Graves Ophthalmopathy
Advances in Diagnosis and Treatment

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Ophthalmic Manifestations

GO is the #1 cause of unilateral and bilateral proptosis in adults
Ophthalmic Manifestations

Lid Retraction - 90%
75% at time of diagnosis

Superior & Inferior scleral show
Ophthalmic Manifestations

Lid Lag in Downgaze  50%
Early sign
Graves Ophthalmopathy

- 6 females : 1 male
- Bimodal peak – mid forties & mid sixties
- Associated dermopathy 4%
- Associated Myasthenia Gravis <1%
Graves Ophthalmopathy
a.k.a. Thyroid Eye Disease

- 70% hyperthyroid at time of dx
- 20% become hyperthyroid within 1 year of GO symptoms
- 6% euthyroid
  - ½ will be hyperthyroid in 5 yrs
- 3% Hashimoto thyroiditis
- 1% primary hypothyroid

- Conversely only 30% of hyperthyroid patients get GO
Graves Ophthalmopathy
Making the Diagnosis in the Eye Clinic

Thyroid Dysfunc

+ Exophthalmos or Optic Nerve Dysfunc or Eye Muscle Abnormality

OR

Eyelid Retraction

+ Thyroid Dysfunc or Exophthalmos or Optic Nerve Dysfunc or Eye Muscle Abnormality
Ophthalmic Symptoms of GO

What requires urgent referral?

• Signs of Compressive Optic Neuropathy
  • Grey-out of VA
  • Abnormal Color VA – red cap test
• Severe Restriction of Motility

• Routine referral for:
  • Blurred Vision
  • Tearing or Dry Eyes
  • Double Vision
  • Eye Pain
Graves Ophthalmopathy Imaging

- CT preferred – see bone that needs decompression
- Axial show Medial & Lateral Recti & Orbital Apex
- Coronal show 4 rectus muscles, Superior Ophthalmic Vein, Apex
- Optic nerve compression easier seen on coronal views

Mid-globe Axial View  Mid-orbit Coronal View  Orbital Apex Coronal View
Differential Diagnosis of Enlarged EOMs on CT/MRI

- Enlargement of Extraocular Muscles is usually due GO
  - Involves muscle belly, spares tendon
  - Frequency of EOM involvement: Inferior > Medial > Superior > Lateral
  - Isolated Lateral Rectus enlargement is not GO unless biopsy proven
Differential Diagnosis
NonThyroid Causes of Enlarged EOMs

• 45% Inflammatory
• 25% Vascular
• 20% Metastatic
• 10% Other

• Important in Euthyroid patients & occasionally a single patient has 2 unrelated disease processes
<table>
<thead>
<tr>
<th>Clinical</th>
<th>GO</th>
<th>Inflammatory</th>
<th>Vasc</th>
<th>Metastatic</th>
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</thead>
<tbody>
<tr>
<td>Periorbital</td>
<td></td>
<td></td>
<td>-</td>
<td>rare</td>
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<tr>
<td>inflammation</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>rare</td>
</tr>
<tr>
<td>Diplopia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Pain</td>
<td>+</td>
<td>+</td>
<td>rare</td>
<td>+</td>
</tr>
<tr>
<td>Proptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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</tbody>
</table>
### Enlarged EOMs on CT/MRI

#### Differentiating GO from other Diseases

<table>
<thead>
<tr>
<th>Imaging</th>
<th>GO</th>
<th>Inflammatory</th>
<th>Vasc</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon enlarged</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/- -</td>
</tr>
<tr>
<td>↑ proptosis w Valsalva</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Irregular borders</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
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Still unsure, may need labs & possibly EOM biopsy
NonThyroid Causes of Enlarged EOMs

**Work up**

- Blood work (Thyroid studies, ANCA, IgG4, ACE, Quantiferon gold)
- CT chest/abd/pelvis &/or PET CT
- Eye Muscle Biopsy w H & E stain
- Tissue stains for Amyloid & IgG4, lymphoma touch prep
- Tissue culture
  - Mycobacteria
NonThyroid Causes of Enlarged EOMs

- **45%** Inflammatory
  - Nonspecific orbital inflammation (NSOI) – 60-70%
  - IgG4 disease (20%)
  - Sarcoid
  - Crohn disease (rare)

- Imaging usually shows enlargement of tendon & muscle belly
  EOMs may look irregular if severe inflammation
Inflammatory Disorders of the Orbit

Nonspecific Orbital Inflammation
60%

IgG4 Disease
20%
Inflammatory Disorders of the Orbit

63 y/o w DM, ocular myasthenia, CLL – present w Optic neuropathy w VA decreased from 20/30 OU to CF OD, 20/100 OS
T3, T4, TSH, TSI – nl
ACE, ANCA, RPR, IgG4 – neg/nl
CT chest/abd/pelvis – nl
→ Eye Muscle Biopsy
Inflammatory Disorders of the Orbit

63 y/o w DM, ocular myasthenia, CLL – present w Optic neuropathy w VA decreased from 20/30 OU to CF OD, 20/100 OS T3, T4, TSH, TSI – nl, CT chest/abd/pelvis – nl
Eye Muscle Biopsy

CROHN DISEASE
NonThyroid Causes of Enlarged EOMs

• 25% Vascular
  • Carotid-cavernous fistula
  • Varix or AVM

• Imaging may show enlargement of SOV, unless thrombosed
• Exam & imaging may show increasing proptosis with Valsalva
• Audible bruit ~ 50%
Differential Diagnosis

Which of these 2 patients has GO?
Differential Diagnosis

GO

Carotid Cavernous Fistula

Enlarged SOV
NonThyroid Causes of Enlarged EOMs

- 20% Metastatic
  - Breast
  - Melanoma, skin
  - Lung
  - GI
  - Renal Cell CA
  - Thyroid CA
  - Other: Merkel, Prostate, Carcinoid

- 10% Other
  - Lymphoma
  - Infection (trichinosis, lyme, cysticercosis, TB, syphilis)
NonThyroid Causes of Enlarged EOMs

Metastasis
Carcinoid

Infection
TB
Assessing GO: Clinical Activity Score (CAS)

Active GO = 3/7 first visit or 4/10 second visit

- Pain/pressure of globe or orbit within 4 weeks
- Pain on eye movement within 4 weeks
- Eyelid erythema
- Eyelid swelling
- Conjunctival injection (1 quadrant or more)
- Chemosis (conjunctival swelling)
- Swelling of caruncle

At Follow up:
- Increase in proptosis 2mm or more within 1-3 months
- Decrease in eye movements of 8 degrees within 1-3 months
- Decrease in 1 line of Vision within 1-3 months
GO & RAI Treatment of Hyperthyroidism

• GO absent & no high risk factors
  • No steroids
• GO absent with + high risk factors (tob, +TSHR-AB, severe hyperthyroid)
  • risk for de novo GO
  • 0.3-0.5mg/kg prednisone
GO & RAI Treatment of Hyperthyroidism

- GO inactive
  - No steroids
- GO mild
  - 0.2mg/kg prednisone
- GO moderate
  - antithyroid drugs to control high risk factors 1st
  - 0.3-0.5mg/kg prednisone
  - alternatively continue antithyroid drugs or thyroidectomy if + high risk factors
- No evidence of superiority: RAI vs antithyroid drugs vs thyroidectomy
Treating Mild GO

- Topical Lubrication – 85% effective
  - Preservative Free artificial tears
  - Lubricating ointment
  - Avoidance of ceiling fans
  - Moisture chamber goggles
- Ophthalmology or Oculoplastics consult
- If Diplopic, must put Prisms in spectacles
  - 6 months of uncorrected double vision = permanent loss of some stereoacuity
- Selenium (Brazil nuts) 100mcg BID x 6 months
- Stop smoking
- Less than 15% of patients will need surgery
- Most surgery is elective
Treating Moderate - Severe GO

- IV methylprednisolone intermediate dose (4.5g total)
  - 0.5g weekly x 6 weeks, then 0.25 g x 6 weeks
- Severe cases – consider High dose IV methylprednisolone (7.5 g total)
  - 0.75g weekly x 6 weeks, then 0.5 g x 6 weeks

- Efficacy 60%
- Steroids: ↓ GAG by fibroblast, ↓ cytokine & Ab production, moderate T & B-cell fxn, ↓ macrophages & neutrophils
- Contraindications: hepatic dysfxn, recent hepatitis, severe cardiac or psychiatric disorders
- Caution in diabetics, hypertension
Compressive Optic Neuropathy (CON)

Disc Edema

Disc Edema & Choroidal Folds
Treating Compressive Optic Neuropathy (CON)

- Hospital admission
- IV methylprednisolone 250mg Q 6hrs x 3 days, then pulse dose
- Orbital decompression
  - Response failure to steroids
  - Recurrent CON on tapering steroids
  - Globe luxation or compression of choroid
GO Before & After 2 Wall Decompression
GO Before & After 2 Wall Decompression

Left Eye

Right Eye
Treating Compressive Optic Neuropathy (CON)

Other Options

- Accepted Theory:
  mechanism of GO is associate w fibroblasts, lymphocytes & cytokines
- Orbital Radiation
  - lymphocyte sterilization
  - differentiation of fibroblasts
  - kills tissue bound monocytes
Orbital Radiation

- Alternative to IV steroids
- Alternative to Orbital Decompression Surgery
- For Compressive Optic Neuropathy
- For Moderate-Severe GO in the Inflammatory Phase
- 20 Gy + 20mg oral prednisone during & 2 wks after XRT

- Diabetes – caution, risk of retinopathy (low)
- Ineffective for congestive signs
- Ineffective in longstanding GO without inflammation
Treating Compressive Optic Neuropathy (CON) & Moderate-Severe Orbitopathy

Targeted Therapies?

• Mechanism of GO
  • accepted association with lymphocytes & cytokines
• Gene expression profiling 2015 – questions this
  • 10 orbital centers, evaluated inflammatory markers in GO vs orbital inflammatory disease
• Cytokines & Chemokines not very elevated in:
  • GO
  • Normal control patients
• Cytokines & Chemokines elevated in:
  • Nonspecific orbital inflammation (a.k.a. orbital pseudotumor)
  • Sarcoid
  • GPA (a.k.a. Wegener granulomatosis)
Treating Compressive Optic Neuropathy (CON) & Moderate-Severe Orbitopathy

Targeted Therapy

• Is there a role for drugs targeting cytokines/chemokines? unclear
• TNF inhibitors (etanercept)
• IL-6 receptor antagonist (tocilizumab)

• Rituximab (maybe)
  • mech: B-cells, block TSHR-Ab & inflammatory cytokines

• other options: Cyclosporine + steroids (maybe)
Targeted Therapy
On the Horizon?

- Insulin-like Growth Factor 1 Receptor (IGF-1R)
  - Enhances action of thyrotropin
  - Overexpressed on orbital fibroblasts, T-cells & B-cells in GD

<table>
<thead>
<tr>
<th>IGF-1R inhibition w Teprotumumab</th>
<th>Phase II trial vs 2001 IV steroid data</th>
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<tbody>
<tr>
<td></td>
<td>teprotumumab</td>
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<tr>
<td>CAS 0-1</td>
<td>70%</td>
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<tr>
<td>↓proptosis</td>
<td>2.5 mm</td>
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<tr>
<td>Optic neuropathy</td>
<td>not studied</td>
</tr>
<tr>
<td>Diplopia</td>
<td>improved</td>
</tr>
<tr>
<td>Response</td>
<td>43%</td>
</tr>
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- Adverse events: hyperglycemia

hyperglycemia, UTI
Elective Surgery and GO

- Most surgery is elective
- Elective Surgery - wait until GO has stabilized
- Customization of surgery is key – not all patients need all areas
- Orbital disease 1\textsuperscript{st}
- Strabismus 2\textsuperscript{nd}
- Lids are Last
Orbital Surgery for GO

FAT, BONE or BOTH?
Orbital Decompression

- Fat alone (1-4 cc)
  - 1-2 cc from deep orbit – ideal
  - 4 cc risk of adherence of eye muscles to connective tissue = severe, intractable strabismus/diplopia
- Bone : 1 – 4 walls  Customizable
- Single wall – Lateral wall is Ideal
  - 2 mm decrease in proptosis – traditional approach + Fat removal
  - 3-5 mm decompression w Extended Lateral Wall removal + Fat
  - rarely induces strabismus
  - can alleviate CON
Extended Lateral Wall Decompression

Dura
Orbital Decompression

- Two Walls – Balanced Decompression ideal
  - Balanced Decompression removes Medial & Lateral wall & fat 4-7 mm
    - Developed by Dr. Charles Leone 1989 in San Antonio
  - Other method: Medial wall & Floor = 3-4 mm
    - 25% increase in diplopia/strabismus

- Three Walls - Lateral, Medial & Floor 4-8 mm
  - 25% increase in postoperative diplopia/strabismus

- 4 Walls – Combined approach with Neurosurgery 7-10 mm
  - for severe exophthalmos
  - rarely done
Orbital Decompression for 2017

- Customized surgery:
  - 1-2 walls + fat - common
  - 3 walls + fat – occasional for marked proptosis
  - fat only – occasional for mild proptosis
- CT image guidance in OR - determine location of critical structures
  - great for teaching advanced techniques
  - Skull base / cribiform plate medially
- Piezoelectric bone removal (ultrasonic) as adjuvant to High Speed Drill
  - Safe, slow removal when in deep orbit
  - Minimal heat transfer so osteoclasts grow more quickly
Complications of Orbital Decompression

- Strabismus/Diplopia
  - worse or new
- Hypesthesia
- Temporalis muscle atrophy
- Enophthalmos - late
- Globe sinking into sinus
- Sinusitis
- CSF rhinorrhea, meningitis, brain abscess
- Recurrent optic nerve compression
- Orbital adherence syndrome
  - Associated with excess fat removal
Elective Surgery

- Wait until GO stable x 6 months
- Orbital decompression for proptosis correction 1\textsuperscript{st}
- Strabismus surgery for diplopia 2\textsuperscript{nd}
Elective Surgery

Lids are Last

- Temporary measures for exposure
  - Lubrication, tape lids shut, Botox or filler to drop lid
- Upper lid retraction repair – lower the upper lids
- Lower lid retractor repair – raise lower lids with grafts
REFERENCES


