The Nuances of Normal Tension Glaucoma

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Financial Disclosure – Justin Schweitzer, OD, FAAO

• Aerie – C/L
• Alcon – C/L
• Allergan – C/L
• Bausch + Lomb – C/L
• Ocular Therapeutix – C
• EyePoint - C
• Dompe - C
• Sun – C/L
• Equinox - I
• Reichert - C
• J&J – C/L
• Glaukos – C/L
• Horizon – C
• Quidel – C
• Sight Sciences – C/L

* Co-Chief Medical Editor: Modern Optometry
Case

65-year-old, Caucasian female referred for a second opinion for possible glaucoma. She states she has never had high eye pressures and doesn’t understand how she could have glaucoma.

Ocular History

- POHX: Cataract extraction OU 2014, YAG capsulotomy OU 2014
- FHX: Mother – glaucoma, age-related macular degeneration
- Previous Treatment Regimen: None
- Current Treatment Regimen: None

IOP max
- OD: 17 mm Hg
- OS: 17 mm Hg

Medical History

- PMHX: Hyperlipidemia
- All Medications: Fluoxetine, Atorvastatin
- Allergies: Penicillin
- Blood Pressure: 118/75

Ocular Exam

- Uncorrected visual acuity (UCVA): 20/20 OD, 20/20 OS
- External exam: Normal appearance, symmetrical
- Pupil exam: Equal, round, reactive to light and J-4 PD
- Slit-lamp exam
  - Lid lashes: Clear, no debris, no sign of MGD OU
  - Conjunctiva: Clear, no injection OU
  - Cornea: Clear, no corneal staining OU, no pigment present OU
  - Anterior Chamber: Clear, no cells, no flare OU
  - Iris: Clear, no exfoliative material present, normal transillumination defects OU
  - Lens: Well centered posterior chamber intraocular lens, open posterior capsule OU

Goldmann Applanation Tonometry: 16 mm Hg OD, 17 mm Hg OS
- Central corneal thickness (CCT): 499 OD, 504 OS
- Gonioscopy: Open to CB in all quadrants, no pigment in the TM, and normal iris apposition
- Corneal Hysteresis: 9.4 mm Hg OD, 9.3 mm Hg OS

OS
- Cup-to-Disc: 0.50/0.50, Flat Discriminated with normal peripapillary atrophy
- AV Ratio: Normal, no tortuosity
- Macula: Flat
- No PPA
- No disc hemorrhage

OD
- Cup-to-Disc: 0.70/0.70, Deep cup, Distinct
- AV Ratio: Normal, no tortuosity
- Macula: Flat
- No PPA
- No disc hemorrhage
Diagnosis
Severe Normal Tension Glaucoma OD
Pre-perimetric Normal Tension Glaucoma OS

Other diagnoses: SPO Cataract Extraction OU, SPO YAG Capsulotomy OU

Initiate treatment with latanoprostene bunod 0.024% qd @ night OU
• Goal IOP reduction of 20% or greater from baseline IOP

Initial Follow-up and Plan

Follow-up at 1 month
latanoprostene bunod 0.024% was well tolerated, easy to instill, and patient states compliance with medication.
Follow-up ocular exam: Vision and SLE stable from last examination 1 month ago.
Tonometry:
OD: 12 mmHg
OS: 11 mmHg

Normal tension glaucoma (NTG) is an optic neuropathy associated with glaucomatous optic nerve head damage progressing retinal nerve fiber layer thinning, characteristic visual field defects, open anterior chamber angles on gonioscopy and maximum intraocular pressure (IOP) below 21 mmHg.
92% of OAG in Japan is NTG
95% of OAG in Korea is NTG
30-50% of OAG in US is NTG
~50% of OAG in the world is NTG


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**FACTS**

- Increased IOP
- Nocturnal and Diurnal IOP Rise
- Female
- Myopia
- Age
- Hypertension
- Low-octet blood pressure
- Not being Excessive
- Migraine/Raynaud’s Phenomenon
- Sleep Apnea
- Thin Cornea or Low Corneal Hysteresis
- Decreased OIP Pressure

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**RISK FACTORS**

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**Nocturnal and Diurnal IOP Rise**

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Nocturnal and Diurnal IOP Rise


Home IOP Monitoring

A device is intended as an adjunct for monitoring IOP of adult patients (self-use). The HOME tonometer is designed for use at home or on the go.

ARGOS-O2 Trial: 1 year results

- 22 Patients
- Major Design Changes:
  - 0.9 to 0.5 mm thickness with 0.1 mm rounded tapering
  - 4 haptics to prevent ciliary sulcus rotation
- IOP Concordance:
  - D30:
    - Eyemate: 22.2 ± 9.2 mmHg
    - GAT: 19.5 ± 6.8 mmHg
  - D360:
    - Eyemate: 15.7 ± 3.8 mmHg
    - GAT: 14.1 ± 2.2 mmHg

American Journal of Ophthalmology
DOI: (10.1016/j.ajo.2019.09.011)
Sensors on the horizon...

- AcuMEMS (Menlo Park, CA)
  - AcuSentry System: implantable sensor
- Glaukos (San Clemente, CA)
  - DOCS Medical IOP Sensor
- Implantable Ophthalmic Products GmbH
  - Suprachoroidal IOP sensor
- Injectsense Inc (Emeryville, CA)
  - Configurable on-demand sensor
- LaunchPoint Technologies (Goleta, CA)
  - Sensor attached to lid & retrieved with ophth hook
- Solo (Waltham, MA)
  - Wireless subclavian sensor

Hypotension and Low Ocular Perfusion Pressure

**Hypotension:**
Abnormally low blood pressure. Defined as 90/60 mm Hg or below

**Ocular Perfusion Pressure:**
The pressure at which blood enters the eye and is defined as the difference between arterial and venous pressures in the eye

\[
\text{Mean OPP} = \frac{2}{3} \text{MAP} - \text{IOP}
\]
\[
\text{Systolic OPP} = \frac{2}{3} \text{SBP} - \text{IOP}
\]
\[
\text{Diastolic OPP} = \frac{2}{3} \text{DBP} - \text{IOP}
\]
\[
\text{MAP} = \frac{\text{DBP} + (1/3 \times (\text{SBP} - \text{DBP}))}{2}
\]

Reduced or Low OPP influences glaucoma's onset and/or progression

OPP is reduced in the presence:

- BP
- OR Both
- IOP
Hypotension and Low Ocular Perfusion Pressure

Degree of Nocturnal BP “Dip” in NTG patients & Glaucoma Progression

Migraines/Raynaud's Phenomenon

Cold fingers or toes
Color changes in your skin in response to cold or stress
Numb, prickly feeling or stinging pain upon warming or stress relief
Migraines/Raynaud's Phenomenon

Treatment

Calcium channel blockers
ex. Nifedipine, amlodipine, felodipine, isradipine

Vasodilators
ex. Losartan, fluoxetine

Would only be in advanced cases and strong belief NTG is associated with Raynaud's

Obstructive Sleep Apnea Syndrome

2%-5% prevalence in middle-age adults

Characterized by intermittent apnea and upper airway collapse during sleep

Ocular manifestations – floppy eyelids, retinal vascular tortuosity and congestion, papilledema, nonarteritic ischemic optic neuropathy, and normal-tension glaucoma

Significant cardiac risk (myocardial infarction)
Obstructive Sleep Apnea Syndrome

Polymerographs (Sleep Study):
- EKG and EDD
- O2 of blood (pulse oximetry)
- Eye and leg movements
- Blood pressure
- Brain waves

Classifying Severity:
- Apnea Hypopnea Index (AHI)
  - Mild (AHI ≤ 15)
  - Moderate (AHI 15 - 29)
  - Severe (AHI ≥ 30)

Obstructive Sleep Apnea Syndrome makes the claim...
...that vascular change may play a role in the mechanism of NTG as an ocular manifestation.

CSF/ICP Pressure


IOP
CSF
CSF/ICP Pressure


Normal Tension Glaucoma – Landmark Studies

Only 50% of treated eyes achieve a 10% IOP lowering
34% of treated NTG patients show progression
19% of NTG patients go blind in 1 eye
1.5% of NTG patients go blind in both eyes

Lowering IOP 20-30% shows progression significantly
A 20-30% reduction of IOP confers a 95.96% chance of stability
Achieving an IOP of 20-11mmHg confers a 95% chance of stability
Achieving a 20% reduction results in a 1.4-fold reduction in Progression
Achieving a 40% reduction results in a 5.7-fold reduction in Progression

When are our glaucoma patients most vulnerable to glaucomatous damage?

What Works When Our Patients Our Most Vulnerable To Glaucoma?
1. Baseline (off all meds)
2. After 4 weeks of travoprost
3. After 3 missed doses

IOP lowering effect:
Daytime: Yes
Nighttime: Yes

25 patients with OHTN or OAG
Randomized crossover study
Timolol 0.5% BID
Latanoprostene bunod q HS

IOP lowering effect:
Daytime: Yes
Nighttime: Yes

Endogenous in the human body
Causes alterations in the cytoskeletal network
Reduced NO in TM, Schlemm's canal, and ciliary muscle
Beta Blockers

Liu JH, et al. AJO 2004
18 patients with OHTN or OAG
Randomized crossover study
Timolol 0.5% q am
Latanoprost q hs

Seibold, et al. JOPT 2017
60 patients with OHTN or OAG
Randomized to timolol maleate 0.5% bid
24 hour IOP measurements

IOP lowering effect:
Daytime: Yes
Nighttime: No

Alpha Adrenergic Agonist

15 patients with OHTN or OAG
Prospective study
Brimonidine 0.1% TID x 4 weeks

Quaranta, et al. IOVS 2006
IOP lowering effect:
Daytime: Yes
Nighttime: No

Aqueous Humor Production Decreases at Night

Carbonic Anhydrase Inhibitor

IOP lowering effect:
Daytime: Yes
Nighttime: Yes?

26 patients with OHTN or OAG on latanoprost monotherapy
- Brinzolamide 1% TID
- Timolol 0.5% q am

ROCK Inhibitors

IOP lowering effect:
Daytime: Yes
Nighttime: Yes

12 patients with OHTN or OAG
Randomized, double – masked, vehicle - controlled 2:1 netarsudil vs vehicle

Ciliary processes
Episcleral veins
Trabecular meshwork
Uveoscleral outflow
Schlemm's canal
Cornea
Lens

MOAs
- aqueous humor production
- trabecular outflow
- episcleral venous pressure

Prostaglandin analogs
Alpha agonists
Beta blockers
CAIs
ROCK inhibitors
netarsudil 0.02% + latanoprost 0.005% (Rocklatan)

- RHO protein kinase (destabilizes actin in TM)
- Rock inhibitor (lowers EVP)
- Latanoprost (uveoscleral outflow)
- NET Inhibition (decrease aqueous production)

Combo Medications

3 options:
- Timolol/Dorzolamide
- Timolol/Brimonidine
- Brinzolamide/Brimonidine

IOP lowering effect:
- Daytime: Yes for all 3
- Nighttime: Yes for all 3
- Dorzolamide

Selective Laser Trabeculoplasty

Selectively targets and laser burns pigmented TM cells

No significant difference in QOL.
VEP probability of 50% at 17th visit being most cost-effective.
71.7% target IOP 80% at each vs 81.1% at target for meds.
78.2% Drop Free @ 3 years in SLT Group.

11/25/21
Selective Laser Trabeculoplasty

Two-Year Clinical Results After Selective Laser Trabeculoplasty for Normal Tension Glaucoma

- 41.1% medication reduction at 24 months
- 11.1% achieved absolute success

What About MIGS

MIGS

Efficacy a Close 2nd


MIGS

Cataract Surgery plus Goniotomy 12-Month Outcomes

<table>
<thead>
<tr>
<th>1 Day</th>
<th>1 Wk</th>
<th>1 Mo.</th>
<th>3 Mo.</th>
<th>6 Mo.</th>
<th>12 Mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of pts ≥ 20% IOP reduction</td>
<td>54.4%</td>
<td>57.8%</td>
<td>55.1%</td>
<td>67.4%</td>
<td>60.9%</td>
</tr>
<tr>
<td>% of pts using ≥ 1 fewer medications from baseline</td>
<td>56.5%</td>
<td>64.4%</td>
<td>63.3%</td>
<td>60.5%</td>
<td>60.9%</td>
</tr>
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Subconjunctival Stent (Xen)

Patients (n=26) with baseline IOP ≤ 16.5 mmHg

Patients (n=26) with baseline IOP > 16.5 mmHg

**MIGS**

Case Report: 54 year old phakic Japanese woman
Severe NTG
41.2% and 28.6% IOP reduction OD and OS
10 mm Hg OD and 10 mm Hg OS – out to 8 months.

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**Trabeculectomy**

First Line Surgical Option

Tube vs Trab Study
- Over 50% of Trabeculectomies Fail at 5 years
- Over 50% of patients with trab or tube lose 2 lines of vision or more.

Long-term Hypotony – 28 to 30%
Treatment in glaucoma

**Atmospheric**

- Without Goggles: 22mmHg
- With Goggles: -10mmHg

**Intraocular**

- Without Goggles: 12mmHg
- With Goggles: 9mmHg

**Intracranial**

- 9mmHg

**Trans-Corneal Pressure Difference**

- 22mmHg

**Trans-Laminar Pressure Difference**

- 3mmHg

Note:

- TCPD is same
- TLPD is normalized

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**Intraocular Pressure (mmHg) Reduction With Goggle Compared to Contralateral/Control Eye**

- Baseline
- 25% Pressure Reduction
- 50% Pressure Reduction
- 75% Pressure Reduction
- Immediately After Removal
- 1 Week After Treatment

(Consistent Cohort, n=51)
Thank You!

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