Normal Tension Glaucoma

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Many glaucoma patients have normal intraocular pressure, indicating that other factors are contributing to their disease. Lacking the red flag of elevated IOP, optometrists need to maintain a high index of suspicion for normal tension glaucoma so that patients can be diagnosed and receive treatment to prevent progression.

Among patients with glaucoma, 30% or more have intraocular pressures (IOPs) within a so-called “normal” range; and among certain glaucoma subpopulations, such as ethnic Japanese, “normal” IOP rates are even higher. Without the most common indicator of glaucoma—high IOP—normal tension glaucoma (NTG) is harder to detect and, in several important ways, more challenging to manage than glaucoma associated with elevated IOP. This review will examine ways in which normal tension and high tension glaucoma differ and outline a management strategy for optimal detection and management of normal tension variants.

WHAT IS NORMAL?

As convenient as it would be to have one, there is no hard and fast line between normal and abnormal IOP. Studies conducted in the 1950s in the general population found that IOPs ranged between 13 and 30 mm Hg, with an average of 19 mm Hg. Other studies showed average IOP in the general population of 15-16 mm Hg by applanation and 16-17 mm Hg by Schiotz tonometry. The idea of a “normal” IOP originated with population studies conducted by Hollows and Graham in the 1960s showing that 2.5% of the general population (two standard deviations above the mean) had intraocular pressures greater than 21 mm Hg. However, the authors cautioned against misinterpreting their data to mean that IOP above that level indicated clinical abnormality.

As early as the 1960s, researchers were aware that factors beyond IOP likely contributed to glaucoma development. For example, Armaly observed that a majority of individuals with IOP greater than 21 mm Hg did not develop glaucoma over the course of the 7 years, nor were patients with low IOP immune to developing glaucoma.

The lack of a distinct boundary between “normal” and “elevated” IOP is further complicated by significant variability in IOP measurement be-
between IOP-measuring devices, between operators, and between days or even different times on the same day.

**BEYOND IOP**

Rather than relying on an arbitrary cutoff point between normal and high tension glaucoma, we can conceive of glaucoma risk as a continuum. Cutoff points give the erroneous impression of a clean division between two populations: one that is at risk and one that is not. But this is somewhat misleading. Barring certain acute conditions, there is no pressure so high that every patient with it will develop glaucoma, nor is there any sustainable pressure so low that the patient has absolutely no chance of developing glaucoma. Furthermore, focusing on an IOP cutoff point can make it seem as if IOP is the sole risk factor, which is not the case.

Beyond IOP, factors that may be involved in glaucoma pathogenesis include optic nerve sensitivity, non-IOP pressure dynamics (eg, perfusion pressure, translaminar pressure), and immunologic factors. Indeed, what we call “glaucoma” is probably a collection of interrelated (or perhaps dissimilar) diseases with a common endpoint of optic nerve damage.

Translaminar pressure (TP), the pressure across the lamina cribrosa, is a gradient that is thought to enable maintenance of normal structure and function of the optic nerve. The lamina cribrosa is a series of channels in the optic nerve that allows the fibers of the optic nerve to pass from inside the eye back toward the brain. Having a low TP, even if IOP is also low, may be a risk factor for NTG. Translaminar pressure is based on cerebrospinal fluid pressure (CSFP), which is assessed by spinal tap, an invasive procedure not practical in everyday clinical practice. Thus, TP remains a variable that is, for the time being at least, confined to research investigation. However, as more is learned about the role of CSFP and TP in the pathogenesis of NTG, there is increased possibility for research into much needed novel therapeutic approaches beyond IOP lowering.

**HIDDEN HYPERTENSION**

Before a patient is identified as having NTG, efforts should be made to detect elevations in IOP that may be present but undetected. IOP tends to fluctuate throughout the day and night and with varying body positions; sleep studies have observed that IOP may peak in early morning. Assessing IOP at multiple times throughout the day can help uncover diurnal fluctuations in IOP, including high IOP not observed at the initial check.

In addition, systemic medications, specifically oral beta-blockers for the treatment of cardiovascular hypertension, can lower IOP as an unintended side effect. It is important to maintain up-to-date medical and medication histories as a matter of good practice and in order to identify treatments that might affect IOP.

Lastly, using the transcorneal IOP assessment methods currently available to us, IOP may read falsely low in eyes with thin central corneas. And IOP may be falsely high across thicker than average central corneas. It is,

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**STATEMENT OF NEED**

Glaucoma, a group of ocular diseases characterized by progressive damage to the optic nerve, is the second leading cause of blindness worldwide. It affects a significant and growing portion of the US population. As primary eye care providers, medical optometrists are well positioned to identify patients at risk and to diagnose, monitor, and treat glaucoma. However, given that the expanded scope of practice incorporating glaucoma treatment is relatively new, many optometrists lack confidence in their ability to treat this potentially blinding disease. In order to instill confidence and help optometrists make sound clinical judgments about the care of glaucoma patients, *Key Issues in Glaucoma Management* will help optometrists better understand the various aspects and nuances of the disease, including our current understanding of the role of intraocular pressure (IOP) in glaucomatous optic nerve damage. Course content will also include current rationale on glaucoma diagnosis and evidence-based strategies for reducing IOP.

Each installment of *Key Issues in Glaucoma Management* will look at an important topic in glaucoma diagnosis or therapy. Each issue will build from a basic level to instill understanding and confidence in medical optometrists. *Key Issues in Glaucoma Management* aims to support optometrists’ clinical reasoning and decision-making abilities and help them turn medical management of glaucoma into a vital segment of their practices.

**REFERENCES**


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therefore, good practice to measure central corneal thickness in conjunction with initial IOP testing to be sure that IOP determination is not influenced by unusual pachymetry.

THE PATIENT EVALUATION

When IOP is “normal,” eyecare providers should be on the lookout for sometimes subtle physical examination findings consistent with NTG. Although there is overlap with hypertensive glaucoma, features commonly seen in association with NTG include optic disc hemorrhages (flame-shaped or splinter hemorrhages) on the inferior or superior temporal disc border, optic nerve cupping with focal loss of the rim, and peripapillary atrophy surrounding the edges of the optic disc (Figure 1). Optical coherence tomographic (OCT) images should be obtained to record and follow the appearance of the optic nerve (Figure 2). Of course, visual fields and IOP should be assessed.

PERFUSION PRESSURE

It is important to include blood pressure measurement as part of the exam when glaucoma is suspected in order to calculate perfusion pressure (PP). When low, this is a red flag for glaucoma risk. Perfusion pressure is calculated by subtracting the highest IOP from the lowest diastolic pressure. For example, if the blood pressure is 120/80 mm Hg and IOP is 20 mm Hg, the PP is 80 – 20 or 60 mm Hg, which is good. If, on the other hand, the patient’s blood pressure is lower, for example 90/60 mm Hg, and IOP is 15 mm Hg, the PP is 45 mm Hg, which is less favorable. As a rough guideline, PP that is lower than 50 mm Hg is concerning and lower than 30 mm Hg is very concerning.

How low blood pressure may contribute to glaucoma pathophysiology remains unclear. Raynaud’s phenomenon is a vasospastic condition characterized by relatively low blood pressure, cold extremities, and thin body habitus that is more common in women and is associated with higher than average rates of NTG.9 This association points to a likely vascular component, perhaps hypoperfusion of optic nerve tissue, in the pathophysiology of NTG. Low nocturnal blood pressure is more prevalent in those with NTG.10 In some cases, it may be useful to discuss with a patient’s primary care provider whether to switch blood pressure medication from nighttime administration to morning to potentially reduce nocturnal hypoperfusion of the optic nerve.

Another comorbidity to bear in mind when evaluating patients with glaucoma is obstructive sleep apnea, which has been shown to increase risk for NTG.11,12 A sleep study to rule out sleep apnea is appropriate and may be useful in patients with normotensive glaucoma who also exhibit signs or symptoms of sleep apnea.

TREATMENT

As with other forms of open-angle glaucoma, therefore, good practice to measure central corneal thickness in conjunction with initial IOP testing to be sure that IOP determination is not influenced by unusual pachymetry.

Core Concepts

- NTG is likely part of a continuum of open-angle glaucomas.
- NTG is an indication that factors in addition to IOP are important in glaucoma pathogenesis.
- All patients with normal IOP need a careful examination of the optic nerve to rule out early or subtle changes consistent with NTG.
- Management of NTG is similar to other open-angle glaucomas.
glaucoma, treatment of NTG centers on IOP reduction. It is reasonable to start treatment with a topical ocular prostaglandin analog and follow patients closely for adequate response, aiming for about 30% IOP reduction. One new agent, latanoprostene bunod, which is not approved in the US but is in phase III clinical trials, combines the PGA latanoprost with a nitric oxide-donating moiety and may have a positive impact on PP as well as on IOP. I often recommend regular exercise (eg, walking 20 minutes per day) to my patients as an adjunct for IOP lowering. Additionally, while there is a paucity of literature linking smoking to glaucoma, I will often recommend smoking cessation classes to my patients who smoke.

In my experience, it is easier to achieve substantial IOP reduction when IOP is elevated compared to when it is normal or low, so aggressive IOP reduction therapy and monitoring at least as intensively as for hypertensive glaucoma is appropriate. For patients unresponsive to a maximum of three medications (two bottles with one bottle a fixed combination), my practice is to refer for selective laser trabeculectomy or even surgical intervention if progression is continuing.

**CONCLUSION**

Normal tension glaucoma is a common and uniquely challenging clinical variant (or group of variants) of glaucoma. Glaucoma patients with normal IOP need careful retinal examinations and aggressive IOP-lowering therapy and follow-up. As research on glaucoma continues, new insights into the non-IOP parameters that contribute to glaucoma will likely emerge and open the door to new treatments.

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Visual Field Testing for Glaucoma

LEO SEMES, OD, FAAO

Visual field testing serves as the primary method for detecting and evaluating functional loss and progressive damage from glaucoma, but its clinical value depends heavily on obtaining good data.

Visual field testing measures the ability of a patient to detect stimuli of varying brightness throughout the field of vision. In glaucoma, where loss of central visual acuity occurs late, visual sensitivity testing within the central 30 degrees is the primary method of assessing a patient’s visual function. Visual field results are typically used to support a glaucoma diagnosis by identifying the initial functional loss and to establish a baseline to guide management on subsequent visits. Visual fields can also help guide treatment by providing an index of stability or progression for patients on treatment to lower IOP. Most of today’s visual field instruments are equipped with event- and trend-based programs for progression analysis, allowing us to assess the stability of the patient’s disease over time and determine whether treatment needs to be more aggressive.

CLINICAL PERIMETRY

The most commonly used visual field test is standard automated perimetry (SAP), a computerized threshold test with a static white stimulus presented on a white background. SAP measures primarily the central 30 degrees of fixation. Light sensitivity within this region reflects the function of the majority of retinal ganglion cells and over 83% of the visual cortex. Among several stimulus presentation patterns, two are standard in visual field analysis in glaucoma: 30-2 (76 points within 30 degrees of visual field) and 24-2 (54 points within 24 degrees of the visual field but retaining the two outermost nasal points from 30-2, which are particularly sensitive to early change in glaucoma). Because of its shorter testing time and lower error rate, 24-2 has become established as the test of choice in glaucoma.

Researchers have recently found that early glaucomatous damage commonly affects the macula, which represents a small portion of the central field of vision (about 8 degrees in diameter) but contains about one third of the retinal ganglion cells. This finding suggests that a 10-2 test may be of particular value in detecting early glaucomatous changes. The 10-2 pattern tests the same number of points as the 24-2 but is limited to the central 10 degrees of visual field. On the 10-2 tests, points are within 2 degrees of each other, whereas the separation of test points on the 24-2 field is 6 degrees. The closer proximity of the test stimulus on a 10-2 allows for the detection of early defects that might not be seen on a 24-2 test. The dense test pattern can be extremely tedious for patients, and its clinical application is not yet established.

In the US, the most widely used instrument for visual field testing is the Humphrey Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA). The preferred test program for diagnosing and monitoring glaucoma is the Swedish Interactive Threshold Algorithm (SITA) Standard, an algorithm also widely used in clinical trials. Developed to shorten test time, the SITA algorithm takes into account information gathered from surrounding locations as well as responses at each point when calculating threshold values.

GLAUCOMATOUS VISUAL FIELD LOSS

Visual field defects in glaucoma result from axonal loss in the retinal nerve fiber layer secondary to damage at the optic nerve head. Accordingly, a visual field defect should reflect the pattern of nerve fibers in the affected retinal area. As the superior and inferior poles of the optic nerve are most susceptible to glaucomatous damage, visual field progression in glaucoma typically begins with the superior and inferior arcuate fibers. There are three established criteria for determining early damage: a cluster of three or more significantly depressed points (outside the 95% statistical range considered to be normal) on a pattern deviation plot;
abnormal glaucoma hemi-field test; and an abnormal pattern standard deviation value (again, outside the 95% statistical range of normal). Pattern standard deviation may be the most important index when looking for very early changes, but the diagnosis of glaucoma should be considered if any one of the three criteria is met, on repeated testing.

The severity of the visual field defect, an indicator of the degree of functional damage, may be used to determine the aggressiveness of initial therapy and, in established patients, to assess the effectiveness of ongoing IOP-lowering treatment. Several severity grading systems have been proposed and used in different clinical trials. The severity scale incorporated in ICD-9 and ICD-10 coding for staging glaucoma was developed in 2011 by an American Glaucoma Society (AGS) work group based on the extent of the visual field defect and its proximity to fixation.

In the AGS staging system, severity of glaucoma (measured in the more affected eye) is graded using the following definitions: 1) mild or early-stage: optic nerve changes consistent with glaucoma but no visual field abnormalities on any visual field test or abnormalities present only on short-wavelength automated perimetry or frequency doubling perimetry; 2) moderate-stage: optic nerve changes consistent with glaucoma and glaucomatous visual field abnormalities in one hemic-field and not within 5 degrees of fixation; and 3) severe- or advanced-stage: optic nerve changes consistent with glaucoma and glaucomatous visual field abnormalities in both hemic-fields and/or loss within 5 degrees of fixation in at least one hemic-field (Figures 1, 2, and 3).

DIFFERENTIAL DIAGNOSIS

When analyzing perimetry results, it is important to recognize that glaucoma is only one of many possible causes of visual field defects. Visual field abnormalities may result from damage anywhere along the visual pathway, from retina to cortex. The visual field patterns of nonglaucomatous retinal or neurological conditions, however, often differ from that of glaucoma. Tissue damage to the outer retina, for example, will cause defects that may or may not respect either the horizontal or vertical midline. Usually these defects are limited to just one eye, and the local pathologies (eg, retinal vascular occlusions) are visible on fundoscopy.

In contrast, visual field damage from neurological disorders affecting the brain (eg, a brain tumor or stroke) is bilateral (in most cases) and presents in a characteristic pattern. Usually it is a defect respecting the vertical meridian, with a distinct pattern of dense depressions. Post-chiasmal lesions, for example, generally result in defects confined to the contralateral visual hemifield, while pituitary tumors affecting the middle portion of the optic chiasm are known to cause bitemporal hemianopsia.

![Figure 1](image1.png)  
**FIGURE 1** Moderate but not consistently repeatable visual field depressions in a 76-year-old ocular hypertensive patient. The lack of repeatability is due to fixation losses.

![Figure 2](image2.png)  
**FIGURE 2** Severe visual field defects in a patient who also has anterior ischemic optic neuropathy (AION). Central depressions, as well as depressions in both superior and inferior hemispheres, can be seen.
testing requires the subject to maintain variations and artifacts, visual field subjective and susceptible to random disappear on repeat testing. By nature visual field tests often show defects that data is its variability. A patient’s first important problem with perimetric etry is based on identification of any stand the test’s limitations. Perim- field results, it is important to under- 

Figure 3 Trend and event analysis showing stability over a decade in a 54-year-old female glaucoma suspect. The event graph (lower panel) indicates a single point of likely progression (filled triangle) and three sporadic points that are flagged for the first time. All of these points are isolated and not indicators of glaucomatous; the picture is consistent with a stable optic nerve appearance.

TEST VARIABILITY

To appropriately interpret visual field results, it is important to understand the test’s limitations. Perim- etry is based on identification of any variation from normal, yet the most important problem with perimetric data is its variability. A patient’s first visual field tests often show defects that disappear on repeat testing. By nature subjective and susceptible to random variations and artifacts, visual field testing requires the subject to maintain a high level of attention during the test, which can be fatiguing to the patient. Some patients tend to do better on the test than others, but even good test-takers have aberrant results from time to time.

Today’s perimetry software, whether for diagnosis or analysis of visual field progression, has become highly robust. But no matter how robust or innovative the software, it ultimately must rely on input from the patient. Most clinicians do not perform the visual field examination themselves. This makes it critical to have a well-trained and experienced technician as test administrator. Careful test administration is important not only for field analysis but also for practical reasons. In many practices, clinicians can be reimbursed for no more than one visual field test per year. If the data collected is of poor quality, the doctor will have to either wait another year or repeat the test in order to establish the patient’s disease status. When it is in the best interest of the patient, this should be done regardless of reimbursement, which varies by jurisdiction.

Explaining the test process carefully to first-time patients may help prevent unnecessary mistakes. Repeat testing can effectively minimize variability and improve accuracy in recognizing the presence or progression of visual field damage. What is most important, however, is to interpret observed changes in light of other clinical findings. Typically, visual field changes in glaucoma patients correlate well with structural changes in the optic nerve and the retinal nerve fiber layer that are observable on clinical examination or imaging studies. If glaucoma is an elephant, then the best way for us to sidestep the fate of the six blind men is to look at all aspects of clinical assessment.

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REFERENCES
1. Elevated IOP can be missed on a single visit because:
   A. It is temporarily low due to normal diurnal fluctuation
   B. The patient was recently lying down
   C. The patient has a normal trabecular meshwork
   D. All of the above

2. Which of the following is a likely cause of simultaneous loss of temporal visual field in both eyes?
   A. Pituitary tumor
   B. Stroke
   C. Glaucoma
   D. Retinal vascular occlusion

3. Ocular perfusion pressure is determined by which of the following formulas?
   A. Cerebrospinal fluid pressure divided by IOP
   B. Two times systolic blood pressure minus diastolic pressure
   C. Translaminar pressure minus IOP
   D. Diastolic blood pressure minus IOP

4. Within the glaucoma patient population, the proportion of patients with normal tension glaucoma is about:
   A. 0.3%
   B. 3%
   C. 30%
   D. 63%

5. On the AGS severity scale, which of the following is most consistent with mild or early stage glaucoma?
   A. Optic nerve changes consistent with glaucoma and glaucomatous visual field abnormalities
   B. Visual loss within 5 degrees of fixation in at least one hemi-field
   C. Optic nerve changes consistent with glaucoma but no visual field abnormalities
   D. None of the above

6. Which of the following is the preferred test pattern for routine visual field testing in glaucoma?
   A. 60-4
   B. 30-2
   C. 24-2
   D. 10-2

7. Appropriate treatments for normal tension glaucoma may include:
   A. High-dose topical steroid
   B. Ocular hypotensive medication(s)
   C. Cessation of daily NSAID usage
   D. Oral omega-3 supplements

8. Which of the following is the major weakness of visual field testing according to Dr. Semes?
   A. It’s time-consuming
   B. It’s expensive
   C. It’s too complex—clinicians can’t understand it
   D. It’s subjective and results can be variable

9. Armaly observed that:
   A. Most eyes with IOP > 21 mm Hg do not develop glaucoma within 7 years
   B. 65% of eyes with IOP > 21 mm Hg develop glaucoma in 7 years
   C. Glaucoma is common in patients with obstructive sleep apnea
   D. None of the above is true

10. According to Dr. Semes, which of the following is a factor that has significant influence on the quality of perimetric data obtained?
    A. The clinician who reviews the data
    B. The test administrator
    C. The manufacturer of the testing instrument
    D. All of the above