCL-IPL	72.7 (10.7)	53.9/41.3	42.5 (15.6)
Inferior			
RNFL	13.6 (2.3)	9.5/9.1	9.7 (3.3)
GCL-IPL	73.6 (10.8)	55.4/47.7	43.2 (12.8)
Temporal			
RNFL	12.8 (2.6)	7.9/7.1	10.9 (3.3)
GCL-IPL	74.9 (8.8)	64.5/45.1	47.1 (18.2)
Average			
RNFL	13.5 (2.1)	9.9/8.2	9.9 (2.2)
GCL-IPL	74.3 (9.0)	60.6/44.9	44.6 (12.8)

* Normal VA and VF.

† Subject eyes.

‡ Includes isolated VA loss, isolated VF loss, and combined VA and VF loss.

TABLE 3. Area Under the Curve and Predictive Values of RNFL and GCL-IPL Measures Used to Discriminate Between OPG Subjects With Normal and Abnormal Vision

Measurement Location	AUC† (95% CI)	PPV‡	NPV‡
Outer, 4.5 mm			
RNFL, fifth percentile	0.89 (0.76–0.96)	92.9	90.9
RNFL, first percentile	0.81* (0.66–0.90)	100	83.8
GCL-IPL, fifth percentile	0.97 (0.88–0.99)	88.9	100
GCL-IPL, first percentile	0.92 (0.82–0.98)	93.3	93.8
Inner, 3.0 mm			
RNFL, fifth percentile	0.94 (0.82–0.98)	93.8	96.8
RNFL, first percentile	0.84* (0.71–0.93)	100	86.1
GCL-IPL, fifth percentile	0.98 (0.92–1.0)	88.9	100
GCL-IPL, first percentile	0.96 (0.88–0.99)	100	96.9
Center, 1.5 mm			
RNFL, fifth percentile	0.78* (0.64–0.89)	90.9	83.3
RNFL, first percentile	0.78* (0.64–0.89)	100	81.6
GCL-IPL, fifth percentile	0.91 (0.79–0.97)	93.3	93.8
GCL-IPL, first percentile	0.90 (0.79–0.97)	100	91.2

CI, confidence interval; PPV, positive predictive value of binary variables; NPV, negative predictive value.

* $P < 0.05$ in comparison to GCL-IPL 95th percentile of inner macula (3.0 mm).

† Calculated by the number of quadrants below the fifth or first percentile.

‡ Predictive value measures based on the presence or absence of one or more abnormal quadrants.

with OPGs. For a surrogate marker to be useful, it must be robust in its ability to discriminate between groups. Our results indicate that both macular GCL-IPL and macular RNFL thickness measures were significantly decreased in children with OPG-related vision loss compared to those with normal vision. More importantly, all GCL-IPL locations demonstrated a high AUC (>0.90) indicating the ability to discriminate between those children with and without vision loss. Ganglion cell layer-inner plexiform layer of the inner macula (3.0 mm) demonstrated the highest AUC and was statistically different than the RNFL measures. Our linear regression model demonstrated a strong association between VA and GCL-IPL when considering the impact of other variables on this relationship.

Although a large multicenter longitudinal study is needed to establish that GCL-IPL thickness is a reliable surrogate marker of vision loss, our findings may be helpful when making treatment decisions in children with OPGs. The positive predictive value of the center (3.0 mm) macula demonstrated that 88.9% of those with decreased GCL-IPL thickness had vision loss. If children with normal vision demonstrate a progressive decline in their GCL-IPL thickness, this may be an indication to initiate early treatment. The positive predictive value was decreased due to two children with NF1, bilateral optic chiasm or tract OPGs, and vision loss in the contralateral eye. It is conceivable that the false positive of both subjects may be a result of undetected VF loss. The 100% negative predictive value of the center (3.0 mm) GCL-IPL measure signified that individuals with normal GCL-IPL thickness do not have vision loss. Therefore, when children cannot cooperate with VA testing, a normal GCL-IPL could be reassuring that the child's vision is normal and treatment with chemotherapy can be deferred.

The timing between a decline in GCL-IPL thickness and vision loss in children with OPGs is unknown. In subjects with traumatic optic neuropathy resulting in severe vision loss, demonstrable changes in the pRNFL and ganglion cell complex

TABLE 4. Factors Associated With VA in Univariable and Multivariable Linear Regression* for Patients With OPGs

Variable	Unadjusted Coefficient	Adjusted Coefficient	95% CI	P Value†
GCL-IPL, 3.0 mm region	−0.017‡	−0.025	−0.04 to 0.00	0.026
Diagnosis				
NF1	—	—	—	—
Sporadic	0.545‡	0.368	0.12 to 0.61	0.004
Glioma location				
Absent	—	—	—	—
Optic nerve	0.256	0.304	0.02 to 0.58	0.031
Optic chiasm§	0.283	0.080	−0.21 to 0.37	0.593
Optic tracts§	0.330	0.245	−0.08 to 0.57	0.145
Treatment status				
No treatment	—	—	—	—
Chemotherapy	0.180	−0.219	−0.40 to 0.03	0.017

* Generalized estimating equation.

† P value in adjusted analysis.

‡ Denotes P value < 0.01 in unadjusted analysis.

§ Includes structures anterior to this location.

(sum of the macular RNFL and GCL-IPL) have been reported to occur 2 to 3 weeks after the injury.^{16,26,27} Since most children with OPGs do present with profound vision loss, it is unclear if changes in OCT measures will progress at the same rate.

There are a number of advantages in imaging the macular GCL-IPL complex as compared to the pRNFL in children with OPGs. Children with OPGs isolated to the optic nerve or chiasm may present with optic nerve swelling that would falsely elevate the pRNFL thickness, whereas the GCL-IPL is unaffected by optic nerve swelling. Also, both the pRNFL and macular RNFL represent an accumulation of axons from many locations across the VF, while the GCL-IPL corresponds to a

specific location within the VF.^{18,28} This ability of GCL-IPL to localize and potentially quantitate the magnitude of VF loss could be particularly helpful, especially in young children who cannot cooperate with quantitative VF testing and who also manifest normal VA (Fig.). The macular RNFL measures are also problematic because the thickness is relatively small and less likely to show as robust of a change. Finally, the pRNFL has great between subject variability and is more influenced by blood vessels and refractive error as compared to the GCL-IPL.^{18–20,29} Despite recent data demonstrating that pRNFL measures acquired using HH-OCT are also able to discriminate between those children with and without vision loss secondary to OPGs,³⁰ a large-scale longitudinal study comprised of presymptomatic subjects who eventually develop vision loss will be required to determine which measure is the most accurate and reliable at detecting new vision loss.

Our study has a number of limitations including the cross-sectional study design, which restricts our ability to imply causality. Despite having good ICC from two raters, the manual segmentation could be prone to operator error, is time consuming, and could conceivably vary between institutions. Fortunately, multiple investigators have shown that manual segmentation of the GCL-IPL are comparable to automated segmentation.^{31–33} The young age and inability of some subjects to complete automated perimetry limited our ability to establish distinct VF deficits with localized thinning of GCL-IPL. Lastly, while the number of studies using handheld SD-OCT in the pediatric population has been increasing,^{24,34–40} the ability of SD-OCT results to improve clinical care has not been firmly established. Therefore, additional research is needed before handheld SD-OCT results can be used to make clinical decisions.

In conclusion, GCL-IPL measures were able to accurately discriminate between subjects with and without vision loss from their OPGs. To be considered a meaningful surrogate marker of vision, longitudinal studies are needed to elucidate the temporal relationship between declining GCL-IPL thickness and vision loss.

FIGURE. Eight-year-old child with a sporadic OPG, normal VA (20/20 OD/OS), VF loss, and decreased GCL-IPL thickness (green = normal, yellow < fifth percentile, red < first percentile).

Acknowledgments

The authors thank Graham Quinn, MD, for critical review of the manuscript.

Supported by the Gill Fellowship Program at The George Washington University School of Medicine (SG), the National Institutes of Health/National Eye Institute K23 EY022673-01 (RAA), the National Institutes of Health/National Eye Institute Pediatric Research Loan Repayment Program (RAA), and the Gilbert Family Neurofibromatosis Institute (RAA, RJP).

Disclosure: **S. Gu**, None; **N. Glaug**, None; **A. Cnaan**, None; **R.J. Packer**, None; **R.A. Avery**, None

References

- Avery RA, Fisher MJ, Liu GT. Optic pathway gliomas. *J Neuroophthalmol*. 2011;31:269-278.
- Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol*. 2007;61:189-198.
- North KN, Riccardi V, Samango-Sprouse C, et al. Cognitive function and academic performance in neurofibromatosis. 1: consensus statement from the NF1 Cognitive Disorders Task Force. *Neurology*. 1997;48:1121-1127.
- Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. *Lancet Neurol*. 2007;6:340-351.
- Avery RA, Bouffet E, Packer RJ, Reginald A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. *Invest Ophthalmol Vis Sci*. 2013;54:1034-1038.
- Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro Oncol*. 2012;14:790-797.
- Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007;26:688-710.
- Hood DC, Anderson SC, Wall M, Raza AS, Kardon RH. A test of a linear model of glaucomatous structure-function loss reveals sources of variability in retinal nerve fiber and visual field measurements. *Invest Ophthalmol Vis Sci*. 2009;50:4254-4266.
- Fisher JB, Jacobs DA, Markowitz CE, et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology*. 2006;113:324-332.
- Danesh-Meyer HV, Carroll SC, Foroozan R, et al. Relationship between retinal nerve fiber layer and visual field sensitivity as measured by optical coherence tomography in chiasmal compression. *Invest Ophthalmol Vis Sci*. 2006;47:4827-4835.
- Danesh-Meyer HV, Papchenko T, Savino PJ, Law A, Evans J, Gamble GD. In vivo retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after surgery for parachiasmal tumors. *Invest Ophthalmol Vis Sci*. 2008;49:1879-1885.
- Grainger BT, Papchenko TL, Danesh-Meyer HV. Optic nerve atrophy in adrenoleukodystrophy detectable by optic coherence tomography. *J Clin Neurosci*. 2010;17:122-124.
- Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254:1178-1181.
- Schuman JS, Hee MR, Puliafito CA, et al. Quantification of nerve fiber layer thickness in normal and glaucomatous eyes using optical coherence tomography. *Arch Ophthalmol*. 1995; 113:586-596.
- Sehi M, Zhang X, Greenfield DS, et al. Retinal nerve fiber layer atrophy is associated with visual field loss over time in glaucoma suspect and glaucomatous eyes. *Am J Ophthalmol*. 2012;155:73-82.
- Kanamori A, Nakamura M, Yamada Y, Negi A. Longitudinal study of retinal nerve fiber layer thickness and ganglion cell complex in traumatic optic neuropathy. *Arch Ophthalmol*. 2012;130:1067-1069.
- Walter SD, Ishikawa H, Galetta KM, et al. Ganglion cell loss in relation to visual disability in multiple sclerosis. *Ophthalmology*. 2012;119:1250-1257.
- Kardon RH. Role of the macular optical coherence tomography scan in neuro-ophthalmology. *J Neuroophthalmol*. 2011; 31:353-361.
- Hood DC, Fortune B, Arthur SN, et al. Blood vessel contributions to retinal nerve fiber layer thickness profiles measured with optical coherence tomography. *J Glaucoma*. 2008;17:519-528.
- Hood DC, Salant JA, Arthur SN, Ritch R, Liebmann JM. The location of the inferior and superior temporal blood vessels and interindividual variability of the retinal nerve fiber layer thickness. *J Glaucoma*. 2010;19:158-166.
- Avery RA, Liu GT, Fisher MJ, et al. Retinal nerve fiber layer thickness in children with optic pathway gliomas. *Am J Ophthalmol*. 2011;151:542-549.
- Chang L, El-Dairi MA, Frempong TA, et al. Optical coherence tomography in the evaluation of neurofibromatosis type-1 subjects with optic pathway gliomas. *J AAPOS*. 2010;14:511-517.
- Lambert SR, Buckley EG, Drews-Botsch C, et al. The infant aphakia treatment study: design and clinical measures at enrollment. *Arch Ophthalmol*. 2010;128:21-27.
- Maldonado RS, Izatt JA, Sarin N, et al. Optimizing hand-held spectral domain optical coherence tomography imaging for neonates, infants, and children. *Invest Ophthalmol Vis Sci*. 2010;51:2678-2685.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121-130.
- Cunha LP, Costa-Cunha LV, Malta RF, Monteiro ML. Comparison between retinal nerve fiber layer and macular thickness measured with OCT detecting progressive axonal loss following traumatic optic neuropathy. *Arq Bras Oftalmol*. 2009;72:622-625.
- Medeiros F. Axonal loss after traumatic optic neuropathy documented by optical coherence tomography. *Am J Ophthalmol*. 2003;135:406-408.
- Raza AS, Cho J, de Moraes CG, et al. Retinal ganglion cell layer thickness and local visual field sensitivity in glaucoma. *Arch Ophthalmol*. 2011;129:1529-1536.
- Curcio CA, Allen KA. Topography of ganglion cells in human retina. *J Comp Neurol*. 1990;300:5-25.
- Avery RA, Hwang EI, Ishikawa H, et al. Hand-held optical coherence tomography during sedation in young children with optic pathway gliomas. *JAMA Ophthalmol*. In press.
- Seigo MA, Sotirchos ES, Newsome S, et al. In vivo assessment of retinal neuronal layers in multiple sclerosis with manual and automated optical coherence tomography segmentation techniques. *J Neurol*. 2012;259:2119-2130.
- Sotirchos ES, Seigo MA, Calabresi PA, Saidha S. Comparison of point estimates and average thicknesses of retinal layers measured using manual optical coherence tomography segmentation for quantification of retinal neurodegeneration in multiple sclerosis. *Curr Eye Res*. 2013;38:224-228.
- Davies EC, Galetta KM, Sackel DJ, et al. Retinal ganglion cell layer volumetric assessment by spectral-domain optical coherence tomography in multiple sclerosis: application of a high-precision manual estimation technique. *J Neuroophthalmol*. 2011;31:260-264.
- Cabrera MT, Maldonado RS, Toth CA, et al. Subfoveal fluid in healthy full-term newborns observed by handheld spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2012;153:167-175.

35. Chavala SH, Farsiu S, Maldonado R, Wallace DK, Freedman SF, Toth CA. Insights into advanced retinopathy of prematurity using handheld spectral domain optical coherence tomography imaging. *Ophthalmology*. 2009;116:2448-2456.
36. Maldonado RS, O'Connell RV, Sarin N, et al. Dynamics of human foveal development after premature birth. *Ophthalmology*. 2011;118:2315-2325.
37. Scott AW, Farsiu S, Enyedi LB, Wallace DK, Toth CA. Imaging the infant retina with a hand-held spectral-domain optical coherence tomography device. *Am J Ophthalmol*. 2009;147:364-373.
38. Vajzovic L, Hendrickson AE, O'Connell RV, et al. Maturation of the human fovea: correlation of spectral-domain optical coherence tomography findings with histology. *Am J Ophthalmol*. 2012;154:779-789.
39. Muni RH, Kohly RP, Charonis AC, Lee TC. Retinoschisis detected with handheld spectral-domain optical coherence tomography in neonates with advanced retinopathy of prematurity. *Arch Ophthalmol*. 2010;128:57-62.
40. Muni RH, Kohly RP, Sohn EH, Lee TC. Hand-held spectral domain optical coherence tomography finding in shaken-baby syndrome. *Retina*. 2010;30:S45-50.