Ms. C, a 59 year-old Asian female presented to our primary care clinic for a comprehensive eye examination. She reported a history of moderate myopia and previously was told she had visual field defects in both eyes due to tilted discs. Her family history is unremarkable, other than one brother who was also told that he has tilted discs. She reported good health, was not taking any medications and her blood pressure was 106/62 mmHg.

Ms. C was correctable to 20/20 in each eye with the following prescription OD: -6.25 -0.75 x080 and OS: -6.00 -0.75 x090. All confrontation testing was normal. Her anterior segment examination was unremarkable: intra-ocular pressure (IOP) was 17 mmHg OD and OS using Goldmann applanation tonometry at 3:58pm and dilated funduscopy revealed optic nerves with very oblique insertion and significant temporal peri-papillary atrophy (PPA). Because of their insertion, the cup-to-disc ratio (C/D) was difficult to determine but was estimated at 0.5 horizontal, 0.7 vertical in both eyes (see Figure 1 and 2). Screening visual field with FDT C20-5 indicated a superior nasal defect OD, and superior and inferior nasal defects OS (see Figure 3 and 4).

Subsequent Humphrey 24-2 SITA Standard threshold visual field revealed a dense superior arcuate defect approaching fixation OD and dense superior and inferior-nasal defects, as well as superior and inferior paracentral defects OS (see Figure 3 and 4).
Figure 5: RNFL OCT OD, OS. Reliable scan (signal strength boxed). OD: RNFL thickness is within norms, but on the RNFL thickness map the disc size is incorrectly estimated as larger than actual disc size. OS: thin inferiorly and borderline superiorly.

At subsequent evaluations, IOP was found to be no higher than 20 mmHg OD, OS. Pachymetry revealed average corneal thickness of 537 and 547 µm, and gonioscopy revealed open angles in both eyes with ciliary body visible in all four quadrants, flat iris approach, 1+ pigment in the trabecular meshwork, and no peripheral anterior synechiae or angle recession OU. OCT of the retinal nerve fiber layer (RNFL) with Zeiss Cirrus SD-OCT showed normal RNFL thickness OD but was considered unreliable due to inaccurate disc size estimation (see Figure 5). RNFL was thin inferiorly and borderline superiorly OS (see Figure 5). Subsequently, the visual field defects were confirmed with repeated testing and the patient was diagnosed as a high-risk glaucoma suspect due to suspicious nerves and significant visual field defects in both eyes. A decision was made to watch for change in the visual field, considering the unusual disc insertion.

Clinical Pearl #1: RNFL OCT Measurements
Although OCT measurement of the RNFL is increasingly becoming standard of care in monitoring for glaucoma, these scans are not always useful in all patients.
The normative database for most OCTs is limited and does not include persons under 18, those with advanced age (eg Cirrus OCT: above age 84), or high refractive errors (eg Cirrus OCT: above -12.00 for myopes and +8.00 for hyperopes). The ethnicities included in the normative database also varies widely by brand.  

Scan reliability can be affected by poor fixation, excessive blinking, media opacities, incorrect identification of retinal landmarks by the OCT software, poor of alignment of the circle scan with the nerve, and missing regions in the scan. 

A reliable scan should have signal strength 6 or higher, be well-centered without gross errors in tracking. 

Make sure the findings corroborate well with the nerve appearance and visual fields. If the OCT indicates that a particular part of the nerve is thin, but it doesn’t appear thin during fundus exam and there is no visual field defect that correlates with that part of the nerve, the OCT findings are less indicative of glaucomatous loss. 

Perform scans at least once a year. Dilation is preferred, but patients with pupils of 4 mm or larger can have an undilated scan. 

A change of at least 10 μm is highly suspicious. However, studies have shown that even a 2 μm change can indicate damage (Spectralis OCT). Currently there is no widely-accepted change in thickness that is considered indicative of glaucoma.

Our case described above raises several questions. Are Ms. C’s large, tilted and myopic appearing discs, is this simply the reason for the visual field defects or could this be glaucoma? If so, what type of glaucoma? Also, are there any other conditions we should be considering? In order to fully characterize our patient’s condition, we need to look at all of the possible causes of her visual field defects, their differentiating characteristics, and use our exam results to determine the most likely diagnosis (see table below).

### Conditions that can Cause Glaucoma-like Visual Field Defects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Differentiating Characteristics</th>
<th>Tests needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Open-Angle Glaucoma</td>
<td>IOP &gt;21 mmHg at any measurement</td>
<td>IOP at different times of the day</td>
</tr>
<tr>
<td>Traumatic Glaucoma</td>
<td>More than 180 degrees of angle recession</td>
<td>Gonioscopy</td>
</tr>
<tr>
<td>Chronic Angle Closure Glaucoma</td>
<td>IOP &gt;21 mmHg at any measurement</td>
<td>IOP at different times of the day</td>
</tr>
<tr>
<td>Pseudoexfoliative Glaucoma</td>
<td>Pseudoexfoliative material on anterior lens capsule, iris, or lens zonules; Iris transillumination defects (TIDs): at pupillary margin; Speckled (non-homogenous) pigment in the angle and at Schwalbe’s line (Sampaolesi’s line); IOP &gt;21 mmHg at any measurement</td>
<td>Slit lamp exam</td>
</tr>
<tr>
<td>Pigmentary Glaucoma</td>
<td>Pigment on corneal endothelium (Krukenberg spindle); Transillumination defects (TIDs) at mid-peripheral iris; Dark, homogenous pigment in trabecular meshwork; IOP &gt;21 mmHg at any measurement</td>
<td>Gonioscopy</td>
</tr>
<tr>
<td>Anomalous disc (eg tilted discs, myopia, optic nerve pit)</td>
<td>No signs of secondary glaucoma (see above); No change of disc appearance; No change of retinal nerve fiber layer (RNFL) thickness; No change of visual field defects</td>
<td>Slit lamp exam</td>
</tr>
</tbody>
</table>


Glaucoma is one of the leading causes of irreversible blindness\(^3\), and as optometrists we dedicate much of our exam to searching for early signs of this disease in order to prevent vision loss. While high IOP is often a useful marker for glaucoma risk, previous research has indicated that more than half of patients with undiagnosed glaucoma have IOPs of 21mmHg or less\(^4\). For glaucoma suspects who have IOP in this range, it is important to understand unique characteristics and signs of NTG in order to know what may raise some red flags for patients with IOP within the normal range.

### Risk Factors for NTG

While NTG is considered to be part of the spectrum of primary open-angle glaucoma (POAG), patients who commonly present with this disease typically have a different profile compared to those with POAG and elevated IOP. Patients with NTG are more commonly women, may have a low body-mass index (BMI), and many have a history of migraine or other vaso-spastic conditions such as Raynaud syndrome\(^5\). It is also more common in Asian populations, particularly Japanese and Mongolian where the vast majority of patients with POAG have NTG\(^4,5\).

### Etiology of NTG

These risk factors appear to be closely related to the unique etiology of NTG. There has been a great deal of research recently into the relationship between blood pressure and NTG; patients with low blood pressure or significant dips in blood pressure at night are at higher risk for glaucomatous field loss\(^6,7\). It is hypothesized that low blood pressure leads to low perfusion of the optic nerve, which deprives the nerve of needed oxygen and nutrients, leading to damage and cell death. Indeed, an even larger number of studies that are examining ocular perfusion pressure (OPP) have noted that patients with low diastolic ocular perfusion pressures (a specific measure of ocular perfusion, see clinical pearl #2) are approximately 2-4 times more likely to develop glaucoma\(^8,9,10\). Lastly, it has been shown that patients who have NTG or are suspects for NTG test positive for sleep disturbances such as sleep apnea and sleep hypopnea, which can cause poor perfusion of many organs, including the optic nerve head\(^11\). This research all points towards the importance of understanding a patient’s systemic vascular health to properly characterize their disease.

While perfusion of the optic nerve has been shown to be an important factor for NTG, it is certainly not the only factor. Recent research has also demonstrated that intra-cranial pressure (ICP) plays an important role in glaucomatous damage. Retrospective studies have shown that patients with NTG have lower ICP on average compared to healthy controls, while patients with ocular hypertension but not glaucoma have higher ICP compared to healthy controls\(^12\). It is theorized that the trans-laminar pressure gradient in combination with the lamina cribrosa’s ability to withstand this pressure gradient causes disruption in axoplasmic flow, mechanical changes in the lamina cribrosa, and eventual posterior bowing of the lamina that we see in late-stage glaucoma\(^13,14,15\). Research has shown that these mechanical changes in the lamina cribrosa begin the early stages of glaucoma and progress as the disease progresses, and many theories have developed concerning how these changes contribute to ganglion cell death\(^16,17\).

### Clinical Pearl #2: Measuring Diastolic Ocular Perfusion Pressure

Several studies have linked low ocular perfusion pressure (OPP) with increased risk of glaucoma (including NTG). Diastolic Ocular Perfusion Pressure = Diastolic blood pressure – IOP

- If this number is less than 55 mmHg, there is a significantly increased risk of glaucoma, and this risk continues to increase with lower numbers

### Structural and Functional Changes Observed with NTG

Just as the etiology of NTG involves vascular disorders, common optic nerve characteristics in NTG involve visible vascular disease. Disc (or drance) hemorrhages are particularly common in NTG, and while they have been shown to be a risk factor for progression\(^18\), studies show that 84% of the time, doctors missed the hemorrhages\(^4\). Because these hemorrhages are often subtle, small and transient, consider regularly acquiring optic nerve photos, as hemorrhages are more easily seen on optic nerve photos than on clinical exam. Optic nerve photos are also useful for monitoring rim changes, as well as changes in peri-papillary atrophy (PPA), an independent risk factor for NTG\(^19\).

Studies have shown that as many as two-thirds of patients with NTG present with defects within 10 degrees of fixation\(^5,20\). Therefore, if an initial Humphrey 24-2 or 30-2 shows any defects within 10 degrees of fixation, a
Humphrey 10-2 should also be performed. Subsequently, both visual fields will be repeated to monitor for progression. Take note: a Humphrey 24-2 only uses 12 points to test the central 20 degrees (10 degrees from fixation in all directions), but a Humphrey 10-2 uses 68 points to test the same area. Therefore, if patients have progression of paracentral visual field defects, it is more difficult to observe in a Humphrey 24-2, but is easily caught with a 10-2. Also, any paracentral progression can potentially have a devastating effect on a patient’s quality of life, so preventing paracentral progression is critical. Considering the fact that the speed of visual field progression in NTG is more variable compared to POAG with elevated IOP, it is critical to closely follow a patient with several visual field tests early in the disease to determine how quickly their disease is progressing.

**Treatment of NTG**

While glaucoma has proven to be a complex disease with many contributing factors, our treatment is still currently limited to IOP-lowering drugs and procedures. However, there are a few things to keep in mind when considering treatment options for a patient with NTG. When used twice daily, beta blockers have been shown to decrease blood pressure and lower heart rate at night, which, as discussed before, is a risk for glaucomatous field loss. While brimonidine was once favored for NTG due to its hypothetical neuroprotective qualities, recent research regarding this has been inconclusive. Topical carbonic anhydrase inhibitors have been shown to increase blood flow velocities at the central retinal and short posterior ciliary arteries, which in theory would be beneficial to patients with NTG, though there have been no studies to date demonstrating that this drug is superior to others for patients with NTG. Of course, prostaglandin analogs are an excellent first-line therapy considering their significant IOP-lowering effects and low risk of systemic side effects. While a target IOP should be determined based on the severity of glaucoma, the highest IOP, the patient’s expected lifespan and other factors, in most cases an initial goal to decrease the IOP by 30% is appropriate since this has been shown to significantly reduce the risk of progression of field loss.

### NTG: Pearls to Remember

- More than half of patients with undiagnosed glaucoma have IOP of 21 or less.
- Patients with NTG have different systemic characteristics compared to those with POAG and high IOP.
- Low blood pressure and low intra-cranial pressure have been proven to be significant risk factors for NTG.
- Disc hemorrhages are more common in patients with NTG, but are commonly overlooked in clinical exam.
- The majority of patients with NTG have paracentral visual field defects, which should be monitored with a more detailed paracentral field test (e.g. Humphrey 10-2).

### NTG: Bringing it All Together

How can one incorporate all of this research and the clinical exam to fully understand our patient’s risks for NTG? First, ask about common systemic characteristics of patients with NTG (see Table NTG: Common Patient Characteristics) to determine how closely the patient matches this profile. Also consider measuring blood pressure in-office to monitor how this correlates with IOP at different times of the day. While there is no current method of measuring ICP in a non-invasive way, there will likely be new ways to perform this measurement in the future. In examining the optic nerve, be particularly vigilant when looking for hemorrhages and consider taking photos to look for any small hemorrhages that might be overlooked during the fundus exam. If a patient has any visual field defects that approach fixation, incorporate additional paracentral visual field tests to characterize the depth and size of these defects. Finally, carefully consider the treatment based on the patient’s systemic health, tolerance of side-effects, and any additional risks created by the treatment itself.

### NTG: Common Patient Characteristics

- Asian
- Female
- Low BMI (number)
- Low blood pressure
- History of Migraine
- History of vaso-spastic disease (eg Raynaud’s Syndrome)
- History of sleep apnea

In returning to our patient, when we look back at her examination findings, we can see that she has many characteristics of a typical patient with NTG. She is Asian, female, and has low blood pressure (with estimated diastolic ocular perfusion pressure of 45 mmHg (diastolic blood pressure - IOP = 62mmHg - 17mmHg) from initial examination findings). Her optic nerves have significant PPA and her visual field shows paracentral defects in both
eyes. Combined together, all of these findings point towards a higher risk of NTG and prompting a more vigilant observation of the patient. For follow up, we evaluated the patient approximately every 3-4 months over a period of 12 months, and as part of our early work-up to characterize the extent of our patient’s visual field loss, we performed several Humphrey 10-2 visual field tests in addition to the standard field testing with Humphrey 24-2 test. Test results indicated extensive loss of sensitivity immediately superior-nasal to fixation OD, and moderate loss of sensitivity superior and inferior-nasal to fixation OS (see Figure 6 and 7). Due to the depth and location of her visual field loss and high risk for glaucoma, she was prescribed IOP-lowering drops and monitored closely for any progression. Her pressures were immediately lowered from a maximum pressure of 20 mmHg OD/OS to 16 OD and 11 OS, approaching the initial target of 14 mmHg for both eyes (30% reduction from initial max). This pressure proved to be difficult to maintain, however, as the patient was not tolerant of most of the drops prescribed. After attempting several different drops, the patient was able to tolerate tafluprost and achieved pressures at or under the goal of 14 mmHg OU. Over the past 7 years she has shown some minor progression of her visual field, confirming the diagnosis of glaucoma. (Of note: during this time her brother who was also previously diagnosed with tilted discs was subsequently diagnosed with NTG and treated as well.) Thankfully, her paracentral defects have not progressed and she has maintained 20/20 visual acuity and remains asymptomatic.

**Figure 6:** Humphrey 10-2 OD. Reliability indices (boxed) indicate good reliability. Dense superior defect adjacent to fixation.

**Figure 7:** Humphrey 10-2 OS. Reliability indices (boxed) indicate good reliability. Moderate superior-nasal and inferior-nasal defects up to approximately 3 degrees from fixation.

**Conclusion**

This case illustrates NTG risk factors, nerve characteristics, and additional techniques for visual field assessment. Knowing these unique characteristics will enable us to more effectively identify and monitor patients who are at risk. Together with new research regarding the etiology of this condition, we are better equipped to serve our patients with NTG.
1. The following are all common characteristics of patients with NTG except:
   a. History of migraines
   b. High BMI
   c. Female
   d. Asian
   e. Low blood pressure

2. The following are typical visual field defects of patients with early NTG except:
   a. Arcuate
   b. Nasal step
   c. Altitudinal
   d. Paracentral
   e. All of the above are typical

3. All of the following statements about OCT scans are true except:
   a. There is no consensus on what amount of thickness change is indicative of glaucomatous damage.
   b. Signal strength of 6 out of 10 indicates a reliable scan.
   c. Poor fixation can reduce the reliability of a scan.
   d. If the nerve is not aligned within the circle scan, it will be unreliable.
   e. There is a good normative database for patients 16 years of age.

4. Which of the following is not an advised treatment for patients with NTG?
   a. Prostaglandin analogs
   b. Alpha agonists
   c. Carbonic Anhydrase Inhibitors
   d. Beta blockers
   e. All of the above are appropriate

5. What is the equation for calculating your patient’s diastolic ocular perfusion pressure?
   a. Systolic BP – IOP
   b. Diastolic BP – IOP
   c. Systolic BP – Diastolic BP – IOP
   d. 2/3 [diastolic BP + 1/3 (systolic BP – diastolic BP)] – IOP
   e. Diastolic BP – ICP – IOP

6. How many points test the central 20 degrees in a Humphrey 24-2 visual field?
   a. 24
   b. 12
   c. 6
   d. 36
   e. 48

7. The following statements about ICP and glaucoma are true except:
   a. Patients with normal IOP and high ICP are more likely to have glaucoma.
   b. Patients with high IOP and high ICP are less likely to have glaucoma.
   c. Patients with high IOP and normal ICP are more likely to have glaucoma.
   d. Patients with normal IOP and low ICP are more likely to have glaucoma.
   e. All of the above are true.

8. For patients with NTG, what purpose do optic nerve photos serve?
   a. To look for drance hemorrhages
   b. To monitor rim thickness
   c. To monitor peripapillary atrophy
   d. To look for nerve fiber layer defects
   e. All of the above are true

9. The following statements about blood pressure and glaucoma are true except:
   a. Low blood pressure leads to high ocular perfusion pressure
   b. Patients with NTG and low blood pressure are at higher risk for glaucomatous visual field loss.
   c. Patients with NTG are at higher risk for glaucomatous visual field loss if their blood pressure dips at night
   d. It is theorized that low perfusion of the optic nerve leads to cell damage and death.
   e. All of the above are true.

10. You see a 72 year old white male for the first time in your clinic. During the exam, you measure the IOP to be 22 OD and 35 OS. Slit lamp exam reveals iris TIDs at the pupillary margin OS>OD and clear deposits on the anterior lens surface in a spoke-like pattern OS>OD. With gonioscopy, scleral spur is visible in all quadrants OU, and there is speckled pigment in the angle OU. Dilated fundus exam reveals C/D of 0.75 OD and 0.85 OS, and there is a superior nasal visual field defect OS with a screening visual field test. What is the most likely diagnosis?
    a. Pigmentary glaucoma
    b. Primary open angle glaucoma
    c. Chronic angle closure glaucoma
    d. Pseudoexfoliative glaucoma
    e. Normal tension glaucoma
References


