ABOUT THE AUTHOR

JING WANG, MD studied medicine at McGill University. She completed her residency in ophthalmology at University of Sherbrooke and two years of adult and paediatric glaucoma fellowship at Moorfields Eye Hospital, London, United Kingdom. She is currently clinical professor and glaucoma specialist at Laval University, Quebec City. Her interests are surgical management of secondary glaucoma, particularly uveitis related and post complex ocular surgery, glaucoma drainage devices and MIGS surgery. She is actively involved in organizing Canadian Glaucoma Society and Canadian Ophthalmological Society Annual meetings.

Glaucoma and myopia: risk factors, pathophysiology, and treatment

Jing Wang, MD

Myopia is one of five most important risk factors for the development of primary open angle glaucoma (POAG) along with older age, elevated intraocular pressure (IOP), sub-Saharan African ethnicity and positive family history of glaucoma.[1] There are a few facets to consider when we discuss myopia and glaucoma. First, axial myopia (high myopia) increases the susceptibility of the optic nerve head (ONH) to IOP-related damage, therefore POAG occurs more frequently in a physiological normal IOP range in patients with high myopia. Second, there is evidence that POAG progresses faster in high myopes when IOP is elevated due to this increased susceptibility. Third, many myopes have undergone laser corrective surgery which can lead to an underestimation in the measurement of IOP and may delay the diagnosis of POAG in this group of patients. Fourth, high axial myopia is associated with atypical optic disc appearance and myopic macular degeneration. Both can cause visual impairment and make clinical assessment of glaucoma difficult. Moderate myopia is also associated with pigmentary glaucoma which is a common sub-type of open angle glaucoma. Finally, myopic patients are at risk of retinal detachment. The surgical treatment of retinal detachment can lead to a secondary form of glaucoma and worsen pre-existing POAG.

Clinicians should be reminded that patients with childhood glaucoma develop secondary myopia as a result of high IOP on very elastic developing eyes, particularly if the IOP was uncontrolled at a young age. The focus of this article is on the relationship between primary myopia and glaucoma.

Myopia is a risk factor for glaucoma - pathophysiology

Population-based landmark studies have consistently identified myopia as an independent risk factor impacting both the prevalence and incidence of POAG across different ethnic groups (Asians, Caucasians and Hispanics).[2-4] Myopia is associated with a 2-3 fold increased risk of developing glaucomatous optic neuropathy (GON).[2] High myopia, defined as -6 or -8 diopters or an axial length of ≥ 26.5 mm, is more strongly associated with POAG than low-to-moderate myopia.[4] However, pigmentary glaucoma, a special type of open-angle glaucoma, is associated with moderate myopia instead of high myopia.[5]

The pathophysiology underlying high myopia as a risk factor for POAG is thought to be related mainly to the biomechanics of the ONH.[6] The ONH is the structure in the posterior ocular fundus that allows the exit of the retinal ganglion cell axons and the entry and exit of the retinal blood vessels through a specialized connective

tissue called the lamina cribrosa (LC). The retinal ganglion cell axons at the level of the ONH form the rim of optic nerve as seen on fundus exam and the part of the LC without retinal ganglion cell axons forms the cup of the optic nerve. The LC is a porous structure continuous with the oval sclera opening which is referred to as the scleral canal; the portion of sclera surrounding the LC is referred to as the scleral flange. The biomechanical properties of the LC and that of adjacent sclera are different. The LC serves as pressure barrier between the intravitreal compartment with the pulsating IOP and the retrobulbar compartment with the cerebral space fluid pressure. Axial elongation of myopic eyes is associated with both enlargement and rotation of the ONH. This disc enlargement is achieved by the stretching and thinning of the LC as well as the enlargement of the scleral canal opening and the thinning of the scleral flange. The thinning of the LC reduces its mechanical support to the surrounding axons, making the latter more susceptible to the stress of IOP. The thinning of the LC potentially steepens the pressure gradient between the IOP and cerebrospinal fluid (CSF) pressure, presumably increasing glaucoma susceptibility of highly myopic eyes. The effect of myopia on the development of POAG is the increased susceptibility of the ONH to IOP-related damage. GON is more likely to occur in high myopia even within a normal IOP range. However, this susceptibility of the ONH is more accentuated with higher IOP. Several smaller clinical studies have suggested that myopia and IOP have synergistic effects on the risk of POAG development and progression.[7]

Myopia and intraocular pressure (IOP)

IOP is not necessarily more elevated in myopic patients compared to emmetropic or hypermetropic patients.[4] Some studies have suggested that the development of POAG in moderate myopia is associated with elevated IOP, but in patients with high myopia and POAG, IOP has been shown to be normal, suggesting an increased susceptibility of the ONH to a normal range of IOP in high myopia.[8] There are two particular scenarios that clinicians should keep in mind. First, moderate myopia is associated with pigmentary glaucoma which is a high-IOP open angle glaucoma. Second, with the popularity and ease of access to laser refractive surgery, many myopic patients have previously undergone Laser in situ keratomileusis (LASIK) to correct their myopia by thinning their corneas. Patients who have undergone LASIK are at a higher risk of developing glaucoma compared to the general population due to their myopia. By thinning the cornea, LASIK surgery renders the measurement of IOP inaccurate and mostly underestimates the true IOP. Numerous studies have tried to select the most accurate tonometer in measuring IOP for patients who have undergone laser refractive surgery.[9] While some tonometers are more accurate than others, the simplest way of monitoring IOP in post-LASIK patients is to use the widely available gold standard Goldmann Applanation Tonometer while keeping in mind that the true IOP may be underestimated. Precise and reproducible measurements of IOP are perhaps more important for longitudinal follow-up of patients and for monitoring their response to IOP-lowering therapy. It can be an exercise in futility to establish baseline IOP in post-LASIK patients with POAG as the target IOP depends ultimately on the speed of deterioration and severity of glaucomatous damage.

Myopia and pigmentary glaucoma

Pigmentary dispersion syndrome (PDS) is a well-recognized clinical entity that is associated with moderate myopia due to posterior bowing of the iris which causes the release of pigments from the posterior iris epithelium and the heavily pigmented trabecular meshwork (TM) due to the deposit of these pigments.[5] Clinical signs include posterior bowing of the iris (reverse pupillary block), trans-illumination of the iris viewed with retroillumination technique, vertical deposits of phagocytosed pigments on the posterior cornea due to the convection of aqueous humour (Krukenberg's spindle), deposits of pigments on the posterior lens zonules and posterior capsules of the lens (Scheie stripe or Zentmayer ring when it is circumferential) **(Figure 1).** On gonioscopy exam, an even, heavily-pigmented, velvety and thickened TM line is pathognomonic of PDS when other clinical signs are absent. Pigmentary glaucoma (PG) is almost always a high-IOP glaucoma with the primary pathology at the TM. This pathology includes the TM being overloaded with phagocytosed pigments leading to TM cell necrosis, the elevation of IOP and development of GON. PDS and PG occur most commonly in young, moderately myopic males. The dispersion of pigments tends to decrease with age. After active pigmentary dispersion stops, the patient's IOP can remain elevated, or it may normalize depending on the degree of TM damage during the active pigmentary dispersion phase. However, clinicians should keep in mind that further deterioration of PG can still occur at normalized IOP if the damage to the optic nerve is severe enough. Regardless of the initial high IOP associated with PG, advanced stage PG typically requires eye pressure to be maintained in the single digit-to-low-teen range in order to slow down or prevent further deterioration.

Glaucoma in high myopia - a diagnostic dilemma

The diagnosis of GON in patients with high myopia can be challenging. Whereas the development of POAG in moderate myopia is often accompanied by elevated IOP, in high myopia, this may not be the case.[8] High axial myopia is associated with parapapillary changes, myopic

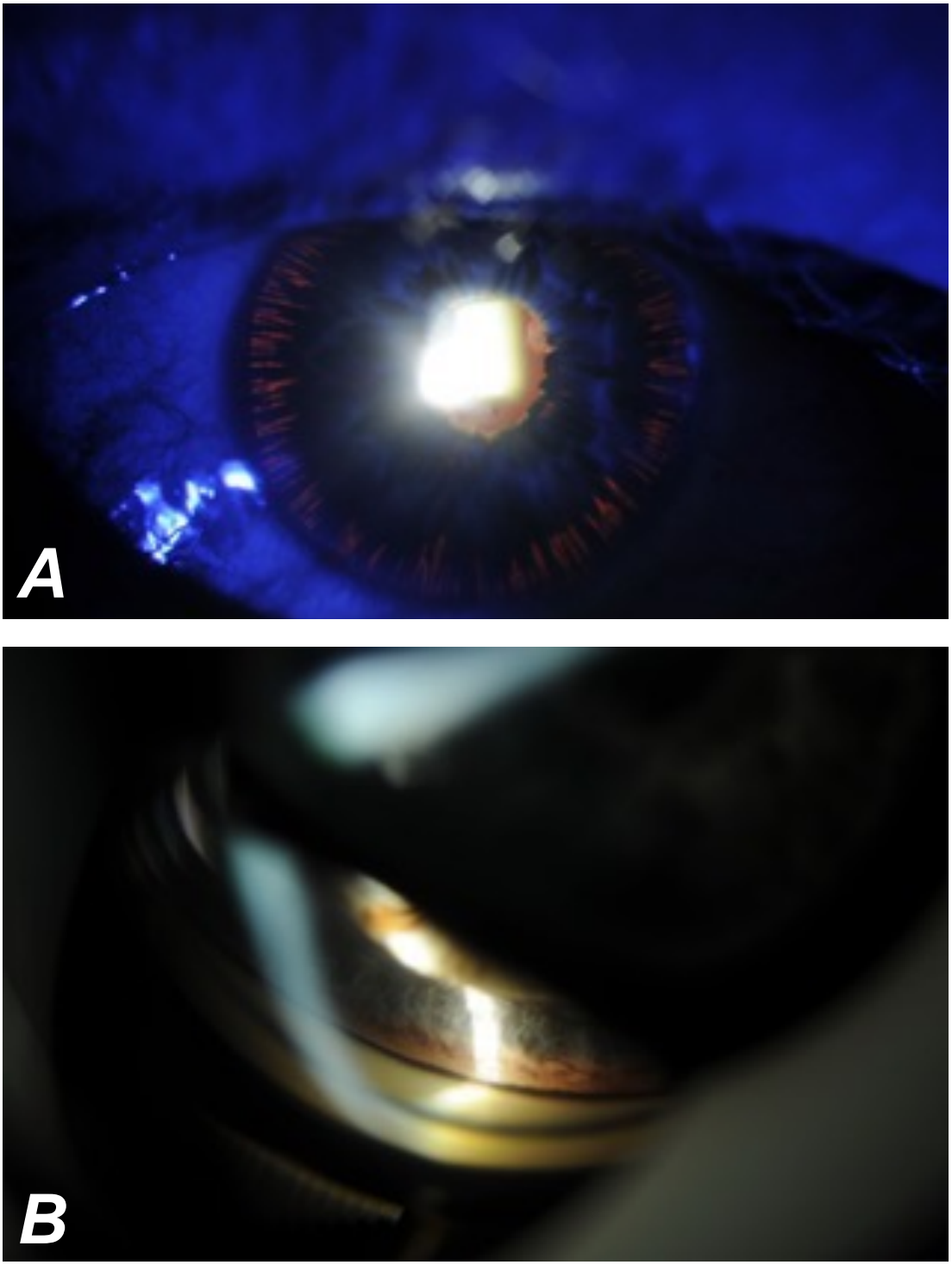

Figure 1. Pigmentary dispersion syndrome (A) Spoke like transillumination viewed with retroillumination technique at slit-lamp; B) Gonioscopic view of heavily pigmented trabecular meshwork and posterior bowing of iris; photo courtesy of Jing Wang, MD

macular degeneration and posterior staphyloma that can lead to visual field deficit similar to that of POAG. In addition, the assessment of the optic nerve in high myopic eyes is challenging for multiple reasons. First, the ONH is rotated due to axial elongation which gives rise to an oblique view on clinical exam. Secondly, both the colour and height contrast between the optic nerve rim and cup in myopic eyes are less obvious due to the enlargement of the ONH in high myopes. Thirdly, parapapillary changes such as those seen in the gamma and delta zones are frequent in high myopic eyes and they are difficult to distinguish from the glaucoma-related changes in the beta

	HISTOLOGICAL FINDINGS	CLINICAL ASSOCIATION
Alpha zone	Irregular pigmentation of retinal pigment epithelium (RPE)	Found in normal eyes
Beta zone	Absence of RPE over Bruch's membrane	Associated with glaucoma and speculated to be IOP dependent
Gamma zone	Absence of RPE and Bruch's membrane with bare sclera	Found in moderate-to-high myopic eyes
Delta zone	Absence of RPE and Bruch's membrane with elongated and thinned peripapillary scleral flange - i.e. the inner zone of Gamma zone	Found in high myopic eyes

Table 1. Four types of parapapillary zones and their clinical associations; photo courtesy of Jing Wang, MD

zone on clinical exam alone **(Table 1).** These myopia-related parapapillary zones also make assessment of the retinal nerve fiber layer (RNFL) in the peripapillary region extremely difficult.[10]

The accuracy of diagnostic imaging tools such as optical computed tomography (OCT) is reduced in highly myopic eyes.[(11)] One of the commonly encountered diagnostic errors using OCT with high myopes is the abnormal RNFL measurement of the RNFL due to the temporal convergence of RNFL bundles. This require clinicians to give careful consideration to the interpretation of the RNFL thickness map.[(12)] The inferior and superior temporal rims and RNFL bundles are thickest in a healthy optic nerve (shown as double humps on the RNFL distribution map). The thinning of these two areas are early signs of GON. The superior and inferior temporal RNFL bundles are temporally displaced in the high myopic eyes compared to the normal emmetropic eyes. This temporal displacement results in false-positive results on the deviation map (i.e. the deviation map will show thinning despite the average RNFL thickness being within the normal limit**.** Besides RNFL thickness, the macular ganglion cell inner plexiform layer (GCIPL) thickness has emerged as another structural parameter for diagnosing and monitoring glaucoma. However, this parameter also has its limitations in high myopic eyes. Long axial length eyes have been reported to have thinner maculae and may lead to false positive findings of thinning on the GCIPL thickness map.[13] Furthermore, the presence of myopic macular degeneration and patchy atrophy can cause abnormalities in the macular region, independent of established glaucoma.

An accurate diagnosis of POAG in high myopia requires a multitude of clinical signs taking into account IOP, disc assessment, and auxiliary tests such as fundus colour photo, OCT and visual field. Clinicians should bear in mind that the IOP can be normal despite the presence of advanced glaucomatous damage or the true IOP can be underestimated if patients have undergone previous LASIK surgery. The disc can be difficult to evaluate due to the above-mentioned reasons. Auxiliary tests can have false positive results and visual field deficit may not always be evident due to glaucomatous change. In cases where the diagnosis is uncertain and the IOP is below the normal range, it is not unreasonable to closely monitor patients through ongoing testing and IOP measurement without any intervention.[14] The hallmark of POAG is that it is a progressive disease. Further deterioration of the visual field with longitudinal follow-up can clarify the diagnosis and help in tailoring the appropriate treatment plan.

Glaucoma management in myopic patients

POAG is often over-diagnosed and over-treated in the setting of high myopia due to false-positive results on OCT, large disc and large cupping, the presence of parapapillary changes and visual field deficits that may not be due to glaucomatous damage.On the other hand, we also encounter many post-LASIK patients who are under-diagnosed and under-treated due to inaccurately low IOP readings. Establishing an accurate diagnosis and initiating appropriate treatment is critical for patients' well-being and quality of life. Clinicians should avoid initiating treatment solely based on OCT abnormalities, especially when the visual field is normal. In the presence of visual field deficit, clinicians should ensure that these deficits are not due to macular atrophy associated with myopic macular degeneration. If the visual field deficit is severe and progressive, clinicians should have a low threshold to initiate or augment treatment.

It is worth emphasizing that while angles are likely to be open in high myopes, gonioscopy is absolutely mandatory in the clinical evaluation of glaucoma. Lenticular myopia can lead to low, moderate or even high myopia. Causes for

lenticular myopia include an evolving cataract, the forward movement of cilio-lenticular complex, and retinopathy of prematurity which can occasionally lead to lenticular myopia and anterior position of the lens and consequent angle closure. In these cases, the angle can be narrow or even closed on gonioscopy. As a result, the treatment approach would be different in the case of angle closure as the goal would include reversing the angle closure in addition to IOP lowering.

Once the diagnosis of POAG has been established, treatment is focused on the lowering of IOP regardless of baseline IOP. The target IOP depends on the severity of the glaucoma and its rate of progression. Both medical treatment with topical glaucoma medication and selective laser trabeculoplasty (SLT) should be considered as first line treatment options.[15] The maximum baseline IOP in untreated high myope and post-LASIK patients can be low (usually in the mid-teens). It is common to see post-LASIK patients with very thin corneas who have developed GON at IOP levels in the low teens. In these situations, a single-digit IOP level is likely required to arrest disease progression. In case of PG, the treatment principle is similar although SLT should be considered with caution given the higher risk of IOP spike. The use of laser iridotomy to reverse the posterior bowing of the iris has not been shown to provide clinical benefit in the treatment of PDS.[15]

When the visual field continues to deteriorate despite aggressive and comprehensive treatment strategies, glaucoma surgery is required to further reduce IOP with the hope of preventing further deterioration. The target IOP fundamentally depends on the severity of glaucoma damage to the visual field regardless of the untreated baseline IOP. In the last decade, numerous angle-based techniques involving minimally-invasive glaucoma surgery (MIGS) have emerged and broadened the surgical options that can be offered to patients. Despite the higher safety profile of MIGS and angle-based surgery, these surgical techniques rarely result in patients reaching single-digit IOP levels that are required in the management of advanced glaucoma. Filtering surgery such as trabeculectomy involving the use of antimetabolites and glaucoma drainage devices is still the most effective IOP-lowering surgery that surgeons can offer to glaucoma patients with severe damage. One particularly frequent complication of filtering surgery in myopic patients is hypotony maculopathy, which arises due to a more elastic sclera in myopic eyes. Hypotony maculopathy can unfortunately develop when the IOP is at the desired target but the macular folds are visually handicapping for the patients. The incidence of hypotony maculopathy is lower with the use of glaucoma drainage devices and newer MIGS filtering surgery, however this lower incidence is partially because the final surgical IOP is not as low as that which can be achieved by trabeculectomy. Ultimately, the visual function of the patient is still more important than the numerical IOP value.

Summary

Myopia and glaucoma are both common clinical entities. The diagnosis of GON can be challenging in high myopic eyes as the patient's IOP may not necessarily be elevated. The atypical disc and myopic macular degeneration in high myopes decreases the accuracy of auxiliary imaging tests and both can cause visual field deficits that resemble POAG. Myopic patients who have undergone previous LASIK surgery have inaccurately low IOP readings with all tonometers, which may delay the diagnosis of glaucoma in this particular sub-group of patients. Clinicians should also pay particular attention to the higher prevalence of PG in myopes and rare cases of angle closure associated with myopia. The management of POAG with coexisting myopia follows the same principles of open-angle glaucoma management - to further lower IOP and to monitor deterioration. Hypotony maculopathy is a particular complication of filtering surgery that is more frequent in myopic eyes.

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