CURRENT PERSPECTIVES ON NORMAL-TENSION GLAUCOMA

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Disclosure Statement

- Dr. Skuta currently serves on the Finance and Claims Committees for the Ophthalmic Mutual Insurance Company.
- He has served as an investigator for the Collaborative Normal Tension Glaucoma Study, the Advanced Glaucoma Intervention Study, the Collaborative Initial Glaucoma Treatment Study, and the Tube versus Trabeculectomy Study.
- He also has served on the Data and Safety Monitoring Committee for the Ocular Hypertension Treatment Study.

- Which of the following conditions would be most likely in a patient with evidence of glaucomatous damage and intraocular pressures currently in the normal range?
  A. Axenfeld-Rieger syndrome
  B. Iridocorneal endothelial syndrome
  C. Pigment dispersion syndrome
  D. (Pseudo)exfoliation syndrome

- In eyes randomized to treatment in the Collaborative Normal-Tension Glaucoma Study, what was the goal with regard to intraocular pressure lowering?
  A. 20%
  B. 30%
  C. 40%
  D. 50%

Definition of Normal-Tension Glaucoma

- Glaucomatous optic neuropathy with optic nerve head-related visual field defects in eye with open anterior chamber angle but without elevated intraocular pressure

What is Normal Intraocular Pressure?

- If mean IOP is 16 mmHg, “normal range” is 10-21 mmHg
- About 10% of US population has IOP over 21 mmHg
- 21 mmHg is very arbitrary cut-off between normal-tension glaucoma and primary open-angle glaucoma
- Risk of glaucoma increases as IOP increases
Normal-Tension Glaucoma

- Up to one-half of eyes with glaucoma have normal IOP on screening and up to one-third will never have documentation of "abnormal" IOP

Normal-Tension Glaucoma: Clinical Features

- Normal IOPs on multiple readings
- Glaucomatous optic nerve cupping
  - More focal damage than "high-pressure" forms of glaucoma
  - Greater tendency toward optic disc hemorrhages
- Visual field defects that are deeper, steeper, and closer to fixation than "high-pressure" disease

Normal-Tension Glaucoma Evaluation: History

- Appears to have strong vascular element
- Patients with progressive NTG more likely to have nocturnal systemic hypotension than patients who are not progressing
- Some data to suggest autoimmune mechanism

Normal-Tension Glaucoma Evaluation: History

- Causes of prior elevated intraocular pressure
  - Corticosteroid use
  - Trauma
  - Inflammation
- Severe systemic hypotension
- Systemic medication that might mask high IOP or cause systemic hypotension

Normal-Tension Glaucoma Evaluation: History

- Bedtime administration of systemic antihypertensive agents
- Vasospastic disease (e.g., Raynaud’s, migraine)
- Sleep disorders (e.g., sleep apnea)
- Family history of glaucoma
Normal-Tension Glaucoma
Evaluation: Examination

- Anterior segment search for signs of prior IOP elevation
- Trauma
- Inflammation
- Pigment dispersion
- Intraocular pressures with consideration of diurnal readings

Normal-Tension Glaucoma
Evaluation: Examination

- Optic nerve
- Glaucomatous optic neuropathy
- Disc hemorrhages
- ? PSE/cyclodochiasis
- Optic nerve drusen
- Retinal disorders producing visual field defects
- Visual fields
- Information on blood pressure measurements

Risk Factors for Progression

- Evaluation of risk factors for progression in 160 subjects observed without treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Ratio</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>2.38</td>
<td>0.0058</td>
</tr>
<tr>
<td>Disc hemorrhage</td>
<td>2.72</td>
<td>0.0036</td>
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<tr>
<td>Female gender</td>
<td>1.85</td>
<td>0.062</td>
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Am J Ophthalmol, 2001

Corneal Thickness and Glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Mean Corneal Thickness (microns)</th>
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<tbody>
<tr>
<td></td>
<td>NTG</td>
</tr>
<tr>
<td>AJO 1998</td>
<td>521 ± 37</td>
</tr>
<tr>
<td>Archives 1999</td>
<td>521 ± 31</td>
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</tbody>
</table>

Normal-Tension Glaucoma: Evaluation

- Neuroradiologic imaging has low yield in patients with classic glaucomatous cupping and visual field loss
- Consider in patients with:
  - Optic nerve pallor in excess of cupping
  - Visual fields not following typical nerve fiber layer pattern
  - Loss of central acuity without clear explanation
Neuroradiologic Imaging

- Factors increasing likelihood of identifying intracranial mass lesion:
  - Age younger than 50 years
  - Visual acuity < 20/40
  - Vertically aligned visual field defects
  - Optic nerve pallor in excess of cupping


Long-Term Assessment of Target IOP

- If worsening despite good IOPs, consider other factors:
  - Noncompliance
  - Diurnal variation
  - Angle closure mechanism
  - Systemic hypotension/decreased ocular perfusion
  - Decreased corneal thickness
  - Sleep apnea syndrome
  - Low intracranial pressure

Perfusion Pressure and Glaucoma

- Association of vascular factors with POAG evaluated in Baltimore Eye Survey
  - Diastolic perfusion pressure = Diastolic BP - IOP

= Persons with diastolic perfusion pressure < 30 mm Hg had age-race-adjusted risk of POAG six times higher than that of those with perfusion pressures of ≥ 50 mm Hg


Sleep Disorders and Glaucoma

- Patients with normal-tension glaucoma or suspects for normal-tension glaucoma appear more likely to have sleep disorder (sleep apnea or hypopnea) than controls
- In patients with difficult-to-explain glaucomatous progression, obtain sleep history and consider sleep evaluation in presence of positive history


Low Intracranial Pressure and Glaucoma

- In patients from Mayo Clinic who underwent lumbar puncture, intracranial pressure (ICP) was significantly lower in primary open-angle glaucoma (POAG) and NTG when compared with age-matched control subjects
- ICP was higher in ocular hypertension (OHT) than in control subjects
- Authors suggested that ICP (i.e., translaminar pressure difference between IOP and ICP) may play role in development of POAG and NTG and in preventing progression of OHT in POAG

Cerebrospinal Fluid Pressure and Glaucoma

- In prospective study at Beijing Tongren Hospital, 43 patients with open-angle glaucoma (14 with normal IOP and 29 with high IOP) and 71 control subjects underwent ophthalmologic and neurologic examinations and measurement of lumbar cerebrospinal fluid pressure (CSF-P).
- CSF-P was significantly lower (9.5 mmHg) in normal IOP glaucoma group than in high IOP glaucoma group (11.7 mmHg) or control group (12.9 mmHg).
- Trans-lamina cribrosa pressure difference (IOP - CSF-P) was significantly higher in both normal (6.6 mmHg) and high (12.5 mmHg) IOP glaucoma groups than in control (1.4 mmHg) group.

Ren et al. Ophthalmology, 2010

Normal-Tension Glaucoma: Current Treatment

- Attempt to achieve 30% reduction in intraocular pressure.
- Medical treatment: consider potential systemic and optic nerve effects.
- Laser trabeculoplasty.
- Glaucoma filtering surgery with antiproliferative agent.

Brimonidine versus Timolol

- Randomized comparative trial.


Brimonidine versus Timolol

- No difference in IOP.

Brimonidine versus Timolol

- Less VF Progression.
- BUT significant loss to follow up and due to side effects.
Collaborative Normal-Tension Glaucoma Study

- 230 patients in 24 international centers
- Funded by Glaucoma Research Foundation, San Francisco, with special grants from Oxnard Foundation and Edward J. Daly Foundation
- Steering and Writing Committee: Douglas R. Anderson, Stephen M. Drance, & Michael Schuldiner

Collaborative Normal-Tension Glaucoma Study: Randomization

- Eyes randomized to no treatment or treatment (target of 30% decrease in IOP)
- Total of 145 eyes randomized
- Five withdrew
- Of the remaining 140 eyes,
  - 79 randomized to no treatment (50 had initial threat to fixation)
  - 61 randomized to treatment (42 had initial threat to fixation)

Collaborative Normal-Tension Glaucoma Study

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Treated Group</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65.5 ± 9.6</td>
<td>66.3 ± 10.3</td>
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<tr>
<td>IOP at randomization (mmHg)</td>
<td>16.1 ± 2.3</td>
<td>16.9 ± 2.1</td>
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<tr>
<td>IOP during follow-up (mmHg)</td>
<td>16.0 ± 2.1</td>
<td>10.6 ± 2.7</td>
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Collaborative Normal-Tension Glaucoma Study: What Did We Learn?

- Lowering IOP protects patients against further damage
- 35% of untreated patients reached endpoint (disc or field progression)
- 12% of treated patients reached endpoint
- Survival analysis confirmed effect of lowering IOP
- Treated group more likely to develop cataract (38%) versus untreated group (14%)

Effect of Lowered IOP

"After IOP was lowered 30% from baseline, rate of progressive field loss was slower than in a group that did not receive treatment."

Collaborative Normal Tension Glaucoma Study

- Number needed to treat = 4.3
- Means that we need to lower IOP in 4-5 patients who are similar to those in the study in order to prevent progression in 1 patient
Collaborative Normal-Tension Glaucoma Study: Unanswered Questions

- Would use of other and newer agents have decreased need for filtering surgery?
- Would filtering procedures with antiproliferative agents have yielded lower long-term IOPs?

Summary and Conclusions

- Collaborative Normal-Tension Glaucoma Study confirmed efficacy of lowering intraocular pressure in reducing risk for progression.
- Especially important to consider factors such as central corneal thickness, systemic hypertension, ocular perfusion pressure, sleep disorders, intracranial pressure, etc.
- Eyes demonstrating progression may require intensive treatment.

Which of the following conditions would be most likely in a patient with evidence of glaucomatous damage and intraocular pressures currently in the normal range?

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B. Iridocorneal endothelial syndrome
C. Pigment dispersion syndrome
D. (Pseudo)exfoliation syndrome

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