Optic pathway glioma volume predicts retinal axon degeneration in neurofibromatosis type 1

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ABSTRACT

Objective: To determine whether tumor size is associated with retinal nerve fiber layer (RNFL) thickness, a measure of axonal degeneration and an established biomarker of visual impairment in children with optic pathway gliomas (OPGs) secondary to neurofibromatosis type 1 (NF1).

Methods: Children with NF1-OPGs involving the optic nerve (extension into the chiasm and tracts permitted) who underwent both volumetric MRI analysis and optical coherence tomography (OCT) within 2 weeks of each other were included. Volumetric measurement of the entire anterior visual pathway (AVP; optic nerve, chiasm, and tract) was performed using high-resolution T1-weighted MRI. OCT measured the average RNFL thickness around the optic nerve. Linear regression models evaluated the relationship between RNFL thickness and AVP dimensions and volume.

Results: Thirty-eight participants contributed 55 study eyes. The mean age was 5.78 years. Twenty-two participants (58%) were female. RNFL thickness had a significant negative relationship to total AVP volume and total brain volume ($p < 0.05$, all comparisons). For every 1 mL increase in AVP volume, RNFL thickness declined by approximately 5 microns. A greater AVP volume of OPGs involving the optic nerve and chiasm, but not the tracts, was independently associated with a lower RNFL thickness ($p < 0.05$). All participants with an optic chiasm volume >1.3 mL demonstrated axonal damage (i.e., RNFL thickness <80 microns).

Conclusions: Greater OPG and AVP volume predicts axonal degeneration, a biomarker of vision loss, in children with NF1-OPGs. MRI volumetric measures may help stratify the risk of visual loss from NF1-OPGs. *Neurology*® 2016;87:2403-2407

GLOSSARY

AVP = anterior visual pathway; **NF1** = neurofibromatosis type 1; **OCT** = optical coherence tomography; **OPG** = optic pathway glioma; **RNFL** = retinal nerve fiber layer.

Optic pathway gliomas (OPGs), low-grade gliomas intrinsic to the anterior visual pathway (AVP; optic nerve, chiasm, or tracts), develop in nearly 20% of children with neurofibromatosis type 1 (NF1).¹ These tumors cause vision loss in no more than half of children with NF1.^{1,2} The clinical monitoring and treatment decisions for children with OPGs secondary to NF1 requires frequent MRIs and ophthalmologic examinations.¹ To date, no clinical or radiologic features have been helpful in identifying which children are at highest risk of vision loss.²

Change in NF1-OPG size after treatment does not help identify which children will experience a more or less favorable visual outcome.³⁻⁵ Past studies used qualitative or rudimentary measurements of tumor size, neither of which provide an accurate assessment of these diffuse and amorphous tumors.⁶ Furthermore, the lack of standardized ophthalmic testing needed to quantitatively evaluate vision loss has likely muddled the comparison between structural (i.e., MRI) and functional (i.e., vision) outcomes.^{7,8}

Modern brain and ophthalmologic imaging techniques can solve the aforementioned challenges by providing automated quantitative measurements of tumor size and visual outcomes,

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respectively. Novel volumetric MRI segmentation algorithms can now perform comprehensive measurements of discrete structures along the AVP.^{9–11} Retinal nerve fiber layer thickness (RNFL), measured by optical coherence tomography (OCT), is an assessment of AVP axonal damage and is an established biomarker and visual outcome measure for children with NF1-OPGs.^{12–14}

In this study, we investigated whether OPG size is related to axonal damage of the AVP in children with NF1.

METHODS **Participants.** Children with NF1 who were receiving clinical care in the neurofibromatosis clinic at Children's National Health System were eligible for inclusion in this convenience sample. This cross-sectional analysis identified patients with NF1 who had undergone OCT as well as MRI that included a high-resolution T1-weighted sequence. Children with known OPGs secondary to NF1 undergo MRI as part of their routine clinical monitoring. To be included in this study, the patient had to meet all of the following criteria: (1) diagnosis of NF1 using established criteria¹⁵; (2) OPG involving the optic nerve (concurrent involvement of the optic chiasm and tracts was permitted); (3) technically sufficient OCT scan of the circumpapillary RNFL acquired during the clinical visit or induction for a sedated MRI scan; (4) acquisition of T1-weighted volumetric MRI sequences ($\sim 0.4 \times 0.4 \times 0.6$ mm³) that permitted visualization of the AVP without metallic artifact (e.g., dental hardware) or patient movement; (5) OCT acquisition during or within 2 weeks of the MRI acquisition; and (6) absence of conditions (current or past), other than their NF1 and OPG, that could alter their brain volume or visual pathway. Patients with previously reported MRI volumetric measures were included in this cohort.⁹

Standard protocol approvals, registrations, and patient consents. This retrospective study was approved by the Children's National Health System institutional review board.

MRI volumetric analysis. Gadolinium contrast-enhanced high-resolution T1-weighted MRI data were acquired using GE Optima MR450w, Discovery MR450, and Discovery MR750 scanners (GE Medical Systems, Waukesha, WI). MRI segmentation and volumetric analysis was performed as previously described.^{9,16} Briefly, both optic nerves, the optic chiasm, and the proximal portion of the optic tracts were manually segmented using the MRI sequence. Segmentation of the optic tracts was limited to 10 millimeters beyond the chiasm as reliable visualization beyond this point was variable among patients. Next, the automated software measured the volume of each individual structure along the AVP (i.e., optic nerve, chiasm, and tracts) which, added together, represented a total volume of the AVP. The dimensions of each optic nerve (average and maximum diameter) and the optic chiasm (height and width) were calculated. Brain volume was calculated from the same MRI sequence using a previously established technique.¹⁷

Optic coherence tomography. Spectral-domain OCT was acquired using either a tabletop (Spectralis; Heidelberg Engineering, Heidelberg, Germany) or hand-held (Bioptigen Envisu; Morrisville, NC) device using previously published protocols.^{13,18} Using the

manufacturer-supplied Nsite Analytics software (version 5.6.3.0), the Spectralis OCT scans were acquired at high speed and centered a 3.5-millimeter circle over the optic nerve head to measure the circumpapillary RNFL. The highest image quality scan without segmentation errors was chosen for that visit. Hand-held OCT acquired a $6 \times 6 \times 2$ mm volume scan centered over the optic nerve using recommended guidelines.¹⁹ Our custom software placed a 3.45-millimeter circle over the geometric center of the optic nerve to measure the circumpapillary RNFL.²⁰ Scans with a quality index below 20 were excluded from analysis.²¹ All OCT scans were manually inspected for acquisition and segmentation errors, and then corrected as necessary. The average RNFL thickness, rather than individual anatomic quadrants, was reported for this study.

Statistical analysis. Descriptive statistics were reported as mean/median (range) for continuous variables and as percentages for categorical variables. Participants could contribute either one or both eyes, as long as the OPG involved that optic nerve. To assess the influence of OPG measurements, total brain volume, and OPG location (optic nerve only, chiasm $\pm$ optic nerve, or optic tract $\pm$ chiasm/nerves) on RNFL thickness measures, unadjusted and adjusted linear regression models that accounted for the correlation between eyes were used.²² Independent variables whose level of significance did not reach $p < 0.05$ during unadjusted analysis were dropped from subsequent adjusted analysis. The diagnostic value of detecting an abnormal RNFL thickness (i.e., <80 microns) was also assessed.

RESULTS Thirty-eight participants contributed 55 study eyes. The mean age was 5.78 years (range 2.65–12.90 years). Twenty-two participants (58%) were female. Twenty-six participants (68%) had been observed without intervention, while 9 (24%) had previously been treated with chemotherapy and 3 (8%) were currently undergoing treatment. All participants were undergoing MRI as part of their routine surveillance. With the exception of 2 participants who could not reliably complete quantitative visual acuity testing, none of the MRIs was performed within 6 months of the participant experiencing vision loss. OCT imaging was performed using a tabletop platform in 30 participants (80%) compared to 8 (20%) that were acquired using a hand-held OCT. OPGs were isolated to the optic nerve ($n = 26$), involved the optic nerve and chiasm ($n = 17$), or included the optic nerve, chiasm, and tracts ($n = 12$).

When analyzing the entire cohort, RNFL thickness declined as both total AVP volume and total brain volume increased in both unadjusted and adjusted regression models ($p < 0.05$, all comparisons, table). For every 1-milliliter increase in AVP volume, RNFL thickness declined by approximately 5 microns. A greater volume of OPGs involving the optic nerve and chiasm, but not the tracts, was independently associated with a lower RNFL thickness ($p < 0.05$). An AVP volume greater than 3.0 milliliters was highly diagnostic (positive predictive value 87%) of an abnormal RNFL (i.e., <80 microns).

Table Factors associated with circumpapillary retinal nerve fiber layer thickness in univariable and multivariable linear regression for all participants with optic pathway gliomas secondary to neurofibromatosis type 1

Variable	Unadjusted coefficient	Adjusted coefficient	95% Confidence interval	p ^a
AVP volume	-5.94 ^b	-4.23	-7.71 to -0.74	0.018
Brain volume	-0.05 ^b	-0.038	-0.07 to -0.01	0.015
OPG location ^c				
Optic nerve	Reference	Reference	Reference	Reference
Optic chiasm	-14.35 ^d	-13.41	-24.08 to -2.74	0.015
Optic tract	-18.64 ^b	-8.00	-21.64 to 5.63	0.244

Abbreviations: AVP = anterior visual pathway; OPG = optic pathway glioma.

^ap Value in adjusted analysis.

^bDenotes $p < 0.01$ in unadjusted analysis.

^cDenotes most posterior location of the OPG.

^dDenotes $p < 0.05$ in unadjusted analysis.

When the AVP volume was below 3.0 milliliters, a normal RNFL (i.e., >80 microns) was highly likely (negative predictive value 94%).

RNFL thickness was not associated with average optic nerve diameter, maximum optic nerve diameter, or optic nerve volume ($p > 0.05$, all comparisons) in participants with OPGs isolated to the optic nerve ($n = 26$).

For OPGs involving both the optic nerve and chiasm ($n = 17$) without extension into the optic tract, RNFL thickness was decreased in participants with a higher AVP volume in unadjusted regression models ($p < 0.05$). Brain volume was not related to RNFL thickness in this group ($p > 0.05$). The volume of the optic chiasm with and without including the optic nerve volume was higher in those participants who demonstrated a lower RNFL thickness ($p < 0.05$). A greater optic chiasm width, but not height, was found in participants with a lower RNFL thickness ($p < 0.05$), even when controlling for brain volume. When the chiasm volume exceeded 1.3 milliliters, it was diagnostic (positive predictive value 100%) of an abnormal RNFL. When the chiasm volume was below 1.3 mL, a normal RNFL was likely (negative predictive value 95%).

Both a greater total AVP volume and a greater optic tract volume was found in participants with a lower RNFL thickness ($p < 0.05$, respectively) whose OPGs involved the entire AVP (i.e., optic nerve, chiasm and tracts, $n = 12$). Brain volume was not related to RNFL thickness in this group.

To determine whether optic tract involvement is an independent factor contributing to RNFL decline, the analysis was repeated considering OPG location (i.e., optic chiasm vs tract). OPG involvement in the optic tracts did not demonstrate a relationship to RNFL thickness in unadjusted and adjusted

analysis that considered total AVP volume, optic chiasm volume, and optic chiasm width ($p > 0.05$, all comparisons).

Post hoc analysis compared the presence of visual acuity loss (i.e., 0.2 logMAR above normal for age) or visual field loss to MRI and OCT measures. All participants with visual acuity or visual field loss had a RNFL thickness below 80 microns. For participants able to perform quantitative visual acuity testing, a worse visual acuity (i.e., higher logMAR values) was predicted by a greater OPG volume, AVP volume, and chiasm width ($p < 0.05$, all comparisons).

DISCUSSION Our study indicates that most children with a larger NF1-OPG and AVP, as measured by quantitative volumetric MRI segmentation, demonstrate damage to the axons of the AVP. Equally as important, participants with relatively smaller OPGs and AVP did not demonstrate axonal damage, suggesting that tumor size is indeed a risk factor for vision loss. Interestingly, total brain volume also increased the risk of vision loss, even when controlling for the influence of OPG volume. A prior study has reported that clinical measures of macrocephaly (i.e., head circumference measures) were associated with a higher prevalence of OPGs, but not damage to the AVP.²³ Our findings that a larger brain volume independently increased the risk of damage to the visual system suggest a common mechanism may also drive OPG growth. We can only hypothesize that the biallelic inactivation of the NF1 gene found in NF1-OPGs may be partially responsible for this observation.²⁴

Our findings that a smaller OPG volume indicates a reduced risk of damage to the visual system could be helpful in clinical management. If future studies can validate our results, the frequency of MRI and vision examinations could possibly be reduced for OPGs with smaller volumes since their chance of vision loss would be low. On the other hand, OPGs with greater volumes that carry a higher risk of AVP damage could be monitored much more closely and even be potential candidates for earlier therapeutic intervention with the hopes of preventing vision loss.

To our knowledge, no studies have directly examined the relationship between the size of the NF1-OPG and its clinical outcome. Most studies have evaluated the change in tumor size, as defined by subjective radiologic interpretation, and found that both increases and decreases in OPG size were associated with both improvement and declines in vision.³⁻⁵ This lack of association between tumor change and visual outcomes may be due to a lack of objective quantitative MRI analysis and variable visual acuity assessments both within and between studies. Our study utilized 2 objective continuous outcome measures, OPG volumetrics and RNFL thickness, neither

of which is influenced by subjective interpretation or patient cooperation with testing.^{9,25} However, even our post hoc analysis demonstrated that a worse visual acuity was predicted by greater OPG and AVP volumes. RNFL thickness is an ideal measure since it provides a comprehensive assessment of AVP integrity that can identify deficits on high-contrast visual acuity, low-contrast visual acuity, and visual field testing.¹⁴ Based on the results of our study, these 2 objective quantitative measures may best help elucidate the relationship between OPG size and visual outcomes.

Previous studies have suggested that OPG involvement in the optic chiasm vs the optic tract carries a higher risk of vision loss.^{3,5,14,26–28} Despite the optic tracts demonstrating a statistically significant increased risk of vision loss compared to the optic chiasm in these studies, the positive predictive value is less than chance.³ Our data do not support increased risk of vision loss from optic tract involvement, but instead suggest that OPG and AVP volume along with total brain volume are highly predictive of damage to the visual pathway. It is important to note that our volumetric measurements of the optic tract were restricted to 10 millimeters posterior to the chiasm, due to poor visualization, and may have influenced our results. While optic tract involvement was not independently related to RNFL thickness, this may be due to our relatively small number of participants with optic tract involvement and vision loss.

A number of limitations should be considered when interpreting the results of our study. First, selection bias is always possible when retrospectively analyzing a convenience sample. Participant ascertainment was based on availability of imaging studies, which fortunately produced demographic characteristics and tumor locations that were comparable to other NF1-OPG studies.^{3,28} Second, the MRIs were performed at different times during the clinical course (i.e., during observation vs treatment vs post treatment). Despite the heterogeneity in the timing of study inclusion and the known longitudinal variability of MRI features (i.e., size, contrast enhancement), our results were robust, arguing that these factors may not have a significant effect. Alternatively, some NF1-OPGs are known to regress spontaneously or after treatment with chemotherapy, both of which would have weakened the relationship between RNFL thickness and MRI volumes. In these cases, RNFL thickness would either remain stable or decline, but it would never be expected to increase. As long as visual acuity remains stable, longitudinal OCT measures remain static as well. Finally, accurate volumetric segmentation of small structures (e.g., optic nerve) requires high-resolution T1-weighted MRI sequences, which may not be routinely performed at all centers. To address this barrier, our

laboratory is developing novel processing algorithms that combine multiple sequence types to permit accurate AVP segmentation.¹⁶

We limited our study to children with OPGs secondary to NF1 as their imaging features and factors used to make treatment decisions can be different from sporadic OPGs.² Sporadic OPGs cause more severe and frequent events of vision loss.² Sporadic OPGs tend to have combined cystic and solid components that make MRI segmentation more challenging but not impossible.^{10,11} It is unclear whether the volume or size of sporadic OPGs affects RNFL thickness.

For young children who cannot cooperate with vision testing or OCT acquisition using tabletop devices, hand-held OCT can be acquired during sedation for a clinically indicated MRI.^{13,18} While hand-held OCT imaging sessions can be completed within a few minutes, they may not be feasible at all centers given the additional ophthalmology imaging staff required and the necessary coordination with the sedation and radiology teams. If OCT is proven to be a reliable outcome measure, the additional effort to acquire these images may be justified, especially in children whose treatment decisions are complicated by the absence of reliable functional measures (i.e., visual acuity or visual fields).

Our study demonstrated that children with larger NF1-OPGs and AVP, along with larger brain volumes, have more damage to the axons of the visual pathway. These findings argue against a long held belief that any NF1-OPG, regardless of size, could cause vision loss. If multicenter prospective studies can confirm our findings, they will not only elucidate the pathologic mechanism of OPGs, but more importantly provide much-needed guidance for clinical and radiographic monitoring of these challenging tumors.

AUTHOR CONTRIBUTIONS

Dr. Avery: drafting and revising the manuscript, study concept and design, analysis and interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. Mansoor: drafting and revising the manuscript, study concept and design, analysis and interpretation of data. R. Idrees: drafting and revising the manuscript, analysis and interpretation of data, acquisition of data. C. Trimboli-Heidler: drafting and revising the manuscript, analysis and interpretation of data, acquisition of data. Dr. Ishikawa: drafting and revising the manuscript, study concept and design, analysis and interpretation of data. Dr. Packer: drafting and revising the manuscript, study concept and design, analysis and interpretation of data, obtaining funding. Dr. Linguraru: drafting and revising the manuscript, study concept and design, analysis and interpretation of data, acquisition of data, study supervision, obtaining funding.

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DISCLOSURE

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