

# NORMAL TENSION GLAUCOMA



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## Normal Tension Glaucoma

1. Discuss clinical features, pathogenesis and management of normal tension glaucoma. (3+3+4) D2011(1999)
2. What is normal tension glaucoma? Etiopathogenesis, clinical characteristics and management of a case of normal tension glaucoma. (2+8) J2016

### Introduction

- Normal-tension glaucoma (NTG) also referred to as low-tension or normal-pressure glaucoma, is usually regarded as a variant of POAG. It is characterized by:
 

i.	IOP consistently equal to or less than 21 mmHg.
ii.	Signs of optic nerve damage in a characteristic glaucomatous pattern.
iii.	An open anterior chamber angle.
iv.	Visual field loss as damage progresses, consistent in pattern with the nerve appearance.
v.	No features of secondary glaucoma or a non-glaucomatous cause for the neuropathy.
- The distinction between NTG and POAG is based on an epidemiologically derived range of normal IOP. It is essentially an arbitrary division that may not have significant clinical value, though it is possible that a spectrum exists in which, towards the NTG end, IOP-independent factors are of increasing relative importance.
- Up to two-thirds of Japanese patients and 30% of Caucasians with OAG may have normal IOP at initial assessments.

### Pathogenesis

- Glaucoma is a multifactorial disease process for which elevated IOP is just one of several risk factors.
- Any etiological factors distinct from those in POAG have not been conclusively determined, although various mechanisms have been postulated including

i. Anomalies of local and systemic vascular function, ✓ Ischemic vascular disease ✓ Systemic hypotension ✓ Vascular autoregulatory defects	ii. Structural optic nerve anomalies iii. Autoimmune disease. iv. Coagulopathies
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- Vascular disease may reduce optic nerve resistance to pressure-induced damage.
- NTG in some patients has been explained by very low CCT, and overall CCT in patients with NTG is lower than in POAG.
- A small proportion of NTG patients have marked nocturnal IOP spikes, sometimes only on testing in supine position
- Some authorities believe normal-tension glaucoma is a variant of POAG in which the optic discs demonstrate greater vulnerability to the effects of IOP.
- Other authorities believe normal-tension glaucoma and POAG have different etiologies.
- Patients with normal-tension glaucoma have been noted to have a higher prevalence of:

1. Hemodynamic crises; 2. Hypercoagulability; 3. Hypertension; hypotension; 4. Abnormal ophthalmodynamometry 5. Increased blood viscosity	6. Elevated blood cholesterol and lipids; 7. Carotid artery disease; 8. Slowed parapapillary, choroidal, and retinal circulations; 9. Peripheral vasospasm, 10. Migraine.
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Local factors	Systemic Factors
<ol style="list-style-type: none"><li>1. Multiple studies have shown abnormalities in local optic nerve or peripapillary blood flow in normal-tension glaucoma as measured by Doppler or laser flowmeters. One such study was able to correlate local optic nerve blood flow abnormalities with functional deficits on the visual field.</li><li>2. Pulsatile ocular blood flow, a possible measurement of ocular perfusion, was found to be reduced in normal-tension glaucoma compared to normal.</li><li>3. Ophthalmic pulse amplitude, a related measurement, may be a marker for general ophthalmic blood flow; this parameter was found to be reduced in normal-tension glaucoma patients compared to normal and those with high-tension glaucoma.</li></ol>	<ol style="list-style-type: none"><li>1. These include abnormal immunoproteins such as anti-Ro/SS-A positivity and heat shock protein antibodies indicating a possible autoimmune mechanism.</li><li>2. Elevated plasma C-reactive protein levels as an indicator of vascular inflammation have been found in normal-tension glaucoma patients compared to normal ones.</li><li>3. Carotid compression could play some pathogenetic role in the condition.</li><li>4. Normal-tension glaucoma patients may have a cerebral ischemic pattern like Alzheimer disease indicating a possible common pathway for the two conditions.</li><li>5. Silent myocardial ischemia and ventricular extrasystoles occur more frequently in normal-tension glaucoma patients (45%), compared with 26% of patients with open-angle glaucoma</li></ol>

### Genetic Factors

- Mutations in the **Optineurin gene** have been associated with normal-pressure glaucoma. Mutations and polymorphisms in this gene located on chromosome 10 seem to be present in about 15% of Japanese patients with normal-pressure glaucoma compared to 5% in the 'normal' population.
- Normal-tension glaucoma patients with the **E50K** mutation in the optineurin gene seemed to have a more severe disease and progressive course than normal-tension glaucoma patients without this mutation.
- Polymorphisms in the **OPA1** gene mutations of which have been associated with dominant optic atrophy have been found in patients with normal-tension glaucoma.

### Risk factors

1. Age	Patients tend to be older than those with POAG, though this may be due to delayed diagnosis.
2. Gender	Some studies have found a higher prevalence in females.
3. Race	NTG occurs more frequently Japanese origin than in European or North American Caucasians
4. Family history	The prevalence of POAG is greater in families of patients with NTG than in the normal Mutations in the OPTN gene coding for optineurin have been identified in some patients with NTG, though also in patients with POAG.
5. CCT	Is lower in patients with NTG than POAG
6. Abnormal vasoregulation	Particularly migraine and Raynaud phenomenon has been found more commonly in NTG than POAG by some investigators; others have found abnormalities just as commonly in POAG. Other systemic diseases associated with vascular risk, such as diabetes, carotid insufficiency, hypertension and hypercoagulability.
7. Systemic hypotension	Including nocturnal blood pressure dips of >20%, particularly in those on oral hypotensive medication.

8. Obstructive sleep apnoea syndrome	may be associated, perhaps via an effect on ocular perfusion
9. Autoantibody levels	have been found to be higher in some groups of NTG patients by some investigators
10. Translaminar pressure gradient	This may on average be larger than in POAG.
11. Ocular perfusion pressure	May be relatively lower than in POAG.
12. Myopia	Is associated with a greater likelihood of glaucoma and of its progression.
13. Thyroid disease	may be more common

## Differential diagnosis

1. Angle closure	should always be ruled out by meticulous dark-room gonioscopy
2. Low CCT	Leading to underestimation of IOP; Suspicion has also been raised that a thin posterior ocular wall may increase mechanical stress in the region of the lamina cribrosa. Prior refractive surgery and corneal ectasia also lead to falsely low IOP readings,
3. POAG	Presenting with apparently normal IOP because of wide diurnal fluctuation. Plotting a diurnal IOP curve over an 8-hour period (phasing) during office hours may detect daytime elevation, but detection of nocturnal IOP spikes requires substantial resource commitment. Intraocular pressure readings can be misleading d/t low scleral rigidity Elevated IOP may have caused damage in the past and now may be in remission because of hyposecretion of aqueous humor that may occur in aged and diseased eyes
4. Previous episodes of raised IOP	May have occurred as a result of ocular trauma, uveitis or local or systemic steroid therapy.
5. Masking by systemic treatment	Such as an oral beta blocker, commenced after glaucomatous damage has already been sustained.
6. Spontaneously resolved pigmentary glaucoma	The typical examination features of pigmentary glaucoma tend to become less evident with increasing age. The IOP in some cases of POAG may also spontaneously normalize over time
7. Progressive retinal nerve fiber defects	Not due to glaucoma such as may occur in myopic degeneration and optic disc drusen.
8. Congenital disc anomalies	Simulating glaucomatous cupping, such as disc pits and colobomas.
9. Neurological lesions	Causing optic nerve or chiasmal compression (including tumors, aneurysms, and cysts) can produce visual field defects that may be misinterpreted as glaucomatous, and neuroimaging should be performed if there is any suspicion; some practitioners routinely perform a cranial MRI in all cases of NTG.
10. Previous anterior ischemic optic neuropathy (AION)/PION	May give rise to a disc appearance and visual field defect consistent with glaucoma. Non-arteritic AION often occurs in a 'crowded' disc, and the fellow eye should be examined for this; prior retinal vascular occlusion should also be considered.
11. Previous acute optic nerve insult	Such as hypovolaemic or septicaemic shock, or head injury.
12. Miscellaneous optic neuropathies	including inflammatory, infiltrative and drug-induced pathology will often be clinically obvious, but can occasionally masquerade as NTG
13. Retinal diseases,	including retinitis pigmentosa and branch vascular occlusion
14. Physiological cupping	Due to large scleral canal
15. Toxic/ nutritional Optic neuropathy	Methanol. Vit B12



## Clinical features

- The clinical features of NTG resemble POAG except for the absence of elevated IOP
- Normal-tension glaucoma is seen in older individuals, especially those over age 60, although it is possible to see rare cases in those under the age of 50.
- The disease appears to occur more often in women than in men.
- A high prevalence of NTG is present in the Japanese population as compared with other racial groups
- History and examination are essentially the same as for POAG but specific points warrant attention

History	IOP
<ol style="list-style-type: none"><li>1. Migraine</li><li>2. Raynaud phenomenon.</li><li>3. Episodes of shock.</li><li>4. Head injury</li><li>5. Eye injury.</li><li>6. Headache and other neurological symptoms (intracranial lesion).</li><li>7. Medication, e.g. systemic steroids, beta-blockers</li></ol>	<ol style="list-style-type: none"><li>1. IOP is usually in the high teens, but may rarely be in the low teens. IOPs are more often 18 or 19mmHg than 10 or 11mmHg</li><li>2. Patients affected with this condition often have borderline or low facilities of outflow and wide diurnal and postural fluctuations of IOP</li><li>3. In asymmetrical disease the more damaged disc typically corresponds to the eye with the higher IOP.</li><li>4. NTG is characteristically bilateral but often asymmetric.</li></ol>
Optic nerve head	
<ol style="list-style-type: none"><li>1. The optic nerve head may be larger on average in NTG in POAG.</li><li>2. The pattern of cupping is similar, but acquired optic disc pit and focal nerve fiber layer defects may be more common.</li><li>3. Peripapillary atrophic changes may be more prevalent.</li><li>4. Disc (splinter, Drance) haemorrhages may be more frequent than in POAG, and are associated with a greater likelihood of progression.</li><li>5. Pallor disproportionate to cupping should prompt a suspicion of an alternative diagnosis.</li></ol>	<ol style="list-style-type: none"><li>6. Some authorities classify NTG into 2 groups based on optic nerve appearance:<ul style="list-style-type: none"><li>✓ a <b>senile sclerotic</b> group with shallow, pale sloping of the neuroretinal rim that is primarily seen in older patients with vascular disease</li><li>✓ a <b>focal ischemic</b> group with deep, focal notching of the neuroretinal rim</li></ul></li><li>7. Some authorities believe that the optic discs are more cupped in normal tension glaucoma, whereas others believe the appearance is the same in the two disorders.</li></ol>
Visual field defects	
<ol style="list-style-type: none"><li>1. Are essentially the same as in POAG</li><li>2. The visual field defects in NTG tend to be more focal (localized), deeper, steeper and closer to fixation, especially with early disease, compared with those commonly seen with high-tension POAG.</li><li>3. Dense paracentral scotoma encroaching near fixation ("shotgun" appearance) is not an unusual initial finding on the visual field tests of NTG patients.</li><li>4. In &gt;50% of patients, field changes are non-progressive over <math>\geq 5</math> years without treatment.</li><li>5. Because of delayed diagnosis, patients tend to present with more advanced damage than in POAG.</li><li>6. A high level of suspicion for a deficit pattern suggesting a lesion posterior to the optic nerve is important</li></ol>	

## Progression risk

- IOPs higher than 15mmHg were twice as likely to progress over a 2-year period as those with IOPs below 15mmHg.
- Patients with wide variation in 24-hour IOP & with disc hemorrhage are at greater risk of progression.
- Drance and coworkers have emphasized that the stable cases are often associated with previous hemodynamic crises, such as episodes of acute blood loss, arrhythmia, and hypotension.

- This same group has suggested that there are two groups of glaucoma patients –
  - ✓ One associated with vasospasm (migraine or Raynaud's phenomenon) and higher IOP,
  - ✓ And one associated with disturbed coagulation, biochemistry suggestive of vascular disease, and little association with IOP.
- Others have identified a subgroup of normal-tension glaucoma patients (approximately one-third) who have focal 'ischemic' changes in the optic nerve and who are also more likely to have hypertension and other cardiovascular problems than those with 'typical' high pressure open-angle glaucoma.
- Risk factors for progression NTG included diabetes mellitus, positive family history, female gender, disc hemorrhage, prolonged cold recovery, increased systolic blood pressure, and history of systemic hemorrhage.
- Patients with advanced optic nerve damage also seem to be at greater risk of progression despite significant pressure-lowering treatment

## Investigation and diagnosis

History of	Blood tests for other causes of non-glaucomatous ON
Previous elevations of IOP, Ocular trauma or inflammation, Steroid administration systemically/eye/nasal/skin. Exposure to toxins, Beta blocker use Hemodynamic crises, including blood loss, Anemia, Hypotensive episodes Low BP. Myocardial infarction, Arrhythmias Stroke Transfusions,	Vitamin B12, Red cell folate, Full blood count, Measurement of hematocrit and hemoglobin levels Erythrocyte sedimentation rate C-reactive protein, Angiotensin-converting enzyme level, Plasma protein electrophoresis Autoantibody screen for antinuclear antibodies. Serologic tests for syphilis, Lyme disease Temporal arteritis, or other causes of systemic Vasculitis
DVIOP	Radiological investigation
Measure the patient's IOP by GAT At various times of the day (diurnal curve), As well as on different days. In the sitting and supine positions May detect elevated IOP in many of these eyes.	Cranial MRI, Carotid Doppler ultrasonography imaging of the carotid arteries, And/or carotid angiography for carotid artery insufficiency.
The slit-lamp examination should rule out	Assessment of systemic vascular risk factors
Pigment dispersion, Exfoliative disease, Recession of the chamber angle Conditions associated with wide swings in IOP.	Blood pressure measurement can be used to calculate ocular perfusion pressure; 24-hour ambulatory monitoring will exclude nocturnal systemic hypotension in selected patients.
Gonioscopy to rule out	Stereoscopic optic nerve evaluation to rule out
Angle closure, Trauma (ie, angle recession), Prior inflammation, Pigment dispersion.	Congenital or acquired optic nerve anomalies coloboma, Drusen, Or physiologic cupping due to a large scleral canal.

- Auscultation and palpation of the carotid arteries may reveal obstructive disease.
- Ocular blood flow assessment (e.g. laser flowmetry) may have useful clinical potential.
- Right and left Visual fields should be carefully viewed simultaneously to find any evidence of respect of the vertical meridians.
- In the setting of atypical findings additional medical and neurologic evaluation should be considered



Unilateral disease, Decreased central vision, Dyschromatopsia, Young age(<60) Presence of a RAPD	Neuroretinal rim pallor, Or visual field loss inconsistent with optic nerve appearance, IOP < 17mmhg before treatment, rapidly progressive despite apparently adequate treatment
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## Treatment

- Further lowering of IOP is effective in reducing progression in many or most patients.
- As a large proportion of untreated patients will not deteriorate (approximately 50% at 5 years), in many cases progression should be demonstrated before commencing treatment.
- Patients with the stable form of the disease probably require no treatment.
- Exceptions include
  - i. Advanced glaucomatous damage,
  - ii. Particularly if threatening central vision,
  - iii. And young age.
- Regular assessment including perimetry should be performed at 4–6 monthly intervals initially.
- The initial goal of therapy is often to achieve a near 30% IOP reduction from a carefully determined baseline IOP.
- If the untreated pressures are in the high teens, then a target of 15mmHg or less seems reasonable
- If the untreated pressures are in the mid-teens, then one should aim for pressures in the 10–12mmHg range.
- **Medical treatment.**
  - i. Betaxolol, brimonidine, and dorzolamide seem to be reasonable agents to consider in low-tension glaucoma, especially if visual field loss or optic nerve damage is progressing with good IOPs.
  - ii. **The alpha-2 agonist** brimonidine may have a neuroprotective effect on the retina and optic nerve in addition to its IOP-lowering effect and may be superior to beta-blockers. Dipivefrin was superior to timolol in preventing visual field progression despite similar pressure-lowering effects.
  - iii. **Carbonic anhydrase inhibitors**, particularly dorzolamide, may improve ocular perfusion.
  - iv. **Prostaglandin derivatives** tend to have a greater ocular hypotensive effect, which may be an over-riding consideration.
  - v. **Topical beta-blockers** can have a dramatic effect on BP in a minority, and may contribute to nocturnal dips, though selective blockade (e.g. betaxolol) may actually have a beneficial effect on optic nerve perfusion.
    - ✓ Betaxolol was better compared to timolol, even though timolol had a more profound pressure-lowering effect.
    - ✓ Betaxolol has also been shown to have some direct neuroprotective characteristics, as well as to produce increased blood circulation around the optic nerve.
  - vi. Many of the traditional medications such as miotics and beta-blocking agents may not produce striking reductions of IOP because the baseline pressure levels are often 15–19mmHg, these agents only produced an average 12–13% reduction
  - vii. Newer agents such as latanoprost and apraclonidine may produce a profound reduction of IOPs, occasionally even into the single-digit range.

- **Laser trabeculoplasty,**

- i. Particularly SLT is a reasonable option to achieve IOP targets.
- ii. The bulk of the evidence suggests that argon laser trabeculoplasty is of limited benefit in normal-tension glaucoma
- iii. But may be worth trying in patients who are reluctant to undergo, or are high-risk candidates for, surgical intervention.

- **Surgery**

- i. The best way to achieve IOPs of 6–10mmHg is through a full-thickness filtering procedure
- ii. May be considered if progression occurs despite IOP in the low teens;
- iii. Full-thickness filtering surgery is said to be most beneficial in those patients whose baseline IOPs are in the upper teens.
- iv. Antimetabolite enhancement of trabeculectomy is likely to be indicated in order to achieve a satisfactorily low pressure.( without MMC 14-15mm of Hg)
- v. Trabeculectomy does lower pressure and seems to slow but not necessarily stop the progression of the condition.
- vi. Patients who have had successful trabeculectomy seem to do better if they also receive systemic calcium channel blocking agents.
- vii. If surgery stabilizes the situation, the fellow eye may be a candidate for filtration in the future.

- **Control of systemic vascular disease**

- i. Such as diabetes, hypertension and hyperlipidaemia may be important, in order theoretically to optimize optic nerve perfusion.
- ii. Disorders such as anemia, arrhythmia, and congestive heart failure should be treated to prevent ischemia of the optic nerve

- **Systemic calcium-channel blockers**

- i. To address vasospasm have been advocated by some authorities.
- ii. CCB agents may increase optic nerve function and improve blood flow to the nerve.
- iii. Nilvadipine, a CCB, improved blood flow around the optic nerve in patients with normal-tension glaucoma.
- iv. Sawada and co-workers have shown prevention of visual field progression using brovincamine, a nimodipine-like agent, compared with placebo.
- v. CCB have a high rate of significant systemic side effects such as flushing and orthostatic hypertension.
- vi. CCB should be reserved for the patient whose glaucoma is deteriorating despite traditional topical agents and surgery

- **Antihypotensive measures.**

- i. If significant nocturnal dips in BP are detected, it may be necessary to reduce antihypertensive medication, especially if taken at bedtime.
- ii. Non-selective topical beta-blockers in particular may cause a profound drop in systemic blood pressure in some individuals.
- iii. Selected patients might be encouraged to increase their salted food intake, in consultation with the patient's cardiovascular physician.



- **Neuroprotective agents**

- i. Of proven benefit are not yet available; memantine is used to retard neuronal death in some CNS disorders, and its use has been adopted in glaucoma by some practitioners.
- ii. Ginkgo biloba (40 mg three times daily) or an antiplatelet agent may confer some benefit in selected cases.

- **Newer therapy**

- i. Recently, attention has turned to agents that might stabilize or improve normal-tension glaucoma by improving blood flow to the optic nerve or by improving nerve function.
- ii. The serotonin antagonist naftidrofuryl has been reported to actually improve visual acuity and visual field performance in normal-tension glaucoma.

## **The Collaborative Normal Tension Glaucoma Study (CNTGS)**

**Purpose-** the Collaborative Normal Tension Glaucoma Study in which patients with progressive normal-tension glaucoma were randomly assigned to observation or treatment

### **Results**

1. IOP lowering by at least 30% reduced the 5-year risk of visual field progression from 35% to 12%, supporting the role of IOP in NTG.
2. Showed that approximately one-third of patients progress at 3 years and about one-half at 5–7 years;
3. In those who progressed, the progression was usually quite slow.
4. This same study showed that risk factors for progression of untreated normal-tension glaucoma are migraine, female gender, and African ancestry.
5. Age, level of IOP, and family history were surprisingly not risk factors for progression.
6. It should be noted that the protective effect of IOP reduction was evident only after adjusting for the effect of cataracts, which were more frequent in the treated group (d/t filtration surgery)
7. Based on the findings of the CNTGS, treatment of NTG is generally recommended unless the optic neuropathy is determined to be stable.
8. Interestingly, 65% of patients in this study did not progress over the study duration despite no treatment, whereas 12% of patients progressed despite a 30% reduction of IOP.
9. Lower treatment benefit among patients with a baseline history of a disc hemorrhage.

## **The Low-Pressure Glaucoma Treatment Study (LoGTS)**

- Showed a high rate of glaucomatous progression in patients treated with timolol.

### **In the Early Manifest Glaucoma Trial**

- IOP lowering with the combination of betaxolol and argon laser trabeculoplasty (ALT) was minimal in eyes with baseline IOPs of 15 mm Hg or lower.
- This suggests that patients with a lower baseline IOP who are progressing may need incisional surgery or medications other than  $\beta$ -blockers to stabilize their disease.



## **I. Glaucoma**

### **A. Elevated intraocular pressure (IOP) not detected**

1. Undetected wide diurnal variation
2. Low scleral rigidity
3. Systemic medication that may mask elevated IOP (e.g., recent beta-blocker treatment)
4. Past systemic medication that may have elevated IOP
5. Elevation of IOP in supine position only

### **B. Glaucoma in remission**

1. Past corticosteroid administration
2. Pigmentary glaucoma
3. Associated with past uveitis or trauma
4. Glaucomatocyclitic crisis
5. Burned-out primary open-angle glaucoma

## **II. Optic nerve damage**

### **A. Congenital optic nerve conditions**

1. Pits
2. Colobomas
3. Tilted discs

### **B. Ischemic optic neuropathy**

1. Arteritic
2. Non-arteritic

### **C. Compressed lesions**

1. Tumors
2. Aneurysms
3. Cysts
4. Chiasmatic arachnoiditis

### **D. Optic nerve drusen**

### **E. Demyelinating conditions**

### **F. Inflammatory diseases**

### **G. Hereditary optic atrophy**

### **H. Toxic drugs or chemicals**

## **III. Ocular disorders**

### **A. Myopia**

### **B. Retinal degeneration**

### **C. Myelinated nerve fibres**

### **D. Branch vascular occlusions**

### **E. Choroidal nevus or melanoma**

### **F. Choroidal rupture**

### **G. Retinoschisis**

### **H. Chorioretinal disease**

## **IV. Systemic vascular conditions**

### **A. Anemia**

### **B. Carotid artery obstruction**

### **C. Acute blood loss**

### **D. Arrhythmia**

### **E. Hypotensive episodes**

## **V. Miscellaneous**

### **A. Hysteria**

### **B. Artifact of visual field testing**