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## Retinal Nerve Fiber Layer Thickness in Children with Optic Pathway Gliomas

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### Abstract

**Purpose**—To determine the relation of high-contrast visual acuity (VA) and low-contrast letter acuity with retinal nerve fiber layer (RNFL) thickness in children with optic pathway gliomas.

**Design**—Cross-sectional convenience sample, with prospective data collection, from a tertiary care children's hospital of patients with optic pathway gliomas associated with Neurofibromatosis type 1, sporadic OPG and Neurofibromatosis type 1 without OPG.

**Methods**—Patients performed best corrected VA testing using surrounded HOTV optotypes and low-contrast letter acuity (5%, 2.5% and 1.25% low contrast Sloan letter charts). Mean RNFL thickness (microns) was measured by a Stratus optical coherence tomography (Carl Zeiss Meditec, Dublin, CA) using the fast RNFL thickness protocol. Eyes were classified as having abnormal vision if they had high-contrast VA > 0.1 logMAR or visual field loss. The association of subject age, glioma location and RNFL thickness with both VA and low-contrast letter acuity scores was evaluated by one-way analysis of variance and linear regression, using the generalized estimating equation approach to account for within-patient intereye correlations.

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**Results**—Eighty-nine eyes of patients with optic pathway gliomas were included and 41 were classified as having abnormal VA or visual field loss. Reduced RNFL thickness was significantly associated with higher logMAR scores for both VA ( $P < 0.001$ ) and all low-contrast letter acuity charts ( $P < 0.001$ ) when accounting for age and glioma location.

**Conclusions**—Eyes of most children with optic pathway gliomas and decreased RNFL thickness had abnormal visual acuity or visual field loss.

Low grade gliomas (World Health Organization grade 1 juvenile pilocytic astrocytomas and grade 2 diffuse fibrillary astrocytomas) are the most common central nervous tumor in children.<sup>1</sup> When low grade gliomas involve structures of the afferent visual pathway (i.e., optic nerve, optic chiasm, optic tract, or optic radiations), they are commonly referred to as optic pathway gliomas. Nearly 20% of children with Neurofibromatosis type 1 (NF1) develop optic pathway gliomas, and up to half can cause vision loss.<sup>2–4</sup> Optic pathway gliomas in children without NF1 are termed sporadic gliomas and are believed to be clinically more aggressive than NF1 associated optic pathway gliomas.<sup>5,6</sup>

Standard measures of high contrast visual acuity (VA)—highly dependent upon the child's cooperation—typically are used to screen and monitor vision outcomes in children with optic pathway gliomas.<sup>3</sup> Vision loss from NF1 associated optic pathway gliomas occurs at a median age of 4.9 years<sup>7</sup> and infrequently occurs after eight years of age.<sup>3</sup> Visual acuity and or visual field loss from optic pathway gliomas can occur despite improvement, stability or progression of radiographic findings. Once vision loss has occurred, it can remain stable, improve or continue to worsen regardless of radiographic changes or therapeutic intervention. Since not all optic pathway gliomas cause vision loss, treatment for an optic pathway glioma is usually initiated only after vision loss has been detected, in the hopes of preventing further vision loss, or after significant radiographic progression with associated symptoms. The management of a child with an optic pathway glioma is more challenging in the absence of knowing the child's visual acuity. Therefore, a reliable quantitative ophthalmologic tool that does not rely on patient cooperation is needed to evaluate optic pathway integrity in children with an optic pathway glioma, particularly in those who are unable to cooperate with visual acuity and visual field examinations.

The retinal nerve fiber layer (RNFL), the most proximal region of the afferent visual pathway, has been examined as a structural marker of visual integrity in patients with compressive optic neuropathy due to sellar masses<sup>8,9</sup> and demyelinating optic neuropathy from multiple sclerosis.<sup>10–13</sup> RNFL thickness, as measured by optical coherence tomography (OCT), is closely correlated with low-contrast letter acuity in patients with multiple sclerosis.<sup>10,11</sup> Studies of optic neuritis show RNFL thinning over time by OCT, yet eyes of patients with multiple sclerosis and no history of optic neuritis also have RNFL thinning.<sup>10,14</sup> To the best of our knowledge, no studies have examined whether RNFL thickness could serve as a structural marker of vision loss in children with optic pathway gliomas.

The primary aim of this study is to determine the relation of VA and low-contrast letter acuity with RNFL thickness, as measured by OCT, in children with optic pathway gliomas.

## Methods

### Patients

A cross-sectional convenience sample with prospective data collection identified candidate subjects between 6 and 21 years of age during their routine clinical visits to the neuro-ophthalmology or neuro-oncology clinics at Children's Hospital of Philadelphia from July 2009 and January 2010. Children between 6 and 17 years of age required parental/guardian

informed consent, and when appropriate child assent, prior to study enrollment. Children 18 to 21 years of age provided their own consent. Children in the NF1 associated optic pathway gliomas group were required to have both a diagnosis of NF1 based on established National Institute of Health criteria<sup>1</sup> and magnetic resonance imaging (MRI) of the brain demonstrating the presence of optic pathway gliomas. Children in the sporadic optic pathway glioma group required documented MRI findings characteristic of a low grade optic pathway gliomas or diagnostic biopsy results. For purposes of descriptive comparison and a secondary analysis, children with a diagnosis of NF1 but without optic pathway gliomas were also enrolled. Patients were excluded if they had a history of ophthalmologic or neurologic disease, other than an optic pathway gliomas, that could have affected their visual acuity or their optic nerve function (e.g., amblyopia, cataracts, glaucoma, retinopathy of prematurity, elevated intracranial pressure requiring ventriculoperitoneal shunting). Healthy control subjects with no significant history of ophthalmologic or neurologic disease were recruited. Institutional review board approval of the protocol and consent form was obtained prior to study initiation.

Using a standardized form, demographic and clinical data were collected from each patient's clinical chart including: presence of NF1, history of optic pathway gliomas treatment (i.e., chemotherapy or radiation) and visual field (VF) testing results. Findings for the most recent MRI were abstracted from the formal reading and classified as follows: no evidence of optic pathway glioma (tortuous optic nerves allowed), optic pathway glioma involving only the optic nerve, and optic pathway glioma involving the optic chiasm and posterior structures including the hypothalamus.

### Neuro-Ophthalmologic Examination

Best corrected visual acuity (VA) was determined using the electronic visual acuity (EVA) system for pediatric patients.<sup>15</sup> The subject was seated three meters from the computer monitor in a windowless room. The examination chair was elevated to a level where the subject's eyes were parallel to the center of the computer monitor. Each eye was tested separately, beginning with the right eye. First, the need for refraction was assessed. Optotypes equivalent to 20/16 were displayed. Children not able to accurately read the 20/16 line were refracted with trial lenses according to a standard protocol.<sup>16</sup> If a refraction has been performed within the past 6 months, this was the subject's starting refraction. High contrast VA was tested according to the Amblyopia Treatment Study visual acuity testing protocol with the EVA monitor placed at 3 meters.<sup>15</sup> The EVA computer monitor was calibrated for appropriate luminance prior to each testing session. Single letter (H, O, T, or V) crowded optotypes were presented in four phases: screening, phase 1 (first threshold determination), reinforcement, and phase 2 (second threshold determination). Final visual acuity was the smallest logMAR level passed in phase 1 or phase 2.

Low-contrast letter acuity testing of each eye was performed in the same windowless exam room with the lights turned off using a retroilluminated cabinet. Sloan low-contrast letter acuity charts at 5%, 2.5% and 1.25% contrast level (Precision Vision, LaSalle, IL) were presented sequentially at 2 meters. Low-contrast letter acuity score (logMAR) for each eye was determined to be the lowest line for which the subject was able to correctly identify at least three of the five letters.

### Definition of Clinical Outcomes

High contrast VA testing was used to classify eyes as having normal VA (logMAR  $\leq$  0.1, 20/25 or better) or abnormal VA (logMAR  $>$  0.1). VF loss, determined by one co-investigator (GTL), was defined as any non-central scotoma (i.e., quadrantanopia, hemianopia, visual field constriction, arcuate defect or altitudinal defect) that was reliably

detected with automated perimetry or confrontation testing. Our younger subjects, especially those with NF1, are not able to reliably complete automated perimetry, therefore the VF results were not quantified, but rather categorized as either present or absent. Type of vision loss was classified into categories: normal VA/normal VF, abnormal VA/normal VF, normal VA/abnormal VF and abnormal VA/abnormal VF. Patients with unilateral glioma of the optic nerve contributed that eye as an optic pathway glioma eye, whereas their fellow eye was classified as not having an optic pathway glioma. Both eyes were classified as having optic pathway glioma, when the optic pathway glioma was present in the optic chiasm and/or posterior structures.

### OCT Imaging

RNFL thickness (microns) of each eye was measured using the “Fast RNFL” thickness protocol with a Stratus OCT (Zeiss Meditec, Dublin CA). Scan quality was optimized before imaging each eye by adjusting the polarization. Scanning commenced when the 3.4 mm diameter circle was centered over the optic nerve head as the subject fixated on an external or internal fixation light. Scans with a signal strength less than 6 were discarded. Three scans were averaged to produce anatomic quadrant and average RNFL thickness in microns. If the pupil diameter was not sufficient to obtain OCT images successfully, mydriatic eye drops (1% tropicamide and 2.5% phenylephrine hydrochloride) were used.

### Statistical Analysis

Demographic and clinical characteristics were summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). RNFL thickness was categorized into quartiles from the optic pathway glioma patients due to the non-linear association between RNFL thickness and the measures of vision. RNFL measurements from healthy controls and NF1 patients without an optic pathway glioma were not used to calculate the quartiles and were presented for descriptive comparison.

One-way analysis of variance (ANOVA) was used to determine if high contrast VA (logMAR) and low-contrast letter acuity (logMAR) was associated with RNFL quartiles in patients with optic pathway gliomas. The generalized estimating equation (GEE) approach to variance estimation was used to account for the correlation between eyes of patients and to provide a robust estimator to accommodate for unequal variance in vision measures among RNFL groups.<sup>17</sup> Similarly, the GEE approach was also used in multiple regression analyses to examine the influence of RNFL thickness quartiles, patient age, and tumor location on both high contrast VA and low-contrast letter acuity in patients with optic pathway gliomas.

Because we were not aware of any previously published studies of RNFL thickness in children with optic pathway gliomas, sample size was calculated using RNFL data from studies of optic neuritis in multiple sclerosis.<sup>10</sup> RNFL differs by roughly 20% between patients with optic neuritis ( $80 \pm 20$  microns) and healthy controls ( $103 \pm 12$  microns). Setting the alpha to 0.01 (based on multiple comparisons) to achieve a power of 0.9 necessitates recruitment of a total of 32 eyes (16 eyes with vision loss and 16 eyes without vision loss). The multivariable model contained 4 variables and thus required a minimum of 80 study eyes (20 eyes per variable) to achieve sufficient precision.

### Results

Sixty-two patients (124 study eyes) were enrolled and attempted to complete the study procedures. OCT imaging was unsuccessful for both eyes in three patients and for one eye in

seven patients due to patient cooperation, immobile eye or facial plexiform fibroma impeding the OCT. During the study, one patient originally diagnosed to have NF1 was found to have a yet unidentified genetic mutation and this child's data were not included in the analysis. Therefore, 58 patients contributed 109 eyes to the study. Forty-eight patients (89 study eyes) had optic pathway gliomas (both eyes, N=41; one eye, N=7) and were included in the primary analysis. Fourteen NF1 subjects without an optic pathway glioma (20 study eyes; mean age 11.3 years; 65% female) and fourteen healthy control (28 study eyes, mean age 11.5 years; 64% female) subjects were enrolled. Table 1 lists the demographic and MRI findings for the NF1 associated optic pathway gliomas and sporadic optic pathway glioma patients.

Of those with NF1 associated optic pathway gliomas and sporadic optic pathway gliomas, 48 study eyes were found to have normal high contrast VA and normal VF, 12 had decreased VA ( $> 0.1$  logMAR) with a normal VF, 12 had normal VA but an abnormal VF, and 17 had both abnormal VA and abnormal visual field (Table 1). Table 2 lists the high-contrast VA, low-contrast letter acuity and RNFL thickness measures for those with normal VA and VF compared with those with abnormal VA and or VF, and healthy controls.

Average RNFL thickness in microns was divided into quartiles based on the 89 study eyes from patients with optic pathway gliomas: Top 25% (mean = 121.4, s.d. = 14.3), 51–75% (mean = 93.5, s.d. = 6.1), 26–50% (mean = 67.5, s.d. = 7.5), and 0–25% (mean = 44.7, s.d. = 6.8). One-way ANOVA of RNFL quartiles demonstrated significant between-group differences in mean values for high-contrast VA ( $F = 27.45$ ,  $P < 0.001$ ), 5% low-contrast letter acuity ( $F = 36.45$ ,  $P < 0.001$ ), 2.5% low-contrast letter acuity ( $F = 36.28$ ,  $P < 0.001$ ) and 1.25% low-contrast letter acuity ( $F = 25.53$ ,  $P < 0.001$ ).

Table 3 lists the unadjusted and adjusted multiple regression analysis of the effect of RNFL quartile, age and optic pathway glioma location on high-contrast VA in optic pathway glioma patients. In unadjusted and adjusted analysis, the bottom two RNFL quartiles were associated with worse VA scores. Figure 1 is a scatterplot of VA and average RNFL thickness. Higher RNFL thickness ( $>80$  microns approximately) was associated with uniformly normal or near normal VA, whereas lower RNFL thickness was associated with worse VA scores, but with wide variability in VA at particular RNFL thickness values.

A multiple regression analysis was repeated using 5%, 2.5%, and 1.25% low-contrast letter acuity as the dependent variable. Table 4 lists the multiple regression results for the 2.5% low-contrast letter acuity. The bottom two RNFL quartiles, as with the high-contrast VA analysis, and optic pathway glioma location in the optic chiasm significantly were associated with VA in the unadjusted analysis. In adjusted analysis, the bottom two RNFL quartiles maintained an association with worse scores for the 2.5% low-contrast letter acuity. Multiple regression analysis for the 5% and 1.25% contrast levels generated similar results (data not shown). Figure 2 is a scatter plot of 2.5% low-contrast letter acuity and average RNFL thickness as a continuous variable. A pattern similar to the one in Figure 1 was observed, having higher RNFL values associated with normal or near normal levels of low-contrast letter acuity whereas lower RNFL thickness was associated with worse scores, but with wide variability in low-contrast letter acuity at particular RNFL thickness values.

The relation between high-contrast VA and RNFL thickness and between low-contrast letter acuity and RNFL thickness, displayed in Figures 1 and 2, respectively, do not conform to a linear relationship. Because some patients with RNFL thickness less than 80 microns were able to achieve a normal high contrast VA, we examined the visual function of the eyes more closely. Figure 3 displays box plots for groups of eyes with normal VA/normal VF, abnormal VA/normal VF, normal VA/abnormal VF and abnormal VA/abnormal visual field.

Post-hoc analysis using a one-way ANOVA of RNFL thickness and category of vision loss demonstrated between-group differences ( $F = 28.28$ ,  $P < 0.001$ ).

RNFL thickness measures were comparable between NF1 patients without optic pathway gliomas (mean = 112.2, s.d. = 16.6) and healthy controls (mean = 113.3, s.d. = 15.3). A secondary analysis of the relation between high-contrast VA, low-contrast letter acuity and RNFL thickness included NF1 patients without optic pathway gliomas ( $N=20$  eyes), thereby resulting in a total of 109 study eyes. Similar to the primary analysis, multiple regression analysis demonstrated that the bottom two RNFL quartiles were associated with worse high-contrast VA ( $P < 0.001$ ) and low-contrast letter acuity ( $P < 0.001$ ) in both unadjusted and adjusted analysis.

## Discussion

This study demonstrates that most children with optic pathway gliomas and decreased RNFL thickness have abnormal VA, visual field loss or both. Some children with decreased RNFL thickness had normal high-contrast VA, but abnormal visual fields. Interestingly, other children were found to have normal VA and normal visual fields despite a significantly decreased RNFL—possibly suggesting that visual acuity or visual field loss may not have been detected with current techniques or the child has yet to manifest symptoms. On the other hand, if our vision testing was accurate, a normal RNFL thickness shows a strong relation to normal VA and visual fields. Therefore, in children who are not cooperative enough to provide a reliable sensory vision examination, a normal RNFL thickness might be reassuring to the clinician that the patient likely has a normal VA and visual field. In contrast, the finding of a reduced RNFL thickness may or may not have a strong relation to clinical visual sensory function and thus should not be taken as absolute evidence of clinically significant visual sensory dysfunction.

Our findings are similar to other studies that use OCT to correlate RNFL axonal loss with visual function.<sup>8–12</sup> Studies of patients with optic neuritis and multiple sclerosis have demonstrated a strong association between reduced RNFL thickness and reduction of high and low contrast visual acuity.<sup>10,12</sup> VA loss and VF loss associated with RNFL thinning in multiple sclerosis are indicators of axonal loss in the anterior (pregeniculate) visual pathway (i.e., optic nerve, optic chiasm or optic tract).<sup>11,12</sup> Danesh-Meyer and colleagues<sup>8</sup> have demonstrated a correlation between RNFL thickness and visual field deficits in adults with tumors compressing the optic chiasm.

Comparable to studies of optic neuritis in multiple sclerosis,<sup>10,12,14</sup> we found that low-contrast letter acuity measures had a strong relation with RNFL using the identical OCT acquisition protocol. Although not formally analyzed, we frequently noticed subtle inter-eye differences (i.e., 0.1 logMAR) in high-contrast VA testing, but discovered more robust differences using low-contrast letter acuity. One possible explanation is that our high-contrast VA protocol using the EVA can overestimate visual acuity, especially in eyes with decreased visual acuity, as compared to ETDRS letters in the clinic.<sup>18</sup> Chang and colleagues have found that children with optic pathway gliomas and normal visual acuity had normal grating acuity but impaired contrast sensitivity using sweep visual evoked potentials.<sup>19</sup> These findings suggest low contrast acuity measures, as in multiple sclerosis, may be more sensitive to visual pathway damage as compared to high contrast VA measures. Comparison of the discrimination ability between high-contrast VA and low-contrast letter acuity requires further study.

Visual evoked potentials (VEP), proposed as an objective measure of visual pathway integrity, have been used in an attempt to detect vision loss<sup>20,21</sup> or to correlate VEP with

visual acuity<sup>22</sup> in children with optic pathway gliomas. The accuracy and utility of VEPs are limited since most optic pathway gliomas involve the optic chiasm, eliminating the ability to make meaningful inter-eye comparisons as the visual pathway of both eyes are affected. Also, very subtle changes (i.e., < 5%) in VEP results can profoundly alter the sensitivity of the test and suggests that VEP is an inadequate management tool in this population.<sup>23</sup> An expert review has determined that insufficient evidence exists to use VEP for the detection or progression of visual loss in children with optic pathway gliomas.<sup>3</sup>

Our cross-sectional study design contains some degree of selection bias because we obtained a convenience sample and this may limit our interpretation of the relation between RNFL thickness and vision in optic pathway gliomas. However, one author (RAA) followed a pre-established study protocol for VA and low-contrast letter acuity testing to minimize the possibility that the examiner's knowledge of clinical diagnosis could influence the patient's performance on the tests of visual function.<sup>15</sup> Also, without knowing the within subject change in RNFL over time, we cannot exclude other factors contributing to our findings, such as the effect of chemotherapy. Longitudinal within subject measures of RNFL before and after vision loss are needed to better establish this relation.

Our secondary analysis that included data from NF1 patients without optic pathway gliomas revealed nearly identical results as the primary analysis. This secondary analysis was performed since children with NF1 frequently have cognitive delays and attention-deficit hyperactivity disorder that could influence their ability to accurately complete the high contrast VA and low-contrast letter acuity tests. Also, children with NF1 demonstrate brain MRI findings such as tortuous optic nerves that are not formally considered an optic pathway glioma, but could conceivably influence both VA and RNFL. If RNFL is to be used as a structural marker or screening tool for NF1 associated optic pathway glioma related vision loss in the future, NF1 children without optic pathway gliomas will undoubtedly be part of the screening population.

The interpretation of the RNFL values is problematic since normative data for children have not been established and our study relied on our own control subjects. We observed a wide range of RNFL, high-contrast VA and low-contrast letter acuity values in children with and without abnormal visual acuity and visual fields. This may be a result of performance variability, especially in children with NF1 and developmental delay. It is also possible that some subjects with decreased visual acuity but normal RNFL may have unrecognized amblyopia. We performed an undilated refraction to determine best corrected visual acuity rather than a cycloplegic refraction. However, if our refraction was incorrect, thus causing the patient to have worse VA, this error would only weaken, rather than strengthen the observed association between VA and RNFL. However, this is unlikely since nearly all children in this cohort benefit from a thorough neuro-ophthalmologic exam on a regular basis by one investigator (GTL), reducing the chance of overlooking a new and clinically meaningful refractive error.

Six patient eyes with normal VA and normal visual fields were found to have decreased RNFL, all of which had fellow eyes with vision loss from an optic pathway glioma affecting the optic chiasm. Two of these patient eyes were myopic, which is known to be associated with a lower RNFL.<sup>24</sup> Also, it is possible that some of these patients had an abnormal visual field that was not detected because of poor patient cooperation.

Our interpretation of the relation between RNFL and high-contrast VA is further complicated by the finding of normal high-contrast VA in children with abnormal visual fields. In most cases, this can be explained by attributing the visual field loss to chiasmal or optic tract damage. Interestingly, all but one subject with normal VA and abnormal visual

field had an RNFL below 80 microns (see Figure 3). This suggests that VA might not be the most sensitive measure in children with optic pathway gliomas, especially in younger children where VA and VF testing is difficult due to patient cooperation.

This study demonstrates that most children with an optic pathway glioma and decreased RNFL thickness have abnormal VA or visual fields from their tumors. This study suggests RNFL thickness is a rapid, non-invasive, objective quantitative measure of visual pathway integrity in children with optic pathway gliomas. If our results can be replicated in younger children, who are at the greatest risk for vision loss from their optic pathway gliomas (i.e., less than six years old), then RNFL thickness may be useful as a marker of VA in patients who are unable to cooperate with standard VA testing. OCT performed while the child is sedated, could possibly be used in this young population. Future longitudinal studies comparing serial measures of RNFL thickness need to examine whether decreasing RNFL might precede VA loss and to determine if OCT could possibly augment the clinical management of children with optic pathway gliomas.

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This study was approved by the Children's Hospital of Philadelphia IRB and was in accordance with HIPAA regulations. Written consent for the study was obtained from the patients and or their legal guardian prior study participation.

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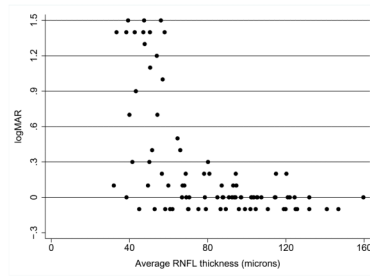
## Biographies



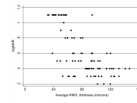
Dr. Robert A. Avery recently completed his neuro-ophthalmology fellowship at the Children's Hospital of Philadelphia/University of Pennsylvania and a Master's degree in Clinical Epidemiology at the University of Pennsylvania. In July 2010, Dr. Avery joined the faculty of the Department of Neurology and the Gilbert Family Neurofibromatosis Institute at Children's National Medical Center in Washington DC where he has a dedicated pediatric neuro-ophthalmology practice and clinical research program.



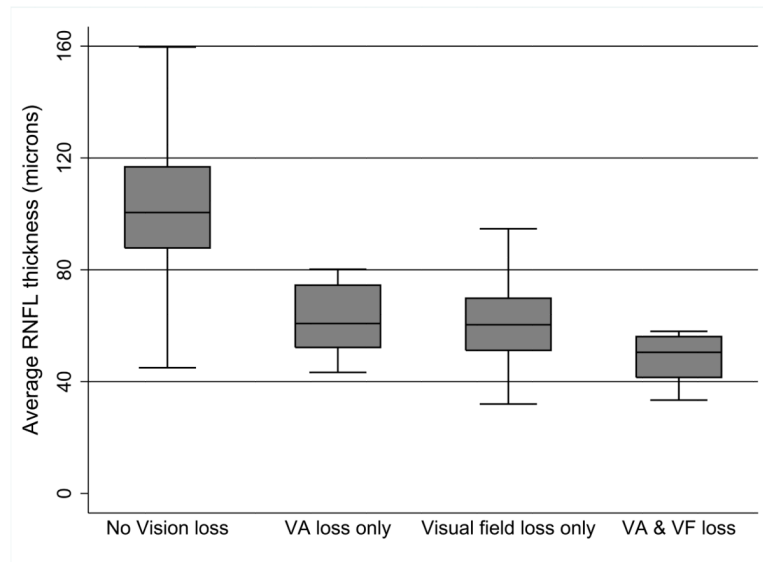
**Laura J. Balcer, M.D., M.S.C.E.**, is a Professor of Neurology, Ophthalmology and Epidemiology at the University Pennsylvania School of Medicine. She is the director of the Multiple Sclerosis Division in the Department of Neurology. Dr. Balcer's primary research focus is on the identification and development of visual and ocular imaging outcome measures for Multiple Sclerosis clinical trials.



**Figure 1.** Relation between high-contrast visual acuity and average RNFL thickness in optic pathway glioma patients. Lower logMAR represents better visual acuity. Abnormal visual acuity (i.e.,  $> 0.1$  logMAR) occurs more frequently when average RNFL thickness is below 80 microns.



**Figure 2.** Relation between 2.5% low contrast letter acuity and average RNFL thickness in optic pathway glioma patients. Lower logMAR represents better low-contrast letter acuity. Ability to identify low-contrast letters decreases when average RNFL thickness is below 80 microns.



**Figure 3.** Relation between average RNFL thickness and category of vision loss in optic pathway glioma patients. One-way analysis of variance for RNFL thickness and category of vision loss demonstrated between-group differences ( $F = 28.28$ ,  $P < 0.001$ ). Abnormal visual acuity or visual field defects primarily occur when the average RNFL thickness was below 80 microns.

**Table 1****Demographic and Clinical Characteristics of Study Eyes with Optic Pathway Gliomas.**

	<b>Study Eyes (N = 89)</b>
Age <sup>a</sup>	11.6/11.0
Range	(6.4–20.8)
Female sex – no. (%)	40 (45)
Race – no. (%)	
White/Caucasian	80 (89.9)
Black/African American	3 (3.4)
Asian	0 (0)
Multiple races	6 (6.7)
Ethnicity – no. (%)	
Non-Hispanic	89 (100)
Hispanic	0 (0)
Diagnosis – no. (%)	
NF1 with optic pathway glioma	61 (68.5)
Sporadic optic pathway glioma	28 (31.5)
Location of optic pathway glioma – no. (%)	
Optic nerve only	20 (22.5)
Optic chiasm and posterior	69 (77.5)
Category of vision loss – no. (%)	
Normal VA/normal VF	48 (53.9)
Abnormal VA/normal VF	12 (13.5)
Normal VA/abnormal VF	12 (13.5)
Abnormal VA/abnormal VF	17 (19.1)
Treatment for optic pathway glioma <sup>b</sup> – no. (%)	70 (78.7)
Age at onset <sup>c</sup>	3.6

<sup>a</sup>In years mean/median and (range);

<sup>b</sup>Includes chemotherapy, radiation or surgical debulking alone or in combination with other treatments;

<sup>c</sup>Mean age at which first treatment was initiated for study eyes.

**Table 2**

## Visual Acuity and Retinal Nerve Fiber Layer Thickness Outcomes in Eyes

	Optic Pathway Glioma Patients, Normal Vision <sup>a</sup> (N=48)	Optic Pathway Glioma Patients, Abnormal Vision <sup>b</sup> (N=41)	Healthy Control (N=28)
High Contrast <sup>c</sup>	-0.0/0.0	0.6/0.3	-0.1/-0.1
Visual Acuity	(-0.1-0.1)	(-0.1-1.5)	(-0.1-0)
Low Contrast <sup>c</sup>	0.3/0.3	0.8/0.7	0.2/0.2
Letter Acuity (5.0%)	(0.1-0.5)	(0.1-1.1)	(0.0-0.4)
Low Contrast <sup>c</sup>	0.4/0.4	0.9/0.9	0.3/0.3
Letter Acuity (2.5%)	(0.2-0.6)	(0.3-1.1)	(0.1-0.4)
Low Contrast <sup>c</sup>	0.6/0.6	1.0/1.1	0.5/0.5
Letter Acuity (1.25%)	(0.4-1.0)	(0.1-1.1)	(0.3-0.8)
Mean RNFL <sup>d</sup> (microns)	101/101 (45-159)	60/56 (32-120)	113/110 (85-155)

<sup>a</sup>Patient eyes with a normal high contrast visual acuity ( $\log\text{MAR} \leq 0.1$ ) and normal visual fields.

<sup>b</sup>Includes patients with abnormal VA/normal VF, normal VA/abnormal VF or abnormal VA/abnormal VF.

<sup>c</sup>Mean/median logMAR and range in parenthesis.

<sup>d</sup>Mean/median RNFL thickness and range in parenthesis.

**Table 3**

Factors Associated with High Contrast Visual Acuity in Univariable and Multivariable Linear Regression for Patients with Optic Pathway Gliomas.

Variable	Unadjusted Coefficient	Adjusted Coefficient	95% Confidence Interval	P <sup>a</sup>
RNFL Quartile				
76–100%	Reference	Reference	...	...
51–75%	0.034	0.034	−0.06, 0.13	0.489
26–50%	0.192 <sup>b</sup>	0.240	0.05, 0.43	<b>0.014</b>
0–25%	0.857 <sup>c</sup>	0.882	0.64, 1.13	<b>&lt;0.001</b>
Age	−0.012	−0.014	−.03, 0.01	0.242
Optic pathway glioma location				
Optic Nerve	Reference	Reference	...	...
Optic Chiasm and Posterior	0.104	0.044	−0.17, 0.09	0.504

<sup>a</sup>P-value in adjusted analysis.

<sup>b</sup>Denotes P-value <0.05 in unadjusted analysis.

<sup>c</sup>Denotes P-value <0.01 in unadjusted analysis.



**Table 4**

Factors Associated with 2.5% Low Contrast Letter Acuity in Univariable and Multivariable Linear Regression for Patients with Optic Pathway Gliomas.

Variable	Unadjusted Coefficient	Adjusted Coefficient	95% Confidence Interval	P <sup>a</sup>
RNFL Quartile				
76–100%	Reference	Reference	...	...
51–75%	0.029	0.026	–0.05, 0.10	0.513
26–50%	0.25 <sup>c</sup>	0.26	0.15, 0.37	<0.001
0–25%	0.595 <sup>c</sup>	0.597	0.49, 0.70	<0.001
Age	–0.001	–0.007	–0.02, 0.01	0.365
Optic pathway glioma location				
Optic Nerve	Reference	Reference	...	...
Optic Chiasm and posterior	0.182 <sup>b</sup>	0.001	–0.08, 0.08	0.994

<sup>a</sup>P-value in adjusted analysis.

<sup>b</sup>Denotes P-value <0.05 in unadjusted analysis.

<sup>c</sup>Denotes P-value <0.01 in unadjusted analysis.