Know These Major Risk Factors in Primary Open Angle Glaucoma

Glaucoma is a concerning health issue due to its asymptomatic nature, risk of blindness, and increasing prevalence. Worldwide, it is the leading cause of irreversible blindness, and it is estimated that 111.8 million people will have glaucoma by the year 2040.[1] Therefore, early diagnosis is important; however, this is no simple task due to its complexity.

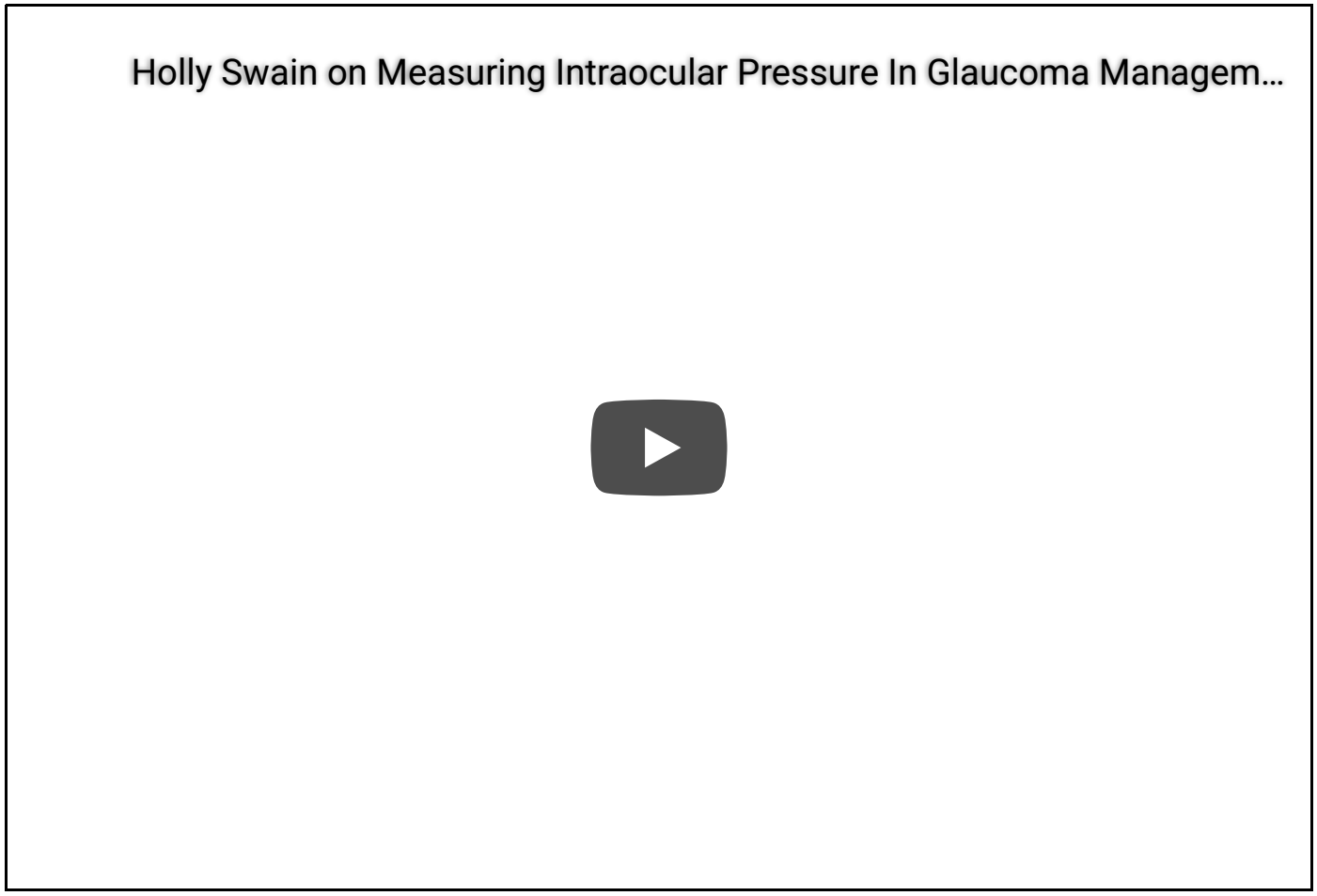
Let us begin with a definition-the AOA defines glaucoma as "a group of eye disorders that lead to progressive damage to the optic nerve."[2] Many different types fall under that definition and will be referred to in this article as "glaucoma."

This article will aim to focus on primary open angle glaucoma, which will be referred to as "POAG."

POAG is a diagnosis of exclusion and has been defined as "a chronic optic neuropathy with characteristic changes in the optic disc and corresponding typical defects in the visual field for which IOP is the only treatable risk factor."[3]

It is helpful to mentally separate these into the categories of non-ocular and ocular risk factors.

Newest ways to measure IOP in glaucoma patients:



Non-ocular Risk Factors

- AGE – Most of the literature states that being over age 60 is a risk factor, but some sources go as young as 40.[2]
- RACE – Studies indicate that African Americans have a six times higher risk of developing glaucoma than Caucasians, and the onset of glaucoma is ten years earlier in African Americans than in Caucasians.[4] Hispanics and Asians are also at an increased risk for glaucoma compared to Caucasians.[4]
- GENDER – There is no clear gender predilection.[5]
- FAMILY HISTORY – Approximately 60% of glaucoma patients have at least one family member who also has glaucoma.[4] Having a first degree relative (immediate family member) with open angle glaucoma (primary or secondary) increases a person's lifetime risk of developing glaucoma from 2.3% to 22%.[4] Having a sibling with glaucoma increases one's risk from 0.7% to 10.4%.[4]

- SYSTEMIC CONDITIONS – Multiple systemic conditions can increase one's risk.
- DIABETES – Multiple case-control studies and population-based cohort studies indicate diabetes likely increases the risk of glaucoma.[6]
- HYPERTENSION – The association between blood pressure and glaucoma has been found in numerous studies. The Blue Mountains Eye Study found that increased systolic blood pressure is linked to increased IOP. Other studies have suggested that low diastolic pressure may be associated with glaucoma.[4]
- MIGRAINE – An increased risk for Open Angle Glaucoma (primary and secondary) has been found in those with migraines, but only for those aged 70-79.[7] Another study indicated that a history of migraines is more common in patients with any form of glaucoma.[8]
- VASOSPASM – Peripheral vasospasm has been listed in some studies as a risk factor for normal tension glaucoma (NTG).[4]
- OBSTRUCTIVE SLEEP APNEA – Obstructive sleep apnea has been associated with glaucoma in some studies. However, more research is needed to confirm if it is indeed an independent risk factor.[9,10]
- SMOKING – It remains unclear whether or not smoking cigarettes increases one's risk for glaucoma.[11]

Ocular Risk Factors

The following are ocular risk factors which may lead to the progression or worsening of glaucoma.

Myopia

Increased axial length and myopia have both been found to be risk factors for open angle glaucoma. It has been suggested that this risk increases with increased myopia.[4]

IOP

It is well established that elevated IOP is a risk factor for glaucoma. One result of the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study is the development of risk calculators for patients with increased IOP.

Pachymetry

The OHTS investigators found that those with CCTs ≤ 555 µm had three times the risk of progressing POAG than those with CCTs > 558 µm. Also, the risk of progressing to POAG doubled for every 40 µm decrease in CCT from the mean of 573.3 µm. Numerous charts and calculators exist to adjust IOP based on CCT. Most use a correction factor of ±1 for every ±20 µm from 545 µm. The researchers called CCT a "predictive factor" as it is still unknown if CCT is an independent risk factor regardless of IOP or if the proposed risk is linked to its association with IOP.[12-15]

Angles

Of course, when considering a diagnosis of open angle glaucoma, it would be a good idea to confirm that the angles are indeed open via gonioscopy and/or anterior segment OCT. Be sure to assess for psuedoexfoliation, angle recession, neovascularization, etc. to exclude secondary open angle glaucoma.

Optic Nerve

C/D: A normal C/D ratio is typically between 0.30 and 0.50.However, if the optic nerve head itself is smaller or larger, then the C/D ratio should be expected to be correspondingly smaller or larger. Therefore, a small C/D ratio in a small disc is not necessarily comforting, but a large C/D ratio in a large disc is not necessarily concerning. Also, keep in mind the ISNT rule and that the horizontal C/D ratio is typically larger than the vertical in a non-glaucomatous eye. The ISNT rule states that the neuroretinal rim should

appear thickest to thinnest, inferiorly, superiorly, nasally, and temporally. Asymmetry between the two eyes of more than 0.20 may indicate early glaucoma.[16]

Nerve

Glaucomatous damage may present with a deepening of the cup, exposed lamina cribrosa (seen as laminar dots), sloping of the disc margins, focal cup excavation, and/or bean potting (seen by a break in the pathway of the vasculature at the optic cup margin).[17]

Peripapillary atrophy (PPA)

PPA appears in two regions: beta zone, which is a crescent-shaped area located adjacent to the optic nerve, and alpha zone, which is located beyond beta zone in relation to the optic nerve head. Beta zone PPA is a chorioscleral crescent representing atrophy of the RPE and choriocapillaris. It is hypopigmented and corresponds with an absolute scotoma.[18] Alpha zone peripapillary atrophy (PPA) is a crescent of hyperpigmented irregularities in the RPE and corresponds with a relative scotoma.[18] Alpha zone PPA may be present in normal and glaucomatous eyes. Beta zone PPA is more common in glaucoma, but it may be present in up to 20% of normal patients.[16,18]

Retinal nerve fiber layer (RNFL)

RNFL defects appear as dark striations or reduced brightness in the peripapillary area. They are typically wedge-shaped and located superiorly and inferiorly. It is believed that these RNFL defects represent the loss of axon bundles. This atrophy typically precedes field loss.[16]

Vascular

Disc hemorrhages can occur above the rim, in the nerve fiber layer, or at the lamina cribrosa and are typically splinter or flame shaped. Their presence is rare in normal eyes and is highly suggestive of glaucoma. Nasalization of the central vessels, baring of the circumlinear vessels, vessel bayonetting, and vessel overpass are each indicative of glaucoma.[16] Nasalization refers to the central vessels being displaced nasally. Baring is characterized by the circumlinear vessels becoming more exposed by receding of the cup. The typically indistinct thin circumlinear vessel borders become more distinct as this occurs. Bayonetting describes a sudden angular change as the vessel traverses the rim. Overpass refers to when a vessel extends into the cup beyond the rim due to rim loss.[18]

Visual Fields

When glaucoma is suspected, the most commonly used perimetry technique is standard automated perimetry (SAP). It is generally considered to be the best method of monitoring glaucoma patients for functional changes. It has been suggested that Short Wavelength Automated Perimetry (SWAP) may detect glaucomatous field loss 3-5 years before SAP. However, this is controversial, and SWAP is not often used.

The Matrix Frequency Doubling Technology (FDT) has been shown to be superior at detecting early glaucomatous changes.[19] It accomplishes this by preferentially stimulating the retinal ganglion cells of the magnocellular pathway. Whatever perimetry machine is used, the 24-2 testing pattern is typically utilized. This tests the central 24 degrees and two nasal locations that are 30 degrees from fixation. The SITA Standard and the Matrix FDT each take about five to ten minutes per eye.

Since there is a significant learning curve to taking a visual field test, the first test should be regarded with suspicion, even if the reliability indices are good. Typically, two consecutive, reliable, and consistent tests are needed to establish a baseline.

The Pattern Standard Deviation (PSD) global index is more relevant in the diagnosis of glaucoma. A repeatable PSD of 5% statistical significance is suggestive of glaucoma. However, other pathologies may also affect the PSD.

Early glaucomatous visual field defects typically present as nasal steps, paracentral scotomas, arcuate bundle scotomas, or temporal wedges. The presence of one or more of these suggests glaucoma. If repeatable, a group of three or more adjacent points showing statistically significant reductions in sensitivity with at least one point reaching the $p < 1\%$ significance level should be considered suspicious. If all points are on the same side of the horizontal meridian, one should consider this indicative of glaucomatous damage.

The Glaucoma Hemifield Test (GHT), which is given on most visual field print outs, analyzes the superior and inferior hemifields and compares for discrepancies between them. This is significant as glaucomatous defects typically present asymmetrically with regards to these two hemifields. Two consecutive "Outside Normal Limits" alerts are suggestive of glaucoma.

The Mean Deviation (MD) global index is a comparison of the deviation of a particular patient from age matched norms. It can be affected by uncorrected refractive error, pupil size, and media opacities and is not specific nor sensitive for glaucoma. A change of 2 dB per year is likely pathologic.[18]

Ocular Coherence Tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) measures the differences in light reflectivity of different tissue layers.

These differences in light reflectivity allow the instrument to segment and measure these layers. By calculating the distance between the ILM and the RNFL border the instrument can quantify the thickness of the RNFL. While

visual fields are poor detectors of early glaucomatous changes and better of late ones, the reverse is true of OCT. It is better at detecting early changes and worse at detecting late ones. Of course, comparing VF defects with OCT defects and finding agreement strongly suggests glaucoma.

Many instruments will compare some values to a normative database. Each manufacturer has its own unique database and each instrument utilizes different methods of measuring and calculating. Thus when comparing results from different instruments, do so with caution.

The best ONH parameters to examine when attempting to distinguish between normal and early glaucoma have been shown to be:

- global RNFL thickness
- vertical rim thickness
- rim area
- RNFL thickness in inferior quadrant
- vertical C/D ratio

Special attention should be paid to the global RNFL thickness as it has a very high accuracy and reproducibility for detecting glaucomatous changes. A change of more than 5 µm on global RNFL thickness is suspicious for glaucoma. Any changes detected should be confirmed with a subsequent confirmatory test as false positive can occur.[20] Many instruments will also report horizontal C/D ratio, cup volume, RNFL symmetry, and disc area.

Most OCTs also have the ability to perform a Ganglion Cell Analysis of the macula. Multiple studies have concluded that the ability to distinguish between normal eyes and glaucomatous eyes via GCA is high and comparable to other SD-OCT studies. GCA measures the thickness of the macular ganglion cell layer and compares it to a normative database. Again, each instrument does this in a slightly different manner and each compares its values to a normative database.[21,22]

Most of the instruments' software package includes some sort of progression analysis program. This can be very valuable as detectable progressive thinning would seem to indicate an active disease process, such as glaucoma.

Other Tests

Electrodiagnositcs and Corneal Hysteresis (CH) are becoming more common when diagnosing glaucoma.

These tests are relatively new and most clinicians do not have ready access to the instruments. However, a brief discussion is warranted.

Diopsys has a pattern ERG and VEP instrument available to clinicians called the Neuro Optic Vision Assessment System (NOVA). One study indicates that pattern ERG can detect early glaucomatous changes as much as eight years earlier than OCT. Another study found that VEP can detect functional loss in patients with structural deficits but normal visual fields.[22,23]

Hysteresis is the energy lost to dissipation when stress is applied to a viscoelastic material, such as the cornea. CH is determined by measuring the pressure at which an airjet causes the cornea to deform inward and the pressure at which it returns to normal. Reichert's Ocular Response Analyzer (ORA) combines noncontact tonometry with CH and calculates a corneal compensated IOP (IOPcc). Studies have shown that IOPcc gives a better indication of the true IOP and that lower CH values are significantly associated with risk of progression. Therefore, the ORA would presumably be beneficial in diagnosing and managing glaucoma.[24-26]

Primary Open Angle Glaucoma is a complex disease that is difficult to diagnose. Considering the patient's risk factors, IOP, ocular anatomy appearance, and advanced diagnostic testing results in a systematic way will greatly aid in the diagnosis.

One important point to remember is that *glaucoma is progressive*. Diagnosis of POAG suspect and initiating additional testing should have a low threshold given that the additional testing is non-invasive. One of the key deciding factors when trying to differentiate between POAG suspect and POAG is if there is any worsening of the structure or function of the optic nerve. Keep this in mind and diagnosing POAG will hopefully be a bit less difficult.

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