Glaucoma Suspect

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ABSTRACT

Glaucoma suspect describes a person with one or more risk factors that may lead to glaucoma, but this individual does not have definite glaucomatous optic nerve damage or visual field defect. The number of individuals with eye findings that raise a suspicion of glaucoma, usually elevated intraocular pressure (IOP) or asymmetric optic disk morphology, far exceeds the number of people who have been diagnosed with glaucoma. Increased IOP, family history of glaucoma and thin cornea are the main three contemporary risk factors. Optic nerve and retinal nerve fiber examination, visual fields and pachymetry are crucial in setting target pressures for glaucoma suspects and deciding the appropriate follow-up/therapy.

Keywords: Glaucoma, Suspect, Risk factors, Tonometry, Field, Management.

INTRODUCTION

A glaucoma suspect is an individual with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing primary open-angle glaucoma (POAG). The clinical findings that define a glaucoma suspect are characterized by one or more of the following in an individual with open angles by gonioscopy: Appearance of the optic disk or retinal nerve fiber layer that is suspicious for glaucomatous damage A visual field suspicious for glaucomatous damage Consistently elevated intraocular pressure (IOP) associated with normal appearance of the optic disk and retinal nerve fiber layer and with normal visual field test results.

A great overlap can exist between findings in patients with early glaucoma and those who are glaucoma suspect without the disease. These patients with suspicious findings are at increased risk of developing glaucoma. The ocular hypertension treatment study (OHTS) recently demonstrated the rate of participants developing glaucomatous optic neuropathy to be 9.5% in five years or close to 2% per year. The rate was previously estimated to be close to 10 per 1000 (1%) per year.

More than 100 million people have elevated IOP. More than 3 million people worldwide are blind secondary to POAG; about 2.4 million people develop POAG each year. Many of these patients are being treated, but the indications for treatment are not clear-cut. Many others are glaucoma suspect based on the suspicious appearance of the optic nerve head or other risk factors.

In India, glaucoma is the third leading cause of blindness with 12 million people affected accounting for 12.8% of the country's blindness. Population-based studies report a prevalence between 2 and 13%.

With an early diagnosis and timely therapy, the goal is to prevent glaucoma-related blindness. The goal of identifying and treating patients who are glaucoma suspect is to preserve visual function by monitoring them for the earliest signs of glaucomatous damage. In individuals who are at a high risk of developing glaucomatous damage, preventive measures, including lowering IOP, may be indicated.

PATHOPHYSIOLOGY

In general, the cause of glaucomatous optic neuropathy is unknown. The disease affects the individual axons of the optic nerve, which may die by apoptosis, also known as programmed cell death. Multiple theories exist concerning how IOP can be one of the factors that initiates glaucomatous damage in a patient. Two of the fundamental theories include the mechanical and vascular theory.

Mechanical Theory

The mechanical compression theory suggests that elevated IOP causes a backward bowing of the lamina cribrosa, resulting in kinking of the axons as they exit through the lamina pores. This may deprive the axons of neurotrophins or interfere with axoplasmic flow, thereby triggering cell death. Neurotrophins increase RGC survival and may be produced by the RGCs themselves. Damaged RGC axons are affected by neurotrophin deprivation. With the loss of neurotrophic support of the RGCs, slow death is inevitable. Brain derived neurotrophic factor (BDNF) is one such neurotrophin that can temporarily increase the survival of the RGCs by inhibiting the excitotoxicity-related cell death. Deficiency of these protective factors may contribute to glaucomatous optic neuropathy.

Vascular Theory

The vascular theory proposes that cell death is triggered by ischemia, whether induced by elevated IOP or as a primary insult. Studies done to evaluate the circulation of the optic nerve...
using the laser Doppler flowmetry have shown diminished blood flow in the optic nerves of eyes with POAG.  

**Contributory Mechanisms**

Complementary to vascular compromise and mechanically impaired axoplasmic flow, additional pathogenic mechanisms that underlie glaucomatous optic neuropathy include excitotoxic damage from excessive retinal glutamate, peroxynitrite toxicity from increased nitric oxide synthase activity, immune-mediated nerve damage and oxidative stress.  

Beyond the neuronal degeneration that results from the primary insult or risk factors in glaucoma, there is an expanding cascade of events referred to as “secondary degeneration”, during which RGCs are gradually damaged from the unfavorable milieu of the neighboring degenerating neurons.  

Many pathophysiological mediators common to all neurodegenerative diseases, including glaucoma, have been identified, such as increase in glutamate, conformationally altered self proteins, increase in inflammation-associated factors [cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF alpha), nitric oxide (NO)], increase in extracellular matrix proteins and growth-associated inhibitors (myelin-related proteins), oxidative stress, and malfunctioning of local immune cells (microglia). These mediators evoke a response for which the tolerance of the neural tissue is minimal.

**RISK FACTORS**

The overall likelihood of developing glaucomatous optic neuropathy increases with the number and strength of risk factors, which include the following:

Elevated IOP, increasing age, family history of glaucoma, thin central corneal thickness, black races and increased CD ratio.

In addition, migraine headache and peripheral vasospasm have been identified in some studies as risk factors for progressing to glaucomatous optic nerve damage. The association between factors, such as concurrent cardiovascular disease, systemic hypertension and myopia, and the development of glaucomatous optic nerve damage has not been demonstrated consistently. The relationship between diabetes mellitus and progression to glaucomatous optic neuropathy is unclear.

IOP: IOP is a definite and important risk factor for developing glaucomatous damage but is not sufficient for a diagnosis. The prevalence of POAG is higher with increasing IOP. One-fifth of patients with ocular hypertension develop field loss within 10 years. Each year, about 2% of all individuals with increased IOP progress to glaucomatous damage. As many as 50% of patients with glaucomatous optic neuropathy or visual field changes have IOP of less than 21 mm Hg on initial evaluation. Some eyes undergo damage at IOP of less than 18 mm Hg; others tolerate IOP of more than 30 mm Hg. A pressure range of 10 to 21 mm Hg is considered normal; a nongaussian distribution occurs with a skew toward higher pressures. Diurnal variation 2 to 6 mm Hg is considered normal, greater than 8 mm Hg variation suggestive of glaucoma. Peak usually occurs in the morning hours. However, the probability of injury increases exponentially with higher IOP. Large diurnal fluctuation in IOP is another independent risk factor for glaucoma.

**Age:** Age older than 40 years is a risk factor for the development of POAG. Up to 15% of African-American men are affected by the ninth decade of life. Consequently, glaucoma is found to be more prevalent in the aging population, even after compensating for the mean rise in IOP with increasing age. However, the disease itself is not limited to only middle-aged and elderly individuals. The prevalence of POAG is 3 to 10 times higher among individuals older than 80 years (than people in their 40s).

**Family history** is a definite risk factor. Heritable susceptibility has been shown. Between 10 and 20% of patients with glaucoma have a positive family history. Ask about family history of glaucoma, especially in first-degree relatives. Family history of glaucoma in a sibling is the greatest risk factor, followed by glaucoma in a parent. Also, ask if glaucoma in other family members resulted in vision loss (the individual may have only had ocular hypertension). The Baltimore Eye Survey found that the relative risk of having glaucoma is increased 3.7-fold for individuals who have siblings with POAG. The Rotterdam Eye Study concluded that the prevalence of glaucoma was 10.4% in siblings of patients with glaucoma and the relative risk of having POAG increased 9.2-fold for individuals with a relative with POAG. High IOP may be the inherited feature of glaucoma, or inherited risk factors independent of IOP may be involved.

**Thin cornea:** OHTS showed central corneal thickness as a significant predictor of the development of POAG. Patients with a central corneal thickness of less than 555 μm had a three times greater risk of developing POAG than patients with a central corneal thickness of greater than 588 μm. Central corneal thickness (CCT) is an important risk factor for the development of glaucoma. CCT likely influences the measurement of IOP with many tonometers, including applanation techniques. Increased CCT beyond the mean of 545 μm causes overestimation of IOP; lower CCT translates into underestimation of the IOP. A thin cornea (e.g. 480 μm) may occur with glaucomatous visual field loss despite normal applanation IOP because the measurements are fallaciously low. Conversely, a thick cornea (e.g. 620 μm) might occur in an eye with high IOP, normal visual fields and a normal optic nerve because it results in false overestimation of true IOP. It is likely that central corneal thickness may itself constitute an intrinsic risk (or protective) factor for glaucomatous optic nerve damage independent of its ability to affect the IOP measurement.

**Race:** As evident from Figure 1 black races are particularly at risk followed by Hispanics. Indian races are more at risk compared to Whites. Nearly 50% of all primary glaucomas in adult Indians are angle closure glaucoma types.
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Journal of Current Glaucoma Practice, September-December 2011;5(3):5-11

WORK-UP

History

Glaucoma in one eye is associated with increased risk of future damage in the other eye. Development of visual field defects, in an average of 5 years, in about 29% of untreated undamaged fellow eyes.

Ocular Trauma

Retinal vascular occlusion: In individuals who are susceptible, increased IOP is associated with a risk of developing central retinal vein occlusion (CRVO).

Current or past use of steroids: Topical steroids may elevate pressure in certain individuals. Optic nerve damage may be residual from previous increased IOP associated with steroid use. The elevation of IOP is usually seen within a few weeks of starting topical steroids. Homeopathic and ayurvedic medication arguably have been shown to accelerate glaucoma process.

Systemic history includes the following conditions that have been associated with risk factors for developing glaucoma:

Low blood pressure: Also includes overmedication of systemic hypertension. A previous episode of hypotensive shock, trauma, vascular surgery, or hemorrhage can be significant; it may indicate that optic nerve damage is not progressive but may have been a onetime insult.

History of vasospastic disorders: A higher prevalence of migraine headaches and Raynaud’s syndrome exists with normal-tension glaucoma.

Medications: In individuals who are susceptible, steroids may cause a rise in IOP. Anticholinergics (antihistamine and antipsychotics) may precipitate angle-closure glaucoma. Cardiovascular disease may be a factor in low-tension glaucoma.

Hypertension

Diabetes mellitus: Small association, some studies have reported a higher prevalence of increased mean IOP and POAG with diabetes mellitus. Diabetes is a questionable risk factor for glaucoma. The association may be a result of self-selection into the health care system.

Family History

Review of old records: Note previous IOP, cup-to-disk ratios, ocular surgery, and past visual fields.

PHYSICAL

IOP measurement: Goldmann-type applanation tonometry is the standard criterion. Often in a busy general ophthalmic practice, the tendency is to diagnose glaucoma based solely on a single Schiotz or non contact tonometry. With well understood fallacies associated with both of these tonometers it is a must to perform applanation tonometry or short of that Pneumotonometer atleast more than once before calling the patient as glaucoma suspect. Where possible, preferred practice is to check IOP numerous times before initiating treatment to assess diurnal variation. Abnormally thick corneas may result in artificially high IOP measurements by application tonometry, while abnormally thin corneas may result in artificially low IOP measurements (Fig. 2).

Corneal pachymetry: Must be done in all glaucoma suspects. Important for two reasons- influences IOP measurement by all tonometers including Goldmann application as discussed above. Also following OHTS study is an independent risk factor for developing glaucoma (Fig. 3). It can be performed optically with an attachment to slit lamp but popular now is the ultrasonic...
pachymeter. Taking an average of three central corneal readings is good practice.

**Slit lamp examination:** Look for signs of secondary causes/risk factors of glaucoma.

Corneal endothelium—Krukenberg spindle, keratic precipitates, pigmentary changes on endothelial cells.

Anterior chamber angle depth—identification of narrow occludable depth.

Iris—mid iris spoke-like transillumination defects (seen in pseudoexfoliation and pigment dispersion). Dandruff-like material on pupillary margin and on lens capsule (pseudoexfoliation).

Neovascularization pseudoexfoliation—increases with advanced age, pigment dispersion (25-50% risk of developing glaucoma).

**Gonioscopy:** Perform on all patients who are glaucoma suspect, and repeat it periodically. It is especially important in the following cases:

- The chamber is shallow, and IOP raised
- With risk factors (e.g. hyperopia, symptoms of subacute/acute angle-closure glaucoma, narrow angle) are evident
- Patient is diabetic, vein occlusion is present
- A history of ocular trauma exists.

Evaluation of following gonio findings may be relevant on gonioscopy in different patients:

- Narrow-angle depth or angle closure
- Angle recession
- Heavy pigmentation of TM (pigment dispersion) or patchy pigmentation of TM (pseudoexfoliation)
- Hemorrhage
- Peripheral anterior synechiae
- Neovascularization of the angle.

**Evaluation of the Optic Nerve Head**

The best examination method is a slit lamp combined with a 78D, or 90D lens through a dilated pupil. Advantages are high magnification, stereoscopic view and excellent illumination. Special attention should be paid to contour and color of optic nerve head (ONH).

Normal vertical cup-to-disk ratio is 0.3. In a normal rim, the inferior portion is thickest, followed by the superior rim, then nasal and last temporal (ISNT rule). Patients with myopia have larger eyes and larger disks and cups. Assessing optic nerve damage in small optic disks with minimal cupping may be difficult. Large optic disks may appear pathologic when they actually show only physiologic cupping.

**Signs of early glaucomatous damage can be subtle (Figs 4A to C).**
- Generalized enlargement of cup, progressive enlargement of cup, vertical elongation of cup, cupping to rim margin.

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![Fig. 3: Risk for developing primary open-angle glaucoma varies with central corneal thickness. The numbers and percentage of participants in the observation group who developed primary open-angle glaucoma (median follow-up 72 months) are indicated below each bar. Participants are grouped by baseline intraocular pressure of IOP < 23.75 mm Hg, 23.75 to < 25.75 mm Hg, and > 25.75 mm Hg and by central corneal thickness measurements of d > 555 µm, >555 to > 588 µm, and > 588 µm. These percentages are not adjusted for length of follow-up.](image)

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![Figs 4A to C: Glaucomatous optic neuropathy: (A) Vertical oval cup. ISNT rule not met, (B) wedge shape RNFL defects on red-free photography, (C) advanced glaucoma changes with asymmetry.](image)
• Focal thinning or notching of neuroretinal rim, thinning of inferior-temporal rim, acquired change in disk rim appearance
• Superficial splinter hemorrhage
• Asymmetry of cupping or rim between two eyes
• Nerve fiber layer dropout or deficit, acquired change in retinal nerve fiber layer
• Exposure of lamina cribrosa
• Peripapillary atrophy
• Baring of circumlinear vessels.

Search for other abnormalities that may account for the visual field defect:
• Tilted disk
• Disk drusen
• Optic pits
• Retinal disease
• Optic atrophy.

Document the appearance of the optic nerve head:
• The preferred technique—baseline stereo disk photographs for future comparison
• Detailed description and drawings
• Automated techniques
  – Scanning lasers ophthalmoscopy (HRT)
  – Polarimetry (GDx)
  – Coherence tomography (OCT) (Fig. 5)

• Evaluation of the retinal nerve fiber layer—Look for nerve fiber layer defects/dropout:
  – Techniques
    - Ophthalmoscopic examination with red-free (green) filter
    - Stereo color photography and red-free photography
  – Instruments for retinal nerve fiber layer analysis
    - GDx, HRT and OCT.

**VISUAL FIELD TESTING**

• Absence of visual field defects does not always suggest absence of glaucoma
• As many as 40% of optic nerve fibers in a single optic nerve may be damaged before visual field defects are found by perimetry
• Interpretation of visual field testing
  – Use comparable tests when comparing fields. For example, one cannot directly compare Swedish interactive thresholding algorithm (SITA) with Fastpac or HVF 30-2 threshold testing
  – If a field defect is detected, ensure that it is reproducible by doing repeat field analysis
  – The abnormal points should be contiguous, paralleling the pattern of the nerve fiber layer in an arcuate pattern respecting the horizontal midline
  – The greater the abnormal points and the deeper the defects, the more likely it represents a true scotoma.

**Fig. 5:** OCT is a preperimetry tool for diagnosis and follow-up of glaucoma suspects. In this scan, left eye is definitely glaucomatous and in right eye, OCT helped diagnose glaucoma and treatment was instituted. Note the superior RNFL defects and corresponding inferior notch in right eye
The standard testing strategy used by many ophthalmologists in past evaluations has been HVF (Fig. 6) 30-2 or 24-2 traditional threshold testing with statistical analysis. Newer strategies are:

- **Humphrey fastpac**: Requires less testing time; decrease in precision of threshold algorithm estimate.
- **Swedish interactive threshold algorithm (SITA)**: Reduces testing time by nearly half without sacrificing accuracy. Less interindividual variability occurs, and gray scale printouts easier to interpret.
- **Short wavelength automated perimetry (SWAP)**: Uses blue target on a yellow background to isolate those visual pathways that are believed to be damaged selectively in early glaucoma. Many studies suggest that it is capable of earlier detection of glaucomatous defects, which may be useful in those patients who are glaucoma suspect and at a high risk. More difficult to perform for the patient and requires longer testing time.
- **Frequency-doubling technology (FDT/FDP) perimetry**: Uses a coarse striped grating of rapidly alternating dark and light bands. Takes 4 to 5 minutes for each eye; screening test takes less than 1 minute. Potential role exists in screening for early glaucoma.

**Other Problems to be Considered**

- Physiologic cupping
- Intermittent angle-closure glaucoma
  - Optic atrophy (e.g. chiasmal tumors, syphilis, ischemic optic neuropathy, drugs, retinal vascular or degenerative disease)
  - Previous ischemic damage to the optic nerve (e.g. previous hypotensive event, vascular surgery, hemorrhage, shock)
  - Hematologic disease (e.g. anemia, polycythemia vera)
  - Congenital optic nerve abnormalities (e.g. myopic disks, coloboma, optic nerve pits).

**MANAGEMENT**

**Target Intraocular Pressure**

In managing the glaucoma suspect, the ophthalmologist strives to achieve a stable range of measured IOPs deemed likely to protect against optic nerve damage. The estimated upper limit of that range is considered the “target pressure”. The target pressure will vary among patients, and in the same patient it may vary during the clinical course. For glaucoma suspects not being treated, the target pressure can be viewed as that pressure over which treatment would be recommended (i.e. the threshold for the initiation of treatment).

If therapy is initiated, the ophthalmologist assumes that the measured pretreatment pressure range is that which places the optic nerve at risk for damage. The OHTS (which limit enrollment to patients with an IOP of 32 mm Hg or below) used a target pressure 20% lower than the mean of several baseline IOP measurements and 24 mm Hg or below. This seems an appropriate initial goal. At present, there is no a priori way to determine the pressure below which optic nerve damage will be prevented in any particular patient. The initial target pressure is an estimate based on experience and judgement of the glaucomatologist. Current IOP and its relationship to the target IOP should be evaluated at each visit. The status of the optic nerve in relation to glaucoma changes is good start point to set target pressure. With each additional risk factor for glaucoma that the individual patient may have the target should be reduced appropriately.

Failure to achieve and maintain a target pressure should trigger a reassessment of the treatment regimen in light of the potential risks and benefits of additional or alternative treatment. In a glaucoma suspect, a definite deterioration in optic nerve structure or visual field (i.e. conversion from glaucoma suspect to glaucoma patient) indicates that the target pressure should be reduced and the patient managed as glaucoma patient.

**Therapeutic Choices**

If the decision to begin treatment is made, the choice of initial therapy depends on numerous considerations, and discussion of treatment with the patient should include appropriate options. In most instances, topical medications constitute effective initial therapy. The prostaglandin analogs are the first choice monotherapy and the beta adrenergic antagonists are often used as second choice for lowering IOP in patients with glaucoma. Other supplemental agents used include alpha 2 adrenergic agonists, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.

To determine the effectiveness of topical therapy, it may be useful to begin by treating only one eye and comparing the relative change of the IOP in the two eyes at follow-up visits. If a drug fails to reduce IOP, it should be replaced with an alternate agent. If a single medication is ineffective in lowering IOP to target levels, combination therapy should be tried. Generally, beyond three topical medications it is good practice to consider...
laser trabeculoplasty as supplement before considering filtering surgery or drainage devices.

**Follow-up**

The frequency and the composition of follow-up evaluation depend on the age of the patient, the level of elevation of IOP, the appearance of optic nerve head cupping, a family history of glaucoma, the presence of additional risk factors, and the stability of the patient’s clinical course.

In general and depending on the patient’s risk factors, check IOP every 3 to 12 months. If the patient is a low-tension glaucoma suspect with normal IOP but suspicious optic nerve head cupping, conduct a diurnal assessment of IOP.

Perform visual field examinations every 6 to 12 months. If a new visual field defect is suspected, the test should be repeated to ensure that the defect is reproducible.

Gonioscopy and optic nerve head evaluation are generally performed annually.

Baseline documentation, such as stereo disk photographs, should be obtained for future comparison to objectively evaluate any possible subtle progression. In selected patients, some ophthalmologists prefer to obtain this documentation yearly for detailed comparison.

If the target IOP has been achieved and there is no progression of damage, it is recommended (American Academy of Ophthalmology: Preferred Practice Patterns, 2005b) to follow up with ONH exam and visual field testing at 6 to 18-month intervals. On the contrary, if there is progression of damage and the target IOP has not been achieved, more frequent testing is required until stability is achieved.

**CONCLUSION**

Most patients who are glaucoma suspect do not develop glaucomatous optic nerve damage and/or visual field loss. Overall, about 2% of individuals with ocular hypertension develop glaucoma per year. The risk is higher for patients with additional risk factors. Glaucoma causes silent damage; follow-up care is essential to exclude any progressive change over time that may warrant treatment. Left untreated, patients with optic nerve damage may progress, resulting in progressive loss of nerve fibers and eventually total optic nerve atrophy and irreversible blindness.

**REFERENCES**