Evaluation of the Optic Nerve and Retinal Nerve Fibre Layer in Myopic Individuals

Ahmad A Aref and Donald L Budenz

1. Assistant Professor, University of Illinois Eye and Ear Infirmary, Chicago, US; 2. Professor and Chairman, Department of Ophthalmology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, US

Abstract
Clinical discrimination between myopic tilted optic discs and glaucomatous optic neuropathy is often challenging, especially when considering that myopia is a risk factor for the development of glaucoma. Myopic tilted discs are usually larger than average, with associated relative cupping and thinner neuroretinal rim tissue. Histopathological study has revealed thinner parapapillary retinal tissue in these eyes. Optical coherence tomography (OCT)-measured average retinal nerve fibre layer (RNFL) thickness has been found to decrease with longer axial length and higher myopic refractive error. Parapapillary RNFL quadrant and clock-hour analyses result in a higher false-positive rate in myopic eyes. Careful slit-lamp examination, quality baseline stereoscopic disc photographs and frequent serial visual field testing are essential to the follow-up of myopic individuals with suspected glaucoma. A novel diagnostic parameter, OCT-derived ganglion cell analysis, may prove to be useful in the diagnosis and follow-up of these individuals.

Keywords
Retinal nerve fibre layer, myopia, glaucoma, optical coherence tomography, optic nerve

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Correspondence: Donald L Budenz, Department of Ophthalmology, University of North Carolina School of Medicine, 5151 Bioinformatics, CB 7040, Chapel Hill, NC 27599-7040, US. E. dbudenz@med.unc.edu

According to pooled data from large, population-based eye surveys, the estimated prevalence of myopic refractive error <1 dioptre [D] or less) in individuals >40 years old is 25.4, 26.6 and 16.4 % in the US, Europe and Australia, respectively. For myopia less than -5 D, the prevalence estimates are 4.5, 4.6 and 2.8 %, respectively.2 The prevalence of myopic refractive error is indeed substantial and is the highest of any ocular disorder in this age group.

Furthermore, optic nerve and visual field abnormalities associated with high myopia are notoriously difficult to differentiate from those associated with glaucomatous optic neuropathy. The challenge of distinguishing otherwise healthy myopic eyes from those afflicted with glaucoma becomes even more complex when considering that myopic refractive error is a risk factor for open-angle glaucoma. Marcus and colleagues3 performed a systematic review and meta-analysis of population-based cross-sectional studies published between 1994 and 2010, in order to determine the association between myopia and glaucoma. Analysis of seven studies that reported risk estimates for both low and high myopia revealed a pooled odds ratio of 1.65 (95 % confidence interval [CI] 1.26–2.17) between low myopia and open-angle glaucoma. The pooled odds ratio for the association between high myopia (>3 D or less) and open-angle glaucoma was found to be 2.46 (95 % CI 1.93–3.15). The authors acknowledge that, due to the presence of myopic visual field defects and relatively larger optic nerve cups in myopic individuals, studies included in this meta-analysis may have overestimated the prevalence of glaucoma and therefore cite a single longitudinal study4 (deemed to be less prone to misdiagnosis of glaucoma) that yielded the same overall results. High myopic error does indeed appear to be an independent risk factor for open-angle glaucoma; however, clinicians must be aware of myriad clinical features that may confound an accurate diagnosis. This article aims to shed light on these clinical features and also to provide practical tips for the examination and follow-up of myopic individuals with suspected open-angle glaucoma.

Features of the Optic Disc and Retinal Nerve Fibre Layer in Myopic Eyes

Optic Disc Size
In a histomorphometric study conducted by Jonas et al.,4 optic discs of highly myopic eyes were found to be significantly larger and more ovaly configured than those of non-highly myopic eyes. In a separate clinical observational study of 1,999 eyes of 1,011 subjects,6 Jonas reported that optic disc area was significantly larger in a subset of myopic eyes (n=50) with refractive error less than -8 D (p=0.01, mean disc area = 3.66 ± 2.99 mm²). Optic disc size was found to be independent of refractive errors in the range of -8 D to less than -4 D. Contrary to these findings, Goldschmidt and Fledelius7 found that a majority of optic discs in a cohort of 36 myopic individuals were 'small, tight, or tilted'. Quantitative data were not presented in that report.

Histopathology
Jonas and colleagues4 performed a retrospective laboratory study investigating the histology of the parapapillary region in eyes with...
high myopia. The group studied the human globes of 36 highly myopic glaucomatous individuals with an axial length >26.5 mm as well as a non-highly myopic group consisting of 45 globes. The distance between the optic nerve border and the beginning of Bruch’s membrane (noted clinically as a myopic crescent) was found to increase with axial length (p=0.001, r=0.69), independently of the presence of glaucoma (p=0.99). In all 15 eyes where this distance was longer than 0.5 mm, the parapapillary sclera was noted to be thinned and elongated. The parapapillary retina in these eyes consisted of only the retinal nerve fibre layer (RNFL) or its remnants, without elements of any other retinal layer, underlying Bruch’s membrane, or choroid. The authors postulate that thinning of the parapapillary sclera in highly myopic eyes may lead to higher tension on the lamina cribrosa, partially explaining a higher susceptibility to glaucoma. This theory is supported by studies that implicate a greater deformability of the lamina cribrosa in myopic eyes.18 An increased distance between the parapapillary choroid (with its associated feeding vasculature) and the optic disc border may influence vascular support and also relate to degenerative changes in the myopic optic nerve head.

**Optical Coherence Tomography**

Optical coherence tomography (OCT) has proven to be a useful tool in the diagnosis and follow-up of glaucomatous eyes. The technology allows the quantification of parapapillary RNFL thickness, which has been shown to be both sensitive and specific for the diagnosis of glaucomatous disease.19 Although the technology has been shown to be of great clinical utility in this regard, the results of such testing may be inaccurate in myopic eyes.19

Vernon and colleagues20 assessed OCT-derived (Stratus™ OCT, Carl Zeiss Meditec, Inc., Dublin, CA) peripapillary RNFL thickness distribution in a group of 31 non-glaucomatous myopic eyes and found that RNFL thickness was lower in this population in all segments compared with a normative population database. Twenty-six eyes in the study (83.9%) had at least one clock hour in which RNFL thickness was below normal at the 5% level and 20 eyes (64.5%) at the 1% level. The disparity was greatest for the nasal side of the RNFL.

Rauscher and colleagues21 also investigated the association between increasing myopia and parapapillary RNFL measurements in 27 non-glaucomatous eyes using the Stratus OCT. The group found that OCT-measured average RNFL thickness decreases with higher axial length (r=-0.70, p<0.001) and higher spherical equivalent (r=-0.52, p=0.005). Supporting these findings, Kim and colleagues22 identified longer axial length as a factor associated with an increased incidence of false-positive test results (odds ratio 2.422, p=0.008) based on abnormal parapapillary quadrant and clock-hour maps as determined by the Cirrus™ OCT (Carl Zeiss Meditec, Inc., Dublin, CA). In this cross-sectional study involving 149 eyes of 227 non-glaucomatous individuals, the superior RNFL quadrant map showed the highest incidence of false-positive results, at a rate of 5.4%.

Histopathological findings by Jonas and colleagues17 indicating thinner parapapillary sclera and stretching of the overlying retinal tissue in myopic individuals may explain the observed OCT-measured RNFL thinning and subsequent higher false-positive rate in this population. Prior studies22,23 also suggest that, due to optic nerve tilting, myopic eyes have an RNFL topographic profile that differs from non-myopic eyes, with thinner measurements in the non-temporal quadrants than in the temporal quadrants, when compared with controls. Chung and colleagues24 tested the hypothesis that this atypical RNFL profile results from inappropriate automatic centering of the parapapillary analysis circle by OCT in these eyes. The investigators performed a study of 69 eyes determined to have myopic tilted discs and no other ocular abnormalities. RNFL thickness was then measured twice using spectral-domain OCT (Cirrus OCT). The first test involved a calculation circle as determined automatically by the OCT software algorithm; the second test involved placement of a manually rendered circle, with positioning centered around the neural canal opening (margin involving the temporal edge of parapapillary atrophy and the nasal scleral lip). Based on RNFL clock-hour analysis, a significantly lower false-positive rate was found when using the manual method for circle centration (p=0.0078, 0.0039, 0.0001 and 0.002 for the 1, 2, 5 and 6 o’clock sectors, respectively). The results of this study offer promise that future OCT software algorithmic methods may provide the ability to account for non-pathological characteristics of the myopic tilted optic disc in order to give more reliable test results. However, with currently available software algorithms, the clinician should remain aware of a higher likelihood of false-positive test results in the myopic population.

**Challenges in the Diagnosis of Glaucoma in Myopic Individuals**

Several clinical features of the myopic optic nerve head can lead to difficulty in differentiation from glaucomatous disease. Larger optic disc size in myopic individuals can confound the accurate diagnosis of a glaucomatous optic nerve due to the presence of physiological optic cupping in larger optic nerve heads.25 Larger beta and alpha zones of parapapillary atrophy have also been reported in myopic eyes.26 These larger zones of parapapillary atrophy, which can be quite difficult to differentiate from the non-pathological myopic crescent, also serve to confound a diagnosis of glaucoma, since beta-zone atrophy itself serves as a marker of glaucomatous disease and progression.25,27

To further complicate the clinical discrimination between myopic pathology and glaucoma, several studies have shown that myopic individuals may exhibit visual field defects similar to those seen in glaucomatous eyes. Doshi and colleagues28 performed a retrospective review of the medical records of 16 young to middle-aged men of Chinese origin, who were mostly myopic (spherical equivalents ranging from -11.25 to +0.25 D). The group was followed for a seven-year period for visual field changes or progressive optic nerve cupping suggestive of glaucoma. Fourteen of the 16 patients in the study had a visual field abnormality in at least one eye with patterns classified as diffuse loss, nasal step, or an arcuate defect. However, during the seven-year follow-up period, none of these patients were noted to have optic nerve or confirmed clinically significant visual field progression. The aetiology of these myopic visual field defects is unclear, but probably relates to peripapillary retinal thinning in these eyes that is non-progressive.

**Clinical Pearls**

With the presented challenges in discriminating glaucomatous disease from non-pathological myopia, the clinician is obliged to perform a more careful and thorough examination in myopic individuals before declaring a diagnosis of glaucoma. The examination of the myopic individual with clinical features suggesting possible glaucoma begins with careful clinical examination and quality baseline documentation of structural and functional measures.
The presence of myopic optic nerve tilted requires careful stereoscopic examination of optic disc contour, rather than colour, to accurately assess cup-disc ratio. This stereoscopic assessment is best performed using a thin slit-lamp illuminating beam that is moved across the optic nerve to delineate the neuroretinal rim from the optic cup. Although a general assessment of disc size is critical to glaucoma evaluation, the examiner must be aware that standard measurement with a condensing lens may be inaccurate in myopic eyes.

The current gold standard for optic nerve imaging is stereoscopic optic disc photography. Quality performance of this test is especially important in the follow-up of myopic individuals as optic nerve appearance is expected to remain stable, as opposed to glaucomatous disease, in which progressive neuroretinal rim thinning and cupping are the rule. Since accurate clinical assessment of optic disc cupping is often difficult in titled, myopic optic discs, the clinician may find other features of glaucomatous disease to be helpful in ascertaining a diagnosis. These features include optic disc haemorrhage and beta-zone parapapillary atrophy, both of which have been associated with the presence of glaucomatous optic neuropathy.1,2,3

OCT is also useful as an adjunctive study of optic nerve structure. Although the advent of spectral-domain technology has led to excellent reproducibility of RNFL and optic disc parameters,4 the authors recommend obtaining three separate OCT scans of each eye in order to ensure intra-visit reproducibility in routine clinical practice. As reported by Kim and colleagues,5 the OCT-derived parapapillary RNFL clock-hour and quadrant analyses in myopic eyes may lead to an increased false-positive rate for the diagnosis of glaucoma.

Therefore, in myopic individuals, the clinician should place relatively little weight on the clock-hour and quadrant analyses and instead more strongly consider optic disc parameters as determinants of possible glaucomatous damage. In addition, following the RNFL and optic disc parameters with OCT over time in myopic individuals may be helpful, since these parameters would not be expected to change in myopic patients but would in a progressive optic neuropathy such as glaucoma. Newer OCT software algorithms have been developed to analyse retinal ganglion cell layer loss in glaucomatous disease.6,7,8 This novel parameter has demonstrated excellent diagnostic accuracy and reproducibility in the assessment of glaucoma.9,10 Unlike parapapillary RNFL analyses, ganglion cell analysis is performed in the region of the fovea. Measurement of macular ganglion cell thickness may therefore be less sensitive to variability with axial length and refractive error.

Serial automated visual field tests are also essential in the follow-up of myopic patients with suspected glaucoma. Although myopic error and longer axial length may be associated with visual field defects, these are typically non-progressive in nature. The clinician should therefore reserve a diagnosis of glaucoma for cases of confirmed visual field progression. This may require more frequent visual field studies in the myopic population with baseline visual field deficit. Computerised visual field analysis using trend-based Visual Field Index™ (VFIR), Carl Zeiss Meditec, Inc., Dublin, CA or event-based Guided Progression Analysis™ (GPA), Carl Zeiss Meditec, Inc., Dublin, CA analyses are often helpful in determining whether visual field progression has occurred.11,12 For an accurate analysis, appropriate myopic correction during visual field testing is critical. Vuot and colleagues13 demonstrated that increasing myopic correction led to improvement and/or complete resolution of visual field defects in 18 out of 36 eyes with tilted optic discs. Visual field studies were performed using standard Goldmann perimetry. The authors recommend fitting myopic patients with the myopic correction that provides maximal improvement of the defective visual field for accurate analysis.