• Review Article •

Commentary review on peripapillary morphological characteristics in high myopia eyes with glaucoma: diagnostic challenges and strategies

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Abstract

● The incidences of open angle glaucoma (OAG) and high myopia are increasing concomitantly. Considering the aging population and concurrent rapid increase in the number of individuals with myopia, the risk of visual defects caused by highly myopic OAG is likely to increase dramatically over the next few decades. However, precise screening and diagnosis of OAG is challenging because of the tilt and rotation of the optic disc, as well as extensive β-zone parapapillary atrophy in highly myopic eyes. Recent advances in optical coherence tomography (OCT) and OCT angiography (OCTA) technologies imply that both modalities are promising tools for the detection of highly myopic OAG. Notably, the diagnosis of OAG remains to be determined with the longitudinal changes of functional damages (*e.g.* visual field defect, visual electrophysiological changes). We herein describe some aspects of microvascular and microstructural pathology in patients with highly myopic OAG and proposes a framework for the development of novel diagnostic and therapeutic strategies.

● **KEYWORDS:** high myopia; open angle glaucoma; parapapillary atrophy; parapapillary microvasculature; optic disc; lamina cribrosa; optical coherence tomography

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INTRODUCTION

Cross-sectional, population-based studies have demonstrated a relatively high incidence of open angle glaucoma (OAG) in individuals with myopia, compared with nonmyopic individuals[1-2]. The Blue Mountains Eye Study demonstrated a two-fold to three-fold increased risk of glaucoma in individuals with myopia[1]. The Beijing Eye Study reported that ≤-6 diopters of myopia may be a risk factor for glaucomatous optic neuropathy[2]. Considering the aging population and concurrent rapid increase in the number of individuals with myopia, particularly in Asia[3], the risk of visual defects caused by highly myopic OAG is likely to increase dramatically over the next few decades[4-5]. Timely diagnosis of OAG in highly myopic eyes in the early stage of the disease is essential for the proper management and prevention of visual loss.

STRUCTURAL CHALLENGES INVOLVING THE MYOPIC DISC

Characteristic thinning of both neuroretinal rim and peripapillary retinal nerve fiber layer thickness (RNFLT) are hallmarks of glaucomatous optic neuropathy. The identification of glaucomatous damages is challenging in eyes with high myopia[6-8] because it is difficult to distinguish myopia-related structural and functional defects from defects caused by glaucoma[9]. Progressive axial elongation may cause deviations in nerve fiber bundle trajectories[1]. Bedggood *et al*[10] found low concordance with the ISNT rule (*i.e.*, for peripapillary RNFLT, inferior quadrant ≥ superior quadrant ≥ nasal quadrant ≥ temporal quadrant) in myopia. Qiu *et al*[11] reported that 88.4% and 37% of eyes with healthy myopia did not follow the ISNT rule with respect to RNFLT and rim area, respectively, in a cross-sectional population study in Shantou, China. Thus, application of the ISNT rule to the RNFLT and rim area has limited utility in distinguishing OAG from high myopia[11]. Structural evaluation of eyes with high myopia is complicated by unusually large or skewed sclera canal shape, optic disc

tilt and rotation, and extensive β-zone parapapillary atrophy (βPPA)[9,12-13].

RELATIONSHIP BETWEEN STRUCTURAL AND FUNCTIONAL DAMAGE IN MYOPIC GLAUCOMA

A correct understanding of the relationship between structural and functional damage helps to accurately distinguish glaucomatous optic neuropathy from high myopia. However, relevant investigations have been limited by two key factors. First, the relationship between RNFLT and visual field (VF) defects is relatively weak due to structural alterations in the optic nerve head (ONH)/RNFLT distribution in eyes with myopic glaucoma[14]. The poor visibility of the RNFLT in red-free photography and the large area of βPPA beyond the optical coherence tomography (OCT) scan circle prevent an accurate optimal OCT scanning[6]. Second, VF defects in eyes with highly myopic glaucoma are often confusing, due to concurrent myopic chorioretinopathy in eyes with high myopia[15] and/or intraindividual/intertest variability involving both structural and functional evaluations[16]. Elevated intraocular pressure (IOP) is a major risk factor for glaucoma; moreover, IOP is positively associated with increasing myopia[17]. However, the broad range of risk factors for elevated IOP indicates that the biomechanics of the ONH play a key role in the development of highly myopic OAG, whereas they may contribute less robustly to changes in IOP. Lan *et al*[18] showed that the association between myopia and glaucoma was more robust at lower levels of IOP. Therefore, microstructural and functional analysis of the optic disc is helpful for exploring the pathogenesis of highly myopic OAG.

DISC CHARACTERISTICS ASSOCIATED WITH HIGHLY MYOPIC OAG

Optic disc tilt and torsion represent skewed insertion of the optic nerve into the eyeballs and may increase IOP-related stress exposure for a subset of retinal ganglion cell axons[8]. To explore the relationship between functional impairment and structural changes in the optic disc, prospective and retrospective studies have been conducted in eyes with different degrees of myopia. Park *et al*[19] found that the degree of disc tilt and torsion was significantly different between eyes with OAG and normal eyes with similar axial lengths. Choi *et al*[20] found that the direction of optic disc tilt was consistent with the location of initial glaucomatous VF defects. The findings of a recent study indicated that superior disc torsion was predictive of an upper wedge-shaped retinal nerve fiber layer defect and lower VF damage in eyes with highly myopic OAG; eyes that had normal-tension glaucoma with high myopia exhibited smaller discs, lower tilt ratios, and greater disc tilt, relative to eyes without high myopia[18]. Considering the influences of mechanical factors on axons, axial elongation-induced RNFLT thinning may be the anatomical basis for glaucoma-related functional damage in eyes with high myopia. In addition to mechanical factors, there remains uncertainty regarding the roles of optic disc-associated hemodynamic mechanisms in the development of myopia-related OAG. Furthermore, longitudinal observations of peripapillary microvasculature and microstructure are helpful for revealing relationships between axial elongation and highly myopic OAG.

LAMINA CRIBROSA MORPHOLOGY ASSOCIATED WITH HIGHLY MYOPIC OAG

At the ONH, retinal ganglion cell axons converge and pass through the lamina cribrosa (LC), a porous connective tissue structure. The LC is a discontinuity (*i.e.*, "weak spot") in the corneoscleral envelope, which supports and nourishes the axons. Posterior bowing or compression of the LC and/or the dislocation of laminar sheets in the LC (caused by IOP elevation or tissue deformation) may impose shear stress on the retinal ganglion cell axons, thereby impeding axonal transport[21]. The LC is considered the primary site of glaucomatous axonal damage. Swept-source OCT facilitates rapid scanning and deep penetration for the evaluation of LC morphology and LC pores. Multiple aspects of the LC have been evaluated to investigate the close relationship between LC morphology and glaucomatous functional impairment. Thus far, large curvature, reduced thickness, tortuous LC pore paths, and the presence of focal lamina cribrosa defects (FLCDs) have been shown to correlate with glaucoma or highly myopic glaucoma[22-24]. Notably, Yoshikawa *et al*[25] compared the mobility of LC depth in a longitudinal study; they found that LC depth significantly decreased 3mo after glaucoma surgery and that the degree of change in LC depth was associated with the degree of change in IOP. In addition to mechanical factors, the axial elongation-related deformation and compression of LC may induce capillary collapse before or inside laminar layers, resulting in ONH ischemia. Suh *et al*[26] reported that circumpapillary vessel density extracted from the retinal nerve fiber layer was significantly lower in OAG eyes with FLCDs than in OAG eyes without FLCDs. In addition, the reduction of vessel density was spatially correlated with the locations of FLCDs[26]. Suh *et al*[27] investigated parapapillary microvasculature dropout (MvD), defined as a complete loss of microvasculature within the choroid or scleral flange, in patients with OAG. They found that higher FLCD prevalence (odds ratio, 6.27; P=0.012) and reduced circumpapillary vessel density (odds ratio, 1.27; P=0.002) were significantly associated with MvD. These studies have shown that the LC provides critical information regarding glaucomatous optic neuropathy. Both myopia and glaucoma can cause connective tissue remodeling microvasculature abnormalities within the ONH. There remains uncertainty regarding the relationships

of LC morphology with both circulatory disorders within the ONH (*e.g.*, prelaminar, LC, and retrolaminar regions) and glaucomatous damage. Population-based epidemiological surveys and longitudinal research (involving LC morphology, VF, and peripapillary microstructure and microvasculature) may aid in elucidating the pathogenesis of highly myopic OAG.

PARAPAPILLARY ATROPHY ASSOCIATED WITH HIGHLY MYOPIC OAG

Microstructure Changes in Eyes with OAG and Parapapillary Atrophy βPPA is a visible region lacking retinal pigment epithelium[28]. Teng *et al*[29] found that βPPA was correlated spatially with locations of future VF defect progression, in patients with OAG who exhibited βPPA and VF defect progression. Jonas *et al*[7] confirmed that the presence of βPPA was more sensitive for detection of glaucomatous optic neuropathy, compared with cup-to-disc ratio. Moreover, a larger βPPA area was associated with greater prevalence of tilted optic disc[30], as well as thinner LC and deeper anterior LC surface[28]. Thus far, the clinical implications of βPPA in OAG have been described in multiple studies[7,28-29], but the pathogenesis of βPPA remains poorly understood. Notably, there is uncertainty regarding the mechanism of retinal ganglion cell axonal damage. Recent advances in OCT technology have provided additional insights into the mechanisms underlying highly myopic OAG. By using OCT, the presence or absence of Bruch's membrane (BM) can be determined; βPPA can then be histologically subclassified into βPPA_{+BM} or βPPA_{-BM}[28]. To investigate the relationship between βPPA and glaucomatous progression, Yamada *et al*[31] conducted a retrospective cohort study with a follow-up period of ≥2y. They reported that patients with larger βPPA_{+BM} width had more rapid VF progression, compared with patients who did not have βPPA_{+BM}. Sung *et al*[32] demonstrated that the width of βPPA_{+BM} was significantly associated with axial length, tilt angle, and optic disc rotation. Meanwhile, Sung *et al*[32] found that larger optic disc tilt, more inferior optic disc rotation, and lower peripapillary vessel density were all factors related to larger βPPA_{+BM} width; none of these factors were related to βPPA_{-BM}. Some researchers have suggested that the βPPA_{+BM} is caused by age-related atrophy of the retinal pigment epithelium and is associated with OAG[7,33], whereas βPPA_{-BM} may be caused by axial elongation and have a protective effect in eyes with OAG[28,31,34]. Conversely, some studies have reported that βPPA_{+BM} is present in teenagers and children with myopia[28,35]. These findings suggest that the effects of βPPA on glaucomatous injuries may be associated with changes in optic disc morphology and hemodynamics. There remains a lack of clarity regarding βPPA pathogenesis and the mechanism by which βPPA causes damage to the retinal nerve fiber layer. Several factors (*e.g.*, the LC and optic disc) might contribute to highly myopic OAG during βPPA development, but the effect of BM presence or absence on OAG remains elusive thus far.

Microvascular Changes in Eyes with OAG and Parapapillary Atrophy In addition to morphologic changes in βPPA, ischemia around the ONH is presumably involved in the pathogenesis of highly myopic OAG[36]. The microvasculature in deep retinal layers and the choroid around the optic disc is of particular clinical interest because these vascular regions are both downstream from the short posterior ciliary artery[27,37], which perfuses the prelaminar tissue and LC[38]. OCT angiography (OCTA) facilitates noninvasive evaluation of the microvasculature located within various retinal[27] and choroidal layers[39]. Hu *et al*[40] investigated the superficial radial peripapillary capillary and choroidal microvascular density in eyes with healthy myopia and βPPA. Compared with eyes that had βPPA_{-BM}, eyes that had βPPA_{+BM} exhibit lower superficial radial peripapillary capillary and choroidal microvascular densities[40]. MvD has been defined as a focal sectoral filling defect without any visible microvascular network identified in parapapillary deep-layer en face images. Lee *et al*[41] demonstrated that MvD accurately coincided with perfusion defects observed by indocyanine green angiography. Recent OCTA studies frequently showed deep-layer MvD within the ONH in eyes with primary OAG and βPPA[27,36,42]. These findings implied that parapapillary MvD represents a true peripapillary perfusion defect in the choroid or inner sclera, which causes reduced blood supply to the ONH[37]. OAG eyes with MvD had significantly thinner RNFLT, worse VF mean deviation, and larger βPPA_{-BM} than OAG eyes without MvD[43]. The presence of MvD was proposed to serve as a strong predictor for an initial parafoveal scotoma[44] and a strong prognostic factor for progressive retinal nerve fiber layer thinning[45]. βPPA_{-BM} zone is characterized by an oblique scleral flange and MvD in this region develops by stretching of the microvasculature in the scleral flange during axial elongation[46]. The choroidal and peripapillary scleral flange both supplies the prelaminar and LC *via* the circle Zinn-Haller. The circle of Zinn-Haller in myopic eyes without scleral flange exposure (βPPA_{-BM} zone) is located at the end of the peripapillary scleral flange where the dura mater merges with the sclera. The scleral flange exposure and displacement is considered a product resulting from temporal stretching of the peripapillary tissues during axial elongation[46]. Meanwhile, the circle of Zinn-Haller location in scleral flange undergoes stretching and shearing forces; given that circle of Zinn-Haller insufficiency would decrease the vascular support of prelaminar and LC, the development of βPPA_{-BM} zone could hamper the axonal transport[46]. Recent studies with OCTA

frequently detected deep-layer MvD in the ONH in primary OAG with βPPA_{-BM}[27,36,42]. Notably, precisely recognizing and segmentation in BM, choroid and sclera is a prerequisite to evaluate the microvasculature within βPPA zone. As the presentation of choroidal atrophy, BM rupture, and posterior staphyloma accompanied by axial elongation are serious obstacles of automatic segmentation provided by OCT or OCTA, up to now, research on microvasculature is limited to patients with non-pathological myopia[26,36-37,39-41].

Both microstructure and microvasculature around the ONH provide some clues concerning the presence and location of glaucomatous damage in eyes with high myopia. We speculate that the pathogenesis of glaucomatous optical neuropathy induced by βPPA_{-BM} differs from those eyes with βPPA_{+BM}, basing on the differences of deep ONH structures (*i.e.*, LC and deep-layer microvasculature). However, the precise relationships of juxtapapillary microvasculature with the ONH and/or LC topography require further investigation. The pathogenesis of optic neuropathy induced by microcirculatory deficiency, independent of IOP, is incompletely understood. A targeted understanding of BM, rather than βPPA, may aid in revealing the essential etiology and pathogenesis of highly myopic OAG.

EXPLORATION OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES

A common diagnostic dilemma of myopic OAG in clinical practice is the presentation of a patient with ONH changes and borderline high or normal IOP. Even if there are VF defects, it may be difficult to determine if the defects are due primarily to myopia or OAG. Based on these facts that myopic ONH appearance and MvD represents the LC shifting and a true peripapillary perfusion defect, respectively, it seems reasonable to posit that the development or progression of optic disc ovality, βPPA_{-BM} zone, and MvD could provide some clues to diagnosis of myopic OAG. Ophthalmologists should carefully assess the functional damages in patients with significant optic disc tilt and MvD regardless of IOP. As some myopes with VF defects may not show characteristic progression of OAG, necessary nutritional support and glaucoma medications may be considerable to improve blood circulation around the ONH and prevent the progression of glaucomatous optic neuropathy in such patients with borderline high IOP values. It remains uncertain, although, whether or not short-term or long-term IOP fluctuations are independent risk factors for development or progression of myopic OAG, monitoring IOP fluctuation and establishment baseline data are important in management myopic OAG[47]. In addition, longitudinal follow-up in the setting of high myopia with ONH changes may be necessary to confirm the diagnosis.

CONCLUSION

In summary, we focused on current findings of microvasculature and microstructure around and within the ONH, and described the detection of highly myopic OAG by both OCT and OCTA. βPPA has been found to influence the outcome of high myopic glaucoma, whereas the influence of BM on the ONH in eyes with high myopia requires further investigation. The diagnostic utility of OCT and OCTA for glaucomatous optic nerve damages and peripapillary microvascular perfusion defect is promising; it is considerable that nutritional support and glaucoma medications for some myopes with βPPA, MvD, borderline high IOP values and atypical VF defects. However, accurate alignment of the OCT scan beam, as well as adequate centering of the scan circle remains difficult in eyes with pathological myopia resulting in improper image acquisition and structural segmentation[6]. Moreover, there remain obstacles to consistently distinguishing structures and complex lesions among individuals. Improvements regarding image capture, picture recognition, standardized nomenclature and automated calculation, by means of software development and machine learning, are important considerations for future research. For note, the diagnosis of OAG remains to be determined with the longitudinal changes of functional damages (*e.g.*, VF defects, visual electrophysiological changes).

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