ORIGINAL ARTICLE

Establishing Optic Nerve Diameter Threshold Sensitive and Specific for Optic Atrophy Diagnosis

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Abstract

Purpose   To determine a potential threshold optic nerve diameter (OND) that could reliably differentiate healthy nerves from those affected by optic atrophy (OA) and to determine correlations of OND in OA with retinal nerve fiber layer (RNFL) thickness, visual acuity (VA), and visual field mean deviation (VFMD).

Methods   This was a retrospective case control study. Magnetic resonance (MR) images were reviewed from individuals with OA aged 18 years or older with vision loss for more than 6 months and an OA diagnosis established by a neuro-ophthalmologist. Individuals without OA who underwent MR imaging of the orbit for other purposes were also collected. OND was measured on coronal T2-weighted images in the midorbital section, 1 cm posterior to the optic disc. Measurements of mean RNFL thickness, VA and VFMD were also collected.

Results   In this study 47 OA subjects (63% women, 78 eyes) and 75 normal subjects (42.7% women, 127 eyes) were assessed. Healthy ONDs (mean 2.73 ± 0.24 mm) were significantly greater than OA nerve diameters (mean 1.94 ± 0.32 mm; $P < 0.001$). A threshold OND of ≤ 2.3 mm had a sensitivity of 0.92 and a specificity of 0.93 in predicting OA. Mean RNFL ($r = 0.05$, $p = 0.68$), VA ($r = 0.17$, $p = 0.14$), and VFMD ($r = 0.18$, $p = 0.16$) were not significantly associated with OND.

Conclusion   ONDs are significantly reduced in patients with OA compared with healthy nerves. A threshold OND of ≤ 2.3 mm is highly sensitive and specific for a diagnosis of OA. OND was not significantly correlated with RNFL thickness, VA, or VFMD.

Keywords   Neuro-ophthalmology · Optic atrophy · MRI · Optic nerve imaging · Orbit · Retinal nerve fiber layer · Longstanding

Introduction

The optic nerve (cranial nerve II) in adults is composed of the axons of approximately 1.2 million retinal ganglion cells (RGCs) that originate from the retina, coalesce at the optic disc, and synapse with the lateral geniculate nuclei within the brain [1]. Diseases that affect the optic nerve and result in vision loss are broadly termed "optic neuropathies", with diverse etiologies that commonly include inflammatory, infectious, and ischemic [2]. A common downstream consequence of all optic neuropathies is optic atrophy (OA), a term used to describe the death of RGCs and resulting degradation of the optic nerve [3].

The diagnosis of OA is primarily clinical and incorporates multiple metrics including visual acuity (VA), visual field (VF), color vision, dilated fundus examination, and optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL). The diagnosis is often made through a holistic assessment of these various modalities by a trained ophthalmologist. The work-up of optic atrophy almost invariably involves magnetic resonance imaging (MRI).

To our knowledge, there is a lack of quantitative MRI criteria for the diagnosis of OA. Radiologists often interpret OA on MRI solely based on subjective assessment. Simplified, objective markers for OA would be useful for neuroradiologists. It is hypothesized that longstanding OA

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Fig. 1 Coronal T2 MRI showing an example of optic nerve diameter measurement in a healthy patient (**a**) and one with optic atrophy (**b**). Inset is zoomed on the measurement of the left eye
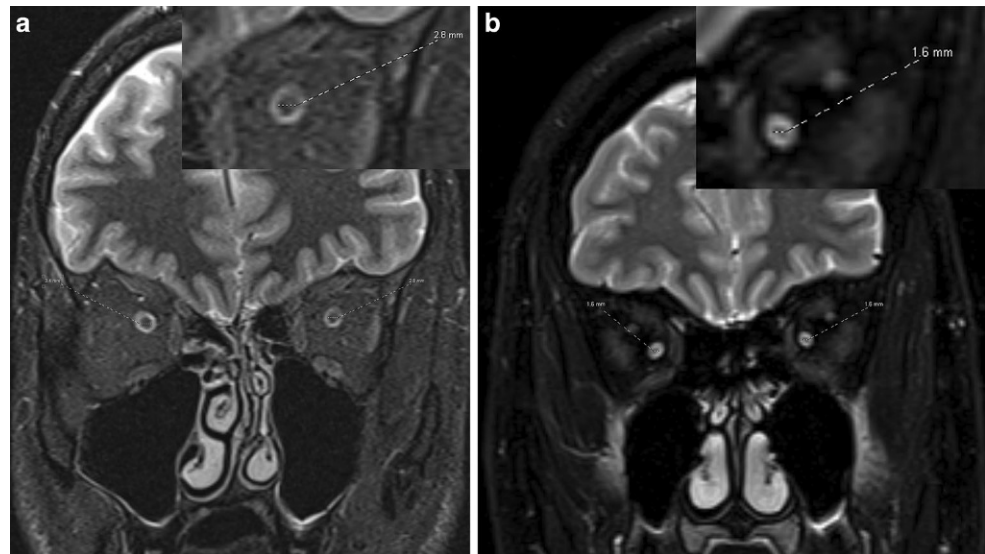
can be determined on MRI. In this study, we sought to determine a threshold optic nerve diameter (OND) to reliably differentiate normal optic nerves from OA on MRI and to determine if OND correlated with metrics of visual function and intraocular structure.

Methods

Patients

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective study with a waiver of informed consent. This study was completed in adherence to the tenets of the Declaration of Helsinki. Data for the OA group were obtained from patients who underwent neuro-ophthalmic examination and MR imaging at the University of Minnesota Medical Center from January 2005 through April 2021. Inclusion criteria for patients were age 18 years or older at the time of the MRI, a clinical diagnosis of optic atrophy established by a fellowship-trained neuro-ophthalmologist, and onset of visual symptoms at least 6 months prior to the eye examination and neuroimaging. The healthy optic nerve (ON) group consisted of 75 randomly selected patients aged 18 years or older at the time of the MRI, a visual acuity of 20/25 or better, and no evidence of optic neuropathy on comprehensive neuro-ophthalmologic examination. Each patient underwent imaging for a cranial nerve 3, 4, or 6 palsy.

MR Technique and Image Analysis

The MRI were obtained by either 3T Skyra or 1.5-T Aera MRI machines (Siemens, Erlangen, Germany). Precontrast and postcontrast T1-weighted spin-echo images and T2-weighted fast spin-echo images with and without fat saturation were obtained as per orbit MR protocol. Images were obtained in at least 2 planes with 3–5 mm section thickness and 0.3–1 mm intersection gap.

A picture archiving and communication system (PACS, Philips, Intellispace 4.4, Amsterdam, Netherlands) was used for image review. These analyses were performed on coronal T2-weighted images in the midorbital section, 1 cm posterior to the optic disc. The OND measurements were made at the broadest section of the nerve body, excluding the optic nerve sheath (Fig. 1). The measurements were made by two unblinded neuroradiologists. Grader 1, a fellowship-trained neuroradiologist with over 8 years experience, measured the normal optic nerves and the atrophic optic nerves on 2 separate occasions. Grader 2, a fellowship-trained neuroradiologist with over 5 years experience, measured the atrophic optic nerves on 1 occasion.

Data collected included demographics, VA, color vision, OCT, and visual fields. OCT-RNFL testing was completed on Spectralis OCT (Heidelberg Engineering, Franklin, Massachusetts, USA) and mean RNFL was recorded from these tests. Visual field mean deviations (VFMD) were obtained from Octopus (Haag-Streit, Bern, Switzerland) automated perimetry using the tendency-oriented perimetry program.

Statistical Analysis

Individual eyes were treated separately in the analysis. Mean OND was compared between OA and healthy patients utilizing a two-sample *t*-test and Fisher's exact tests were used for comparison of continuous and categorical characteristics, respectively. Receiver operator curve (ROC) analysis was utilized to determine optical atrophy diagnosis sensitivity and specificity for given threshold diameters. An

Table 1 Patient characteristics among healthy optic nerves and those with atrophy

		Healthy	Optic atrophy	*p*-value
n	–	75	47	–
Age mean, years (SD)	–	55.68 (14.35)	51.34 (13.83)	0.102
Gender (%)	Female	31 (42.4)	30 (63.8)	0.025
	Male	44 (57.6)	17 (36.2)	–
Race (%)	White	59 (78.7)	37 (78.7)	0.225
	African American	3 (4.0)	6 (12.8)	–
	Asian	4 (5.3)	1 (2.1)	–
	Declined	9 (12.0)	3 (6.4)	–
Diameter mean, mm (SD)	–	2.73 (0.24)	1.94 (0.32)	<0.001

Table 2 List of primary conditions resulting in optic atrophy in study sample and their associated percentages of the sample

Primary condition	No. affected (% of total = 47)
Meningioma	13 (28)
Multiple sclerosis	7 (15)
Pituitary neoplasm	6 (13)
Demyelinating optic neuritis	5 (11)
Other malignancy	3 (6)
NAION	2 (4)
Neuromyelitis optica	2 (4)
Nutritional	2 (4)
Retinal vasculitis	1 (2)
Sarcoid	1 (2)
Unknown	1 (2)
Other	5 (11)

NAION nonarteritic anterior ischemic optic neuropathy

optimal diameter threshold was chosen based on Youden's index. Pearson's correlation coefficient was calculated to assess the linear relationship between OND and RNFL, VFMD, and visual acuity. Multivariable linear regression was used to assess for confounding effects with regards to age, MRI field strength, and cause of OA. Calculations were performed using MATLAB R2022b (MathWorks, Natick, Massachusetts). ROC plot was produced using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). *P* values ≤0.05 were used to determine significance.

Results

The initial query for patients diagnosed with OA yielded 518 unique patients. A review of these patients was then completed to compile a list of those who matched the required criteria. The final compiled list consisted of 47 patients with optic atrophy (63.8% women, mean age 51.3 years), 16 with unilateral and 31 with bilateral OA, resulting in 78 eyes with OA (Table 1). Etiologies for the development of optic atrophy in these patients are shown

in Table 2. Additionally, 75 subjects (42.4% women, mean age 55.9 years) without optic atrophy who underwent brain MRI were assessed and data from 127 eyes were obtained.

OND for the healthy ON population (mean, 2.73 ± 0.24 mm) was significantly greater than that of the OA population (mean, 1.94 ± 0.32 mm; $P < 0.001$) (Fig. 2). A receiver operator curve was utilized and demonstrated that a threshold of ≤2.3 mm could identify OA with a sensitivity of 0.92 and specificity of 0.93 (Table 3; Fig. 3). The intraclass correlation coefficient (ICC) for intrarater reliability was 0.98 (95% confidence interval, CI: 0.97, 0.99) and 0.89 (95% CI: 0.83, 0.93) for the right and left eyes, respectively. The ICC was 1.0 (95% CI: 1.1) for the interrater reliability for the right and left eye. Analyses of correlations between OND and other ophthalmic testing modalities did not demonstrate any statistically significant results, with correlations between optic nerve diameter and RNFL ($r = 0.05$, $p = 0.68$), VA ($r = 0.17$, $p = 0.14$), and VFMD ($r = 0.18$, $p = 0.16$) all yielding insignificant, poor correlations. Multivariable regression showed no effects of age, cause of OA, or MRI field strength on the results (Supplemental Tables 1–3).

Discussion

The purpose of this study was to investigate whether optic nerve diameter, an easily accessible and objective marker, could be utilized to predict or support the diagnosis of optic atrophy. This study demonstrates a threshold optic nerve diameter with a high level of sensitivity (0.92) and specificity (0.93) for optic nerve atrophy. Interestingly, these data did not show significant correlations between OND and RNFL thickness, VA, and VFMD.

Previous literature on objective measures that can be utilized in OA is sparse. Zhao et al. objectively measured cross-sectional area in optic atrophy [4]. Their assessment demonstrated that utilizing a threshold optic nerve area of 4.0 mm² or less was predictive for a diagnosis of optic atrophy, with a sensitivity of 0.85 and a specificity of 0.83.

Fig. 2 Comparison of optic nerve diameters between healthy (mean, 2.73 ± 0.24 mm) and optic atrophy patients (mean, 1.94 ± 0.32 mm, $p < 0.001$)
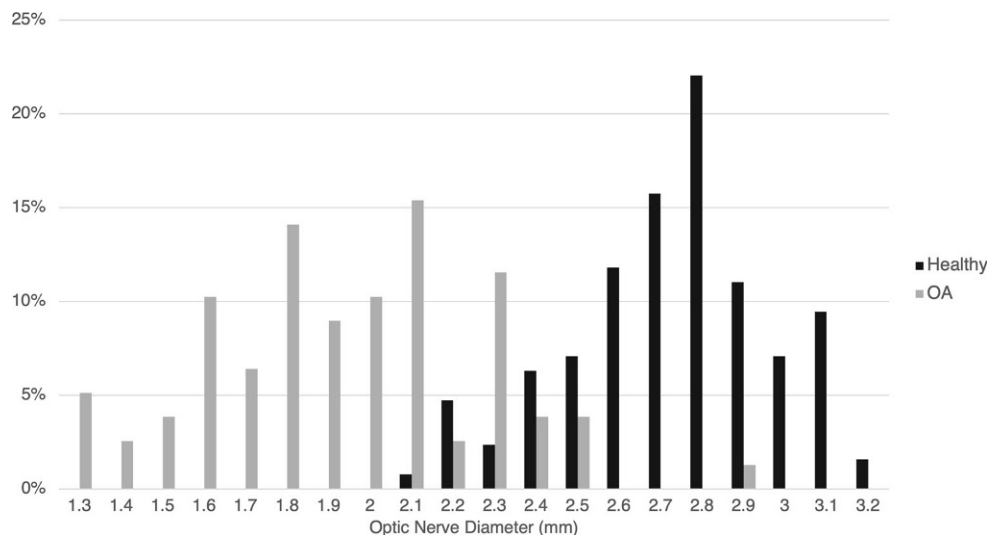
Fig. 3 ROC curve for optic nerve diameter predicting optic atrophy compared to healthy controls (AUC = 0.973) with dashed line representing assignment based on random chance
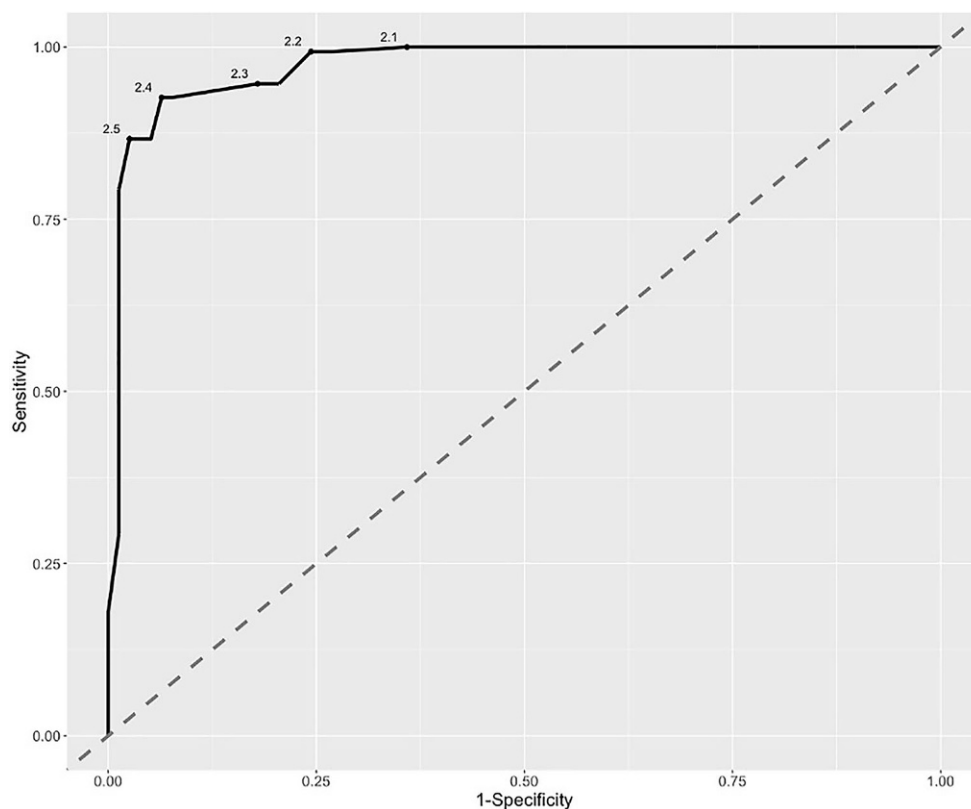
Our analysis demonstrating a threshold diameter of 2.3 mm correlates to an area of approximately 4.15 mm². A highly sensitive and specific objective measure to predict OA will help promote consistent diagnoses of optic atrophy for radiologists and clinicians evaluating optic nerve health.

It is not surprising that VA and VFMD did not correlate to OND, as these functional parameters do not tend to correlate with RNFL [5, 6]; however, the absence of a statistically significant relationship between OND and RNFL thickness in OA patients was unexpected. In their comparatively similar study, Zhao et al. assessed this association and reported a statistically significant association between RNFL and optic nerve area; however, several differences in methodology exist between our studies that may explain these findings. In their study, the duration of OA is not identified. We chose a minimum of 6 months duration so that the RNFL and OND would presumably have reached their nadir particularly following an acute optic neuropathy such as ischemic optic neuropathy or optic neuritis. It seems likely that OND and RNFL thinning occurs at dif-

Table 3 Sensitivity and specificity measurements obtained utilizing various threshold optic nerve diameters with an AUC of 0.973

Threshold diameter (mm)	Sensitivity (# from $n = 78$)	Specificity (# from $n = 150$)
<2.1	0.7308 (57)	0.9933 (149)
<2.2	0.7949 (62)	0.9467 (142)
<2.3	0.9231 (72)	0.9267 (139)
<2.4	0.9487 (74)	0.8667 (130)
<2.5	0.9872 (77)	0.7933 (119)

ferent rates. Zhao et al. also chose to use radiology residents to measure the ON area where "the nerves appeared most round and most perpendicular to the coronal plane", whereas we chose a standardized location of 1 cm posterior to the globe as measured by a fellowship-trained neuroradiologist. Their study evaluated only 26 eyes compared to our 76 eyes. It is possible that the association they found would have disappeared with a larger study population. Finally, unlike our study, not all of their controls underwent neuro-ophthalmic examination (35 of 45 did not appear to have an ophthalmic examination) and patients with asymptomatic optic nerve atrophy may have been included.

Optical coherence tomography (OCT) has been paramount in the field of ophthalmology since its introduction in the early 1990s [7, 8]. Measuring RNFL using OCT is a cornerstone in the diagnosis and management of various ophthalmological conditions, including glaucoma and other optic neuropathies [9–15]. The RNFL thickness has also been studied for potential associations with other biological characteristics and conditions. Notably, among patients with multiple sclerosis, significant correlations have been demonstrated between RNFL and optic nerve volume, in addition to brain atrophy [16, 17]; however, there have been many different factors that appear to impact the thickness of the RNFL, including age, sex, ethnicity, and axial length [18, 19]. Indeed, even more unexpected associations have been reported in the literature, including sleep apnea, cognitive function, and substance use [20–24]. Thus, there are likely confounding variables that were inadequately controlled for in the current study, which may be obfuscating an underlying relationship between optic nerve diameter and RNFL thickness.

Limitations to this study include the inherent difficulties of all retrospective chart reviews, the limited number of cases, and limited control for confounding clinical and demographic factors potentially affecting radiographic OND. The MRIs were performed on different machines with variable magnet strength, but this increases the generalizability of our findings. The graders were not blinded to the diagnosis of optic atrophy vs. healthy optic nerves, which could introduce bias; however, the graders were blinded to each other's measurements and previous measurements, and the intrarater and interrater reliability were very high. Despite

these limitations, we believe that our findings remain valid and identify a clinically useful radiographic threshold for OND in OA.

Conclusion

This study demonstrates that a threshold optic nerve diameter (measured 1 cm posterior to the globe) of 2.3 mm or less is highly sensitivity and specific in predicting the diagnosis of optic atrophy. No significant correlations were found between optic nerve diameter and RNFL, VFMD, or visual acuity. The lack of a significant correlation between optic nerve diameter and RNFL was unexpected. Further research is warranted to further assess the relationship between optic nerve diameter and OCT testing results.

Declarations

Conflict of interest M.L. Prairie, M. Gencturk, C.M. McClelland, N.A. Marka, Z. Jiang, M. Folkertsma and M.S. Lee declare that they have no competing interests.

Ethical standards For this article no studies with animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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