“Normal” Tension Glaucoma

Deepta Ghate MD
Truhlsen Eye Institute, Omaha NE

- NTG definition
- Optic disc examination in NTG
- CNTGS study
Low Tension Glaucoma: A Critical Review and New Material

- Reviewed 767 NTG cases
- Defined LTG
  - IOP ≤ 24 mm Hg
- Said LTG was a different disease
  - Early dense visual field defects extending within 5 degrees of fixation
  - Sudden visual loss
  - Limited sensitivity of the field defect to even a marked lowering of IOP
  - Slow progression of visual field defect
- IOP in the statistically normal range (< 22 mm Hg)
- ONH cupping and RNFL loss often with disc hem
- VF defects consistent with ONH damage
- Open angle without any evidence of secondary causes of possibly previously elevated IOP
- Absence of other causes of visual field loss of ONH damage that could mimic glaucoma

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Textbook definition of NTG

- IOP in the statistically normal range (< 22 mm Hg)
- ONH cupping and RNFL loss often with disc hem
- VF defects consistent with ONH damage
- Open angle without any evidence of secondary causes of possibly previously elevated IOP
- Absence of other causes of visual field loss of ONH damage that could mimic glaucoma

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IOP in the “statistically normal range”

<table>
<thead>
<tr>
<th>Investigators (year)</th>
<th>Number of individuals</th>
<th>Geographical location</th>
<th>Sex</th>
<th>M</th>
<th>IOP SD</th>
<th>M + 2SD</th>
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</thead>
<tbody>
<tr>
<td>Leythdecker et al (1958)</td>
<td>10,000</td>
<td>Born (West Germany)</td>
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<td>15.3</td>
<td>2.57</td>
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<td>Katafuti and Somaithii (1991)</td>
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<td>Hollow and Graham (1966)</td>
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<tr>
<td>Shiose, Surv 1990</td>
<td>$left eye.</td>
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<tr>
<td>Arnott (1965)</td>
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<td>Hollows and Graham (1966)</td>
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<td>Wallec and Lowell (1969)</td>
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<td>Dalby (Sweden)</td>
<td>M</td>
<td>14.0</td>
<td>2.46</td>
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Shiose, Surv 1990
### IOP in the “statistically normal range”

#### Mean and Variation of Normal Intraocular Pressure Measured with Schiotz Tonometer

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<td>Ablair (1970)</td>
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<td>15.9</td>
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$\text{II Left eye.}$

#### Mean and Variation of Normal Intraocular Pressure Measured with Goldmann Applanation Tonometer

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- Western population: mean 15-16 mm Hg, SD 2.5-3
- Japanese population: IOP mean 14.5 mm hg (SD 2.7)
- Los Angeles Latnio Study: IOP mean 14.3 (SD 3.3)
- Barbados eye study: In populations of African descent: IOP mean 18.7 mm Hg (SD 5.2)

Colton, Surv 1980, Kawase BJ 2008
IOP and Glaucoma

Baltimore Eye Study
Orange circles: African-Americans
Blue: White population

Egna-Neumarkt Eye Study
Italy

Normal Tension Glaucoma epidemiology - cut off of 21 mm Hg

- White populations
  - Beaver Dam Eye study: 32% of all glaucomas NTG
  - Rotterdam Eye Study – 39% of all glaucomas are NTG
  - Egna-neumarket study in Italy – 20% of all glaucomas are NTG
  - Greece-Thessaloniki study – 59% of all glaucomas are NTG
  - EMGT in Sweden: 52% of all new glaucomas were NTG

- Baltimore Eye Study: 24% of all glaucomas NTG
- Black populations (Barbados eye study): 33% of all glaucomas are NTG
- Los Angeles Latino Study: 82% of all glaucomas were NTG
- Tajimi study in Japan: 92% of all glaucomas were NTG
- Rural South India: 67% of all glaucomas were NTG
IOP in NTG

- Diurnal fluctuations? In NTG, 55% of pk IOPs occurred outside of clinic hours (Yamagini Ophthalmology 1993)
- Nocturnal supine IOPs may be higher than 21 mm Hg (Sakata IOVS 2013)
- CCTs are thinner in NTG eyes as compared to POAG or OHT eyes – may lead to a lower IOP measurement

GOKWHIP

- Refractive surgery, corneal surgery
- Previously high IOP
  - Pigmentary glaucoma – burned out stage
  - Previous attacks of ACG before cataract surgery
  - Previous trauma and angle recession
  - Hyphema in past
  - Steroid response in past
The Cup/Disc Ratio

The Findings of Tonometry and Tonography in the Normal Eye

Mansour F. Armaly, M.D., and Roger E. Sayegh, M.D., Iowa City

Ranking of Optic Disc Variables for Detection of Glaucomatous Optic Nerve Damage

Jost B. Jonas,¹ Antonio Bergua,¹ Paul Schmitz-Valckenberg,² Konstantinos I. Papatstathopoulos,³ and Wido M. Budde⁴

500 normal, 132 preperimetric glaucoma (OHT with RNFL defects), 840 glaucomas (VF defects)

Vertical C/D ratio mean ± 1 SD
Corrected for disc size

Inf NRR width (mm) mean ± 1 SD
Optic cup

- Rotterdam study [Ramrattan 1999]: Vertical CD ratio in people > 55 y without glaucoma was 0.5 (SD 0.14, 97.5th : 0.7, range 0.04-0.81)
- LALES: CD ratio in normal population of Latinos: 0.5 (SD 0.1) as compared to 0.7 (SD 0.1) in glaucomas and 0.4 (SD 0.1) in OHT
- 10-11% have a C/D ratio > 0.5, 2-5% have a C/D ratio > 0.7
- C/D ratio is similar to parents/siblings
- Asymmetry > 0.2 occurs in 1-6% of the normal population and 24-50 % if patients with glaucoma

Kanifar 2002, Verma 2004

Collaborative Normal Tension Glaucoma Study

In a survey of AGS members [Panarelli, J Glaucoma 2015]

- 85% felt that they are more likely to treat patients with NTG with a goal of lowering IOP by 30% because of CNTG study
- 85% said their practice has been significantly impacted by the CNTG study
Collaborative Normal Tension Glaucoma Study

- To figure out which of these 2 hypotheses was true (Anderson, Curr Opin Ophthalmol 2003):
  - The first hypothesis is that the disease is IOP-independent
  - The second hypothesis is that IOP participates in producing the optic nerve damage in NTG

Patients and Methods:
- 230 patients from 24 centers: glaucoma with reproducible field defects
- After washout, 10 IOP readings were taken, the median was required to be 20 mm Hg or less, IOP never measured over 24 mm Hg and no more than one reading of 23-24 mm Hg

Exclusion Criteria
- Anyone on systemic beta blockers or clonidine
- Eyes with previous surgery or lasers, Any non-glaucomatous eye disease, VA <20/30
- Advanced visual field loss

Collaborative Normal Tension Glaucoma Study

- Randomization: 30% IOP lowering or observation
- Treatment
  - No beta blockers, no adrenergic agonists
  - Systemic CAI when study eye randomized
  - Treatment at discretion of physician- laser, surgery followed medical failure
  - Surgery 20% IOP reduction was considered ok without necessitating additional surgery

End points
- Disc progression on disc photos
- HVF progression
Natural History of Normal-Tension Glaucoma

- Patients who were never treated
- Of the 160 eyes, 52 progressed (32.5%) over 5-7 years
- Risk factors
  - Asians did better, Black people did worse (small numbers)
  - Women did worse than men (OR 1.85)
  - People with migraines did particularly badly (OR 2.58)
  - Eyes with disc hemorrhages progressed more rapidly (OR 2.78)

Risk Factors for Progression of Visual Field Abnormalities in Normal-tension Glaucoma

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Percent “Yes”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>5.20</td>
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<tr>
<td>Renal stones</td>
<td>3.27</td>
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<tr>
<td>Cardiac arrhythmia</td>
<td>6.00</td>
</tr>
<tr>
<td>Major cardiovascular disease</td>
<td>1.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.87</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2.37</td>
</tr>
<tr>
<td>Major surgery</td>
<td>18.79</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>23.67</td>
</tr>
<tr>
<td>Angina</td>
<td>3.62</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.60</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.60</td>
</tr>
<tr>
<td>Malignancy</td>
<td>9.40</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3.66</td>
</tr>
<tr>
<td>Nonmigraine headache</td>
<td>12.68</td>
</tr>
<tr>
<td>Migraine</td>
<td>15.63</td>
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<tr>
<td>Raynaud phenomenon</td>
<td>3.70</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.06</td>
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<tr>
<td>Low blood pressure tendency</td>
<td>1.80</td>
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<tr>
<td>Vertigo or dizziness</td>
<td>1.90</td>
</tr>
<tr>
<td>Fatigue or weakness</td>
<td>3.77</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1.89</td>
</tr>
<tr>
<td>Muscle tremor</td>
<td>1.89</td>
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<tr>
<td>Anxiety</td>
<td>4.43</td>
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<tr>
<td>Mental depression</td>
<td>2.52</td>
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<tr>
<td>Disorientation</td>
<td>0.63</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Glaucoma</td>
<td>37.42</td>
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<tr>
<td>Diabetes</td>
<td>30.07</td>
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<tr>
<td>Stroke</td>
<td>24.24</td>
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<tr>
<td>Physical finding</td>
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<tr>
<td>Disk hemorrhage</td>
<td>14.10</td>
</tr>
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</table>

Intraocular Pressure Reduction in Normal-tension Glaucoma Patients

- 145 eyes randomized, 5 treated eyes excluded (did not reach desired IOP)
- Equal demographic, IOP and visual field data
- 57% of IOP reduction on just pilocarpine +/- ALT, 43% needed trabeculectomy
- End points reached in 28/79 untreated (35%) vs 7/61 eyes (12%) in the treated group over 5 years
- NNT 5 (95% CI 2.6-9)
The Effectiveness of Intraocular Pressure Reduction in the Treatment of Normal-Tension Glaucoma

- Intent to treat analysis performed
  - All data and analysis same except visual fields to determine progression were those taken at time of randomization
  - 5 patients who did not reach their IOP goal were included in analysis
  - 31/79 controls (39%) and 22/61 (36%) treated patients reached the end point
  - Not statistically significant, NNT 32

- Cataracts occurred in 11/79 (14%) control eyes, and 23/66 (33%) of treated eyes (48% in surgery group)
- Cataract patients were censored
- Now the survival analysis shows 80% survival in treated group and 60% survival in control group at 3 years and 80% in treated and 40% in control group at 5 years

Problems with CNTGS

- Intent to treat analysis did not demonstrated any difference in rates of progression between treated and control groups
- Difference demonstrated only after cataract group (50% with trab vs 14% control) was “censored”
- 5 treated subjects who failed to achieve the IOP goal were excluded
- Deterioration in visual fields was only measured from the time treated patients achieved stable IOP vs controls
- Neither the absolute nor the percent change in IOP showed any significant association with survival within either group

- Other problems
  - Is it really NTG? IOP 23-24 mm Hg was accepted
  - No analysis for different levels of IOP initially – is the treatment same for patients with IOP of H teens-L20s vs IOP of L-M teens

Alfred Sommer AJO 1999
Differentiating Glaucoma from Not Glaucoma?

2 glaucoma specialists and 1 neuro-ophthalmologist looked at disc photos of 29 nonglaucomatous cups and 32 glaucoma cups

• All glaucoma eyes correctly identified
• Of the nonglaucomatous eyes
  • 13/29 eyes (44%) misdiagnosed as glaucoma by one observer
  • 6/29 eyes (21%) misdiagnosed as glaucoma by at least 2
List of diseases that cause cupping

- GLAUCOMA
  - Ischemic optic neuropathy
    - Mainly arteritic
  - Compressive optic neuropathy
    - Anterior visual pathways- orbit, sella
  - Hereditary
    - Lebers optic neuropathy
    - Autosomal dominant optic neuropathy
    - Traumatic optic neuropathy

- Optic neuritis
- Radiation optic neuropathy
- CRAO
- Methanol poisoning
- Periventricular leukomalacia or children with cerebral palsy
- Neuro-degenerative diseases
  - MS
  - Alzheimers

NTG or not NTG

<table>
<thead>
<tr>
<th>NTG</th>
<th>Compressive ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA≥20/40: 77% sens, 52% sp</td>
<td>Age &lt;50: 46% sens, 93% sp</td>
</tr>
<tr>
<td>F/H of glauc: 21% sens, 96% sp</td>
<td>Diffuse or temp rim loss: 77% sens, 64% sp</td>
</tr>
<tr>
<td>Cup&gt;pallor: 90% sens, 46% sp</td>
<td>VF defects</td>
</tr>
<tr>
<td>CD asym ≤0.2: 69% sens, 32% sp</td>
<td></td>
</tr>
<tr>
<td>Vertical rim loss: 64% sens, 77% sp</td>
<td>U/I VF defect: 43% sens, 80% sp</td>
</tr>
<tr>
<td>Disc hemm: 14% sens, 100% sp</td>
<td>Bordering Vx midline: 48% sens, 81% sp</td>
</tr>
<tr>
<td>VF defects</td>
<td>Homonymous or bitemp VF defects: 84% sens, 77% sp</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>B/I VF defects: 80% sens, 43% sp</td>
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<tr>
<td>Bordering Hx midline: 62% sens, 77% sp</td>
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<tr>
<td>NFL defects: 77% sens, 84% sp</td>
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Red Flags for not Glaucoma

- Symptoms
  - Sudden visual loss
  - Severe visual loss (less than 20/40)
  - Color vision loss - Red desaturation
  - Headache, pain
- age younger than 50 years
- Large RAPD
- Severe asymmetry
- Neurologic visual field defects and discrepancy between C/D ratio and the degree of visual field loss
- Pallor> cupping
- Rapid progression of visual loss

NTG work up

- Any patient with red flags or any progression at low IOPs (low-mid teens)
- History:
  - Sleep apnea - Sleep study
  - Medications: ethambutol, INH
  - BP medications and timing – Diurnal BP monitoring
  - Neurodegenerative diseases
  - Strokes
  - Migraines
- Blood work
  - CBC, ESR, CRP
  - Autoimmune diseases – ANA
  - B12, Folate
  - Thyroid panel
- Imaging: MRI brain and orbit
  - Yield variable in different studies for compressive lesions (0-6.5%)
  - Vascular insults more common such as SCI (34%), small vessel disease

Conclusions

- IOP cut off for NTG is arbitrary
- Optic disc parameters overlap between normal patients and glaucoma patients
- It is vital to rule out non-glaucomatous causes of cupping for any patient with red flags or any field progression at low IOPs
- If treatable causes are ruled out, can consider lower targets after discussion with patients about potential morbidity