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The Role of Magnetic Resonance Imaging in Diagnosing Optic Nerve Hypoplasia

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Abstract

Purpose—To establish objective lower limits of normal optic nerve (ON) size in children based on high-resolution orbital magnetic resonance imaging (MRI).

Design—Case control study of patients with ON hypoplasia vs. normal controls.

Methods—A neuroradiologist made four measurements of each ON at two locations (5 mm posterior to the optic disc and just posterior to the optic canal) in patients with ON hypoplasia and controls aged 0–17 years from an academic eye center and children’s hospital. Primary analyses were performed using mixed linear models.

Results—Measurements were made in 26 cases of clinically confirmed ON hypoplasia and 31 controls (Median age: ON hypoplasia, 1 year; controls, 5.5 years). 9/26 (35%) cases and 19/31

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(61%) controls underwent high-resolution T2-weighted imaging of the orbits. Mean ON diameter was 1.36 mm (95%CI: 1.19–1.54;p<0.001) smaller for clinically hypoplastic ONs than for controls. Optic nerve diameter increased by 0.05 mm per year of age (95%CI: 0.03–0.07;p<0.001). A lower bound to the 95% prediction interval for normal optic nerves was $[2.24 \text{ mm} + 0.052 \times (\text{age in years})] \text{ mm}$ and excluded all but one case.

Conclusions—Age was independently associated with normal ON size by MRI and should be taken into consideration when evaluating ON hypoplasia, based on MRI criteria. We have provided a formula to assist clinicians in objectively determining if ON hypoplasia is present.

Introduction

Optic nerve (ON) hypoplasia is a leading cause of childhood visual impairment in the United States and Europe.^{1,2,3} Children with bilateral ON hypoplasia usually present in infancy with poor vision and nystagmus, while unilateral or asymmetric ON hypoplasia may be detected later due to strabismus.^{4,5} Indirect ophthalmoscopy is usually sufficient to diagnose severe ON hypoplasia, but in mild to moderate cases, diagnosis is more challenging. Even when the optic disc is seen or fundus photography is obtainable, apparent optic nerve size may be misinterpreted due to distortion from refractive error or variability in the axial length of the globe.⁶

While magnetic resonance imaging (MRI) is usually obtained for known or suspected ON hypoplasia to evaluate a child for associated central nervous system abnormalities, few studies have investigated the usefulness of MRI as a diagnostic modality for ON hypoplasia^{7,8,9} and none have used objective measurements of optic nerve size in a large group of known ON hypoplasia patients with matched controls. Our goals were to evaluate the role of high-resolution, orbital MRI in documenting optic nerve size, compare optic nerve size of ON hypoplasia cases and controls, and to attempt to establish a lower limit of normal for optic nerve size in a pediatric population based on MRI imaging.

Materials and Methods

Emory University Institutional Review Board approval was obtained for this retrospective and prospective case-control series performed at two tertiary referral centers, the Emory Eye Center and the Children's Healthcare of Atlanta at Egleston Department of Radiology. The Emory University IRB approved retrospective chart review for case patients at the Emory Clinic and at Children's Healthcare of Atlanta at Egleston and the prospective enrollment of control patients utilizing approved Informed Consent and Assent documents. The study was conducted in accordance with Health Insurance Portability and Accountability Act regulations. The records of pediatric patients (age 0–17 years) with the diagnosis of optic nerve hypoplasia were retrospectively collected via a query of two electronic databases, one within the Emory University School of Medicine Department of Ophthalmology and the other within the Children's Healthcare of Atlanta at Egleston Department of Radiology that queried MRI reports. The Emory Eye Center database was queried from 2009–2011 using the ICD-9 code 743.10 for optic nerve hypoplasia. The Children's Healthcare of Atlanta at Egleston Department of Radiology database was queried for the same time period using a keyword search for “optic nerve hypoplasia.” The ophthalmic medical records of the

patients identified at Emory Eye Center were then retrospectively reviewed to confirm the clinical diagnosis of ON hypoplasia and to ensure that each patient did not meet any exclusion criteria. Exclusion criteria consisted of any abnormality of the central nervous system or eye other than isolated ON hypoplasia, history of brain or ocular surgery, prematurity (<34 weeks), or history of conditions associated with increased intracranial pressure (e.g., meningitis, hydrocephalus). The results of the Radiology database search were reviewed to ensure patients had had an MRI of the orbits that included a volumetric, heavily T2-weighted orbital sequence. Results from both sites were then cross-referenced to ensure that all study patients had clinically documented ON hypoplasia and appropriate MRI sequences available for review. All patients clinically diagnosed with optic nerve hypoplasia at Emory Eye Center are referred for neuroimaging consisting of an MRI brain and orbits with and without gadolinium as part of their routine management to rule out any associated central nervous system abnormality.

Control patients were prospectively enrolled. Informed consent was obtained from the parents of all study participants. Control cases consisted of patients undergoing MRI of the brain for neurologic indications not expected to affect the optic nerves. Children receiving sedation had a complete history and physical exam performed by the sedating physician; otherwise, parents documented a brief past medical history and list of medications for their child. The MRI requisition completed by the referring physician was reviewed. For patients not meeting exclusion criteria, consent to perform an additional volumetric heavily T2 weighted sequence through the orbits was then obtained from the accompanying parent by a pediatric neuroradiologist (ND). Control patients were scanned on either a Siemens 3.0T TrioTim (Erlangen, Germany) or Siemens 1.5T Aera (Erlangen, Germany). All control patients with the exception of one, regardless of scanner, underwent a 3D T2 Sampling Perfection optimized Contrasts using different flip angle Evolutions (SPACE) sequence (TR/TE/ST 1090/73/0.3, matrix 320×274 at 3.0T or 1200/266/0.6, matrix 320×323 at 1.5T) through the orbits. One patient underwent a 3D T2 Constructive Interference in Steady State (CISS) sequence (TR/TE/ST 5.34/2.37/0.4, matrix 320×323 at 1.5T) through the orbits.

A pediatric neuroradiologist (ND) reviewed the noted MRI sequence through the orbits for case and control patients. The neuroradiologist was blinded to the clinical diagnosis including the clinical laterality of ON hypoplasia and the original radiology report in retrospective cases. For each case patient, only the T2-weighted sequence through the orbits was reviewed, whereas for the control patients, brain and orbit images were reviewed. Images of the orbits were then loaded into an advanced, post-processing software program (General Electric Advanced Workstation version 4.0, GE Healthcare, Little Chalfont, United Kingdom) within our institution's patient archiving and communication systems (PACS). Before measuring the optic nerve, the neuroradiologist recorded whether or not subjective ON hypoplasia was present and on which side.

Bilateral measurements of the optic nerves were taken 5 mm posterior to the optic disc (intraorbital segment) and immediately posterior to the optic canal (prechiasmatic segment). Steps employed to ensure accurate and reproducible measurements orthogonal to the plane of the nerve included the following: For the intraorbital segment, a crosshair tool aligned along the anterior-posterior oblique plane of the nerve was used to reconstruct the nerve at

0.4–0.6 mm slice thickness in the orthogonal coronal oblique plane 5 mm posterior to the optic disc (Figure 1). Within this plane, craniocaudal and transverse measurements were obtained on magnified images. Post-processing was used to obtain an orthogonal measurement of the nerve. For the prechiasmic segment, the cross hair tool was aligned along the transverse oblique plane; the transverse measurement of the nerve was taken on magnified images immediately posterior to the posterior margin of the optic canal (Figure 2). Post processing reconstruction to the craniocaudal axis was used to estimate the craniocaudal height just posterior to the posterior margin of the optic canal (Figure 3).

Discrete margins of the nerve were required for measurements to be obtained. If the measurement could not be satisfactorily performed at the intended level or reasonably within 1–2 mm of the intended location, the nerve was deemed not measurable. The size of the optic canal in the transverse oblique plane was also recorded on the axial images. Once all measurements were recorded, the neuroradiologist reviewed his subjective preliminary diagnosis as to the presence and laterality of ON hypoplasia and determined whether or not the objective measurement would change his initial diagnosis. If applicable, a change in diagnosis was then recorded. Thirteen patients (26 eyes) consisting of a mix of cases and controls were randomly selected and remeasured in a masked fashion by the neuroradiologist. Patient demographics including sex and age of the patients at the time of the MRI study were also recorded.

Statistical analysis

R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, <http://www.R-project.org>) was used for statistical analysis. Medians and interquartile ranges (IQRs) were reported for continuous data and percentages were reported for categorical data. Continuous variables were compared using the Mann-Whitney U or Kruskal-Wallis tests, as appropriate. Categorical variables were compared using χ^2 or Fisher exact test, as appropriate. Random intercept (for subject) mixed linear regression modeling was used for multivariate control with outcome of the mean of the five optic nerve measurements (craniocaudal and transverse intraorbital optic nerve, craniocaudal and transverse prechiasmic, and transverse oblique optic canal). Intraclass correlation coefficients (ICC) were calculated to evaluate intraobserver agreement. P-values less than 0.05 were considered significant.

Results

One hundred and twenty-five Emory Eye Center charts retrieved using the ICD-9 Code 743.10 (optic nerve hypoplasia) search 2009–2011 were reviewed (Figure 4). Of these patients, 55/125 (44%) had a clinical diagnosis of ON hypoplasia and documentation that MRI of the brain and orbits was performed. Thirteen of the 55 (24%) had appropriate MRI imaging sequences available for review at Children's Healthcare of Atlanta at Egleston. Given the low yield of this search, the database of the Children's Healthcare of Atlanta at Egleston Department of Radiology was also queried using the same diagnosis code but for the time period 2007–2011. 54/239 (23%) patients identified had the necessary imaging sequences available for review, and 22/54 (41%) had clinic notes available in the Emory Eye

Center system. The patient lists resulting from the database searches at both institutions were cross-referenced and, once duplicates were excluded, a total of 26 cases with both retrievable clinical notes and the necessary MRI sequences confirming ON hypoplasia in one or both eyes had been identified.

Cases included 13 male and 13 female study patients with a median age of 1.1 years. In all 26 cases, the presenting complaint was eye misalignment, nystagmus, or apparent poor vision. Patients in the study group had undergone several similar types of volumetric high resolution T2 sequences either at a magnet strength of 1.5T or 3.0T as these patients underwent MRI at different time points over multiple years. Twelve patients underwent a 3D T2 Fast Imaging Employing Steady State Acquisition (FIESTA) sequence on a 1.5T GE Signa Excite. Four patients underwent a 3D T2 SPACE sequence and five patients underwent a 3D T2 CISS sequence on a 3.0T Siemens TrioTim.

Forty-two controls were screened of whom 12 were excluded (6 due to motion artifact, 3 due to improper MRI sequence parameters, 1 with irretrievable images, 1 with previously abnormal MRI, and 1 with Hemoglobin SC disease). Therefore, 30 control patients were analyzed (20 male/ 10 female, median age: 5.5 years). Indications for MRI included seizure without other medical problems, headache, and altered mental status. All control patients had normal MRI brain examinations and without abnormality on the obtained 3D T2 SPACE sequence through the orbits. Nineteen controls (63%) were evaluated using a 3.0 T magnet while the remainder were done using a 1.5 T magnet. Intraobserver reliability for optic nerve measurements was very high (ICC: 0.98; 95%CI: 0.965–0.992).

Based on linear mixed effects modeling controlling for age, case status, and magnet strength, mean optic nerve measurement was 1.36 mm (95% CI: 1.19–1.54; $p < 0.001$) smaller for clinically hypoplastic ONs than for controls (Table). Non-clinically affected optic nerves in patients with unilateral clinical ON hypoplasia had measurements that were 0.22 mm (95% CI: 0.002–0.44; $p = 0.047$) smaller than controls. ON size increased by 0.05 mm per year (95% CI: 0.03–0.07; $p < 0.001$). The linear lower bound to the 95% prediction interval for normal ONs was $[2.24 \text{ mm} + 0.052 \times (\text{age in years})]$ mm and discriminated all cases but one (Figure 5).

Discussion

We found ON hypoplasia can be quantified by MRI and propose an age dependent cutoff for diagnosis of ON hypoplasia based on MRI of $[2.24 \text{ mm} + 0.052 \times (\text{age in years})]$ based on the 95% prediction interval for normal optic nerves. We found that the mean optic nerve measurement on MRI was 1.36 mm smaller for clinically hypoplastic nerves than for controls. In addition, we found that MRI was sensitive enough to detect that the non-clinically hypoplastic optic nerve in the fellow eye of children with unilateral clinical ON hypoplasia was 0.22 mm smaller than that of control eyes.

Our findings are novel and relevant because MRI imaging of the brain and orbits is usually obtained only to evaluate a child for other central nervous system abnormalities in the setting of a clinical diagnosis of ON hypoplasia, rather than to provide assistance with and

confirmation of the diagnosis of ON hypoplasia. Furthermore, in current practice, neuroradiologists diagnose ON hypoplasia based upon highly subjective observer experience potentially influenced by the clinical history. With the exception of more severe cases of ON hypoplasia, such an approach is highly prone to interobserver variability and ultimately may exclude the very patients (i.e., patients with mild or moderate ON hypoplasia) that most need corroborating information in order to make diagnosis.

Objective evaluation of optic nerve size therefore may be helpful in diagnosing ON hypoplasia. Modalities historically utilized for evaluating the optic nerve include clinical measurement using indirect ophthalmoscopy¹⁰, fundus photography^{11,12}, both A- and B-scan ultrasound^{13,14,15}, computerized tomography (CT) prior to the advent of MRI, Heidelberg Retinal Tomograph II¹⁶, spectral domain optical coherence tomography (SD-OCT)^{17,18}, and magnetic resonance imaging (MRI).^{7,8,9,19,20,21,22,23,24,25}

Each of these modalities has its limitations. Funduscopic examination and fundus photographs can be difficult to obtain in young children without anesthesia and measurements of optic nerve size based on them must be adjusted for refractive error and axial length of the child's eye⁶. Measurements of the optic nerve obtained by means of ultrasound may be limited due to poor penetration of sound waves into the retrobulbar region and misalignment.²⁴ Sonographic techniques rely upon advanced sonographers with meticulous technique and experienced interpretation.^{14,24} Because of its relatively poor soft tissue contrast, CT is incapable of accurately assessing ON size except in severe cases in which the nerve may be grossly enlarged or decreased in volume. In addition, because of radiation dose implications, CT is less desirable as a screening tool in the pediatric population. Third, as with ultrasonography, CT is not well poised to evaluate the brain and hypothalamic pituitary axis in patients suspected of having ON hypoplasia--a crucial, potentially life-saving step in the evaluation of such patients. Most recently, the role of SD-OCT in examining peripapillary retinal nerve fiber layer thickness has been explored in normal children 5–15 years of age with the establishment of a normative average global peripapillary nerve fiber layer thickness of 107 $\pm$ 1.2 micrometers.¹⁷ Normative values for the youngest children, however, and relative values for those with ON hypoplasia remain to be defined.

While obtaining MRI imaging of the brain and orbits for small children does require sedation or anesthesia with its inherent risks, significant advantages of MRI over other modalities for neuroimaging pediatric patients with optic nerve hypoplasia include excellent soft tissue contrast and resolution and the absence of ionizing radiation. Furthermore, MRI is the gold standard for imaging the intracranial contents including the pituitary gland, a standard evaluation for patients with ON hypoplasia. Recent developments in MRI now allow high-resolution imaging and measurement of the optic nerve in clinical settings. Karim et al noted an average difference between MRI and histologic measurements of 0.066 mm with a maximum difference of 0.157 mm.²⁴ Hellstrom et al published a series demonstrating high correlation between the diameter of the intracranial nerve as measured by MRI and the size of the optic disc in patients with ON hypoplasia. In fact, in four patients with normal vision with funduscopic optic disc measurements below the 5th percentile, MRI correctly albeit subjectively classified such patients as being normal. In this very small

series, the authors thereby concluded that when using funduscopy optic disc measurements as the gold standard, MRI was instead the superior diagnostic tool.⁸ Brodsky et al. and Hellstrom found good correlation between optic nerve size on MRI compared with clinical diagnosis but relied on a subjective grading scale to estimate optic nerve size.^{7,8} Birkebaek et al measured cross-sectional area of the optic nerves in groups of children with isolated and non-isolated ON hypoplasia but did not compare these findings to those of a control group.⁹

The present series relied on the use of 3D high-resolution, volumetric heavily T2 weighted sequences with slice thicknesses usually in the range of 0.4–0.6 mm to measure optic nerve dimensions objectively at two separate locations. In addition to being higher resolution, our technique has several advantages over the T1-weighted sequences used in prior studies: better contrast between optic nerve and subarachnoid fluid, fewer volume averaging artifacts, no need for intravenous contrast, ability for volumetric analysis to ensure that all digital measurements occurred exactly orthogonal to the plane of the optic nerve, and only 4–5 minutes of additional scanner time. The use of digital measurements in our study--aided by tools such as magnification and window and level manipulations--may also have improved accuracy of measurement compared with earlier studies that employed manual techniques of measurement.^{19,20,22}

Limitations to our study included the potential for measurement bias given the fact that the interpreting neuroradiologist could not be effectively masked to the optic nerve pathology. However, the neuroradiologist's subjective impression was sometimes contradicted by his objective measurements. Indeed, the neuroradiologist's subjective impression of optic nerve size was overturned by his objective measurements in three cases. Second, there was a significant difference in median age (1.1 years versus 5.5 years) between the case and control groups because ON hypoplasia typically comes to attention at a younger age. While our statistical models controlled for age, the possibility of residual confounding nevertheless remains. Third, slice thickness for controls was generally 0.3 while it was 0.4–0.8 for cases. Higher resolution could arguably result in a more precise measurement, but would not cause a systematic bias in the measurement. Fourth, it is noted that one patient with clinical ON hypoplasia fell above our cutoff. Review of the medical record suggested that this is primarily the result of an equivocal clinical diagnosis of optic nerve hypoplasia. However, even if we consider clinical diagnosis to be the reference standard, our cutoff had 96% sensitivity (25/26 MRI positive among those with clinical ON hypoplasia). Finally, no attempt was made to correlate optic nerve size with visual function. Brodsky noted that isolated measurement of the optic disc itself is not necessarily reflective of the number of axons within the optic nerve.⁵ Borchert also questioned whether relative disc size correlates with visual function and can be used to approximate visual acuity.¹²

In the present study evaluating the role of MRI in diagnosing optic nerve hypoplasia, age was independently associated with normal optic nerve size by MRI. Therefore, patient age needs to be considered when evaluating ON hypoplasia based on MRI criteria. We suspect that optic nerve size increases with age due to myelination which progresses during childhood.^{25,26} We have provided a formula [$2.24 \text{ mm} + 0.052 \times (\text{age in years})$] to assist clinicians in objectively determining if ON hypoplasia is present. The authors do not suggest

that normal children in the absence of clinical findings or suspicion be imaged to determine whether ON hypoplasia exists or that MRI in isolation should be used to derive such a diagnosis. Volumetric T2 high resolution MRI of the orbits measured by an experienced neuroradiologist may assist in objectively determining whether ON hypoplasia exists. For example, in children who appear to have amblyopia in the absence of amblyogenic risk factors and whose vision does not seem to improve significantly with amblyopia therapy, MRI may be helpful. Pineles and Demer concluded that amblyopia in some cases may be explained by mild to moderate optic nerve hypoplasia.²⁷ It may be interesting to look longitudinally in future studies at how optic nerve size changes from infancy to adulthood as well as to see how well optic nerve size as measured by MRI correlates with ultimate visual outcome.

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Figure 1.

Method of Intraorbital Optic Nerve Measurement for Cases with Optic Nerve Hypoplasia and Normal Controls using Magnetic Resonance Imaging of the Orbits. Axial T2 SPACE source image (Left) of the intraorbital segment of the optic nerve. Digital crosshair tool is placed on a magnified image of the intraorbital right optic nerve 5 mm posterior to the optic disc (Top right) exactly orthogonal to the plane of the nerve. A coronal transverse oblique image (Bottom right) is digitally generated which then allows for craniocaudal and transverse measurements of the optic nerve.

Figure 2.

Method of Prechiasmatic Optic Nerve Transverse Measurement using Magnetic Resonance Imaging of the Orbits. Axial T2 SPACE source image (Left) of the prechiasmatic segment of the optic nerve immediately posterior to the optic canal. Digital crosshair tool is placed on a zoomed image of the prechiasmatic segment (Top right) exactly orthogonal to the transverse oblique plane of the nerve. A coronal transverse oblique image (Bottom right) is digitally generated which allows for transverse measurement of the optic nerve.

Figure 3.

Method of Prechiasmatic Optic Nerve Craniocaudal Measurement using Magnetic Resonance Imaging of the Orbits. Sagittal T2 SPACE source image (Left) of the prechiasmatic segment of the optic nerve immediately posterior to the optic canal. Digital crosshair tool is placed on a magnified image of the prechiasmatic segment (Top right) exactly orthogonal to the craniocaudal oblique plane of the nerve. A coronal cranio-caudal oblique image (Bottom right) is digitally generated that then allows for craniocaudal measurement of the optic nerve.

Figure 4.
Flow Diagram Outlining Method of Optic Nerve Hypoplasia Case Identification for Optic Nerve Measurements by Magnetic Resonance Imaging of the Orbits.

Figure 5.

Association Between Optic Nerve Size Determined by Magnetic Resonance Imaging of the Orbits for Controls Compared to Cases of Optic Nerve Hypoplasia. Black boxes represent individual control optic nerve measurements. The solid black line shows the mean optic nerve size of controls by linear regression. The dashed black lines indicate the 95% prediction intervals of the mean optic nerve size of controls. Down-pointing triangles are measurements of optic nerves with clinical ONH. Up-pointing triangles represent the clinically unaffected eye of patients with clinically unilateral ONH. The contralateral optic nerve of ONH patients was generally smaller than control optic nerves. The bold gray line is

a linear lower bound of the 95% prediction band $[2.24 \text{ mm} + 0.052 \times (\text{age in years})] \text{ mm}$ that discriminated all but one of the cases of optic nerve hypoplasia.

Table

Multivariable linear mixed effects model (random intercept for patient) predicting the mean in mm of five optic nerve-related measurements (craniocaudal and transverse intraorbital optic nerve, craniocaudal and transverse prechiasmatic, and transverse oblique optic canal) performed using volumetric, heavily T2-weighted orbital magnetic resonance imaging sequence for patients with and without optic nerve hypoplasia.

Variable	Coefficient	95% CI	P-value
Clinical ONH	-1.36	(-1.54 to -1.19)	<0.001
Case status *	-0.22	(-0.44 to -0.002)	0.047
Age (years)	0.05	(0.03 to 0.07)	<0.001
3T field strength **	0.23	(0.08 to 0.39)	0.004

ONH=optic nerve hypoplasia, CI=confidence interval

* This represents the difference in measurement between cases' non-clinically affected eyes and those of controls.

** vs. 1.5T