Epidemiologic and diagnostic considerations for Graves’ orbitopathy (GO)

1. How common?
   - population based study, 1976-1990, 120 incident cases, 86% female, 16 females/10^5/year, 2.9 males/10^5/year, Am J Ophthalmol 120:511, 1995

2. Thyroid status? (n=120)
   - hyperthyroid: 90%
   - hypothyroid: 0.8%
   - Hashimoto: 3.3%
   - euthyroid: 5.8%

3. How common are the findings? (n=120) Am J Ophthalmol 121:284, 1996
   - lid retraction: 91%
   - proptosis (>20 mm): 62%
   - extraocular myopathy: 43%
   - optic neuropathy: 6%
   - myxedema: 4%
   - acropachy: 1%

   - supportive: 74%
   - steroids: 5%
   - XRT: 1%
   - decompression: 7%
   - EOM surgery: 9%
   - eyelid surgery: 12%

5. What is necessary for diagnosis? Consider lids, muscles, thyroid function and immune status. (Diagram)

6. Suggested lab tests
   - TSH, free thyroxine, total T3, TRAb (thyroid receptor antibody) or TSI (thyroid stimulatory immunoglobulin)

7. Differential considerations – CT imaging helpful
   - dural fistula
   - frontal mucocele
   - exophytic optic nerve sheath meningioma
   - sphenoid wing meningioma
   - lymphoma
   - inflammatory orbital pseudotumor/IgG4-RD

Risk factors for GO and its progression

- Smoking
- Dysthyroidism
- Genetics/ancestry
- RAI
- Gender/age
- TRAb
- Others (orbital anatomy, thyroid hormone levels)

**Disease activity defined by Clinical Activity Score (CAS)**
- Elements
- CAS ≥ 3 represents active disease
- Active disease is predictive of response to immunomodulatory therapy

**Table 1. Assessment of Graves’ Orbitopathy: Clinical Activity Score Elements**

<table>
<thead>
<tr>
<th>Elements</th>
<th>Each visit</th>
<th>Comparison with previous visit</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful feeling behind the globe over last 4 weeks</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Pain with eye movement during last 4 weeks</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Redness of the eyelids</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Redness of the conjunctiva</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Swelling of the eyelids</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chemosis (edema of the conjunctiva)</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Swollen caruncle (flesh body at medial angle of eye)</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Increase in proptosis ≥ 2 mm</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Decreased eye movements ≥ 5° any direction</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Decreased visual acuity ≥ 1 line on Snellen chart</td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*A 7-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a CAS ≥ 3.*

Sources: Adapted from Mourits et al., 1989 (506); and Mourits et al., 1997 (507).

**Disease severity**
- Mild
- Moderate-to-severe
- Sight-threatening

_assigned to Table 2.

**Table 2. Graves’ Orbitopathy Severity Assessment**

<table>
<thead>
<tr>
<th>Gradea</th>
<th>Lid retraction</th>
<th>Soft tissues</th>
<th>Proptosisb</th>
<th>Diplopia</th>
<th>Corneal exposure</th>
<th>Optic nerve status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt; 2 mm</td>
<td>Mild involvement</td>
<td>&lt; 3 mm</td>
<td>Transient or absent</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 2 mm</td>
<td>Moderate involvement</td>
<td>≥ 3 mm</td>
<td>Inconstant</td>
<td>Mild</td>
<td>Normal</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 2 mm</td>
<td>Severe involvement</td>
<td>≥ 3 mm</td>
<td>Constant</td>
<td>Mild</td>
<td>Normal</td>
</tr>
<tr>
<td>Sight threatening</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Severe</td>
<td>Compression</td>
</tr>
</tbody>
</table>

Upper limits of normal

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>F/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>23/24 mm</td>
</tr>
<tr>
<td>White</td>
<td>19/21 mm</td>
</tr>
<tr>
<td>Asian</td>
<td>16/17 mm (Thai) or 18.6 mm (Chinese)</td>
</tr>
</tbody>
</table>

*Mild GO: patients whose features of GO have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. Moderate-to-severe GO: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Sight-threatening GO: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.*
Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient’s baseline, if available. 

Sources: Adapted from ATA Hyperthyroidism Guidelines (Thyroid 2011).

Severe complications of GO

- Optic neuropathy (DON)
- Corneal ulceration
- Globe subluxation/luxation

Medical (non-surgical) therapy

- Cool compresses, artificial tears, sunglasses
- Selenium – mild disease
- Oral steroids – more side-effects than IV steroids
  - Best risk/benefit regimen is methylprednisolone 500 mg weekly x 6 followed by 250 mg weekly x 6 (Kahaly JCEM 2005 and Bartalena JCEM 2012)
- IV steroids – moderate-to-severe disease; risk of liver damage
- Immunomodulatory drugs under investigation: Rituximab, IVIG, tocilizumab
  - IVIG had promising results but abandoned due to difficult logistics and uncertainty in moderate-to-severe disease
  - Rituximab tested in 2 RCTs with contradictory results (no better than placebo in Mayo trial vs. 100% efficacy at inactivating GO in a European trial by Salvi et al.)

Orbital decompression for Graves’ Orbitopathy

In general, symptoms of Graves’ ophthalmopathy arise because of a discrepancy between the increased swelling of the retrobulbar tissues and the fixed volume of the orbit.

Indications for orbital decompression:
- optic neuropathy
- severe orbital inflammation
- excessive proptosis	prior to extraocular muscle surgery
-exposure keratitis
cosmesis
-pain relief
-corticosteroid dependence

### Proptosis Reduction as a Function of Number of Walls Decompressed

<table>
<thead>
<tr>
<th>Walls decompressed</th>
<th>Globe recession</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (medial wall)</td>
<td>0-4 mm</td>
</tr>
<tr>
<td>2 (lateral wall + floor + medial wall)</td>
<td>3-6 mm</td>
</tr>
<tr>
<td>3 (medial + lateral walls + floor)</td>
<td>6-10 mm</td>
</tr>
<tr>
<td>4 (all 4 walls)</td>
<td>10-17 mm</td>
</tr>
</tbody>
</table>


### Advantages and Disadvantages of Four Types of Orbital Decompression

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Transantral decompression (floor + medial wall)</td>
<td>Anatomy unfamiliar to most ophthalmologists</td>
</tr>
<tr>
<td>Good operative visualization and control of intraoperative sinus bleeding</td>
<td>More postoperative facial swelling</td>
</tr>
<tr>
<td>Decompresses posterior ethmoids (important for relief of optic nerve compression)</td>
<td>More postoperative diplopia</td>
</tr>
<tr>
<td>Short operative period (2 hours for bilateral procedure, and brief hospitalization (overnight)</td>
<td>Numb upper lip</td>
</tr>
</tbody>
</table>

- Anterior decompressions (1,2,3 or all 4 walls)
  - Easy to individualize therapy
  - Anatomy familiar
  - Less postoperative diplopia
  - Nasal endoscope may be used for medial wall and medial floor
  - Shorter hospital stay (overnight)
  - Longer surgery (4-5 hours for bilateral 3-wall operation)

- Transfrontal decompression (roof + lateral wall)
  - Less postoperative diplopia
  - Haircut
  - Upper lip not numb
  - Effective for optic neuropathy
  - Possible frontalis paresis
  - Postoperative pulsating globe
  - Longer surgery (4-5 hours for both eyes)
  - Longer hospital stay (3-4 days)

- Orbital fat decompression
  - Upper lip not numb
  - Not useful with active disease
No postoperative sinus complications  Not useful if minimal fat apparent on imaging studies
Can perform blepharoplasty at same time  Temporary diplopia possible due to trauma to inferior oblique muscle
Short hospital stay (overnight) or outpt  Minimal proptosis reduction (usually)

**Side Effects of Transantral Orbital Decompression**

- Diplopia
- Sinusitis
- Cerebrospinal fluid leak, meningitis
- Lip numbness
- Entropion
- Nasolacrimal duct obstruction

**Strabismus surgery for Graves’ Orbitopathy**

1. Diplopia classification (measure distance and near fixation):
   - none
   - when tired
   - at extremes of gaze
   - continuous, but can be corrected with prisms in glasses
   - continuous, can not be corrected with prisms in glasses

2. Diplopia incidence:
   - 25/175 (14%) University of Iowa
   - 20/120 (17%) Mayo
   - when fatigued: 4
   - at extremes of gaze: 9
   - correct with prism: 3
   - constant: 4

3. Timing of surgery:
   - If decompression: 1-6 weeks later
   - No decompression: 3-6 months of inactive and stable disease off steroids

4. Types of diplopia:
   - horizontal
   - vertical
   - torsional

5. Adjustable versus conventional surgery

6. Hypertropia from tight superior rectus
   - larger recession than corresponding vertical deviation from tight IR
   - disinsertion or traction suture

7. Lateral rectus resections for large eso deviations and for residual “divergence insufficiency”

**Eyelid Surgery for Graves’ Orbitopathy**

1. follows decompression (if needed) or strabismus surgery (if needed)
2. consider surgery (if non-urgent/emergent) after 6 months of stable disease, off steroids
3. can “mask” proptosis or provide corneal coverage
4. consider lateral tarsorraphy, recession of upper lid retractors, spacer graft to lower lids
Role of Radiation Therapy in Mild, Moderate Graves without optic neuropathy

1. 42/53 consecutive patients, no optic neuropathy, diabetes, previous decompression or EOM surgery
2. Secure diagnosis of Graves’ ophthalmopathy, fairly symmetric ophthalmopathy (< 4 mm proptosis asymmetry), all euthyroid, no steroids for at least 2 weeks
3. Age: mean 48.0 (range 38.1-76.9 yrs), 36 F, 21 smokers
4. Each patient served as own control, 1 orbit randomly selected and treated, other orbit treated 6 months later, 2000 cGy. Onset of eye symptoms to XRT, mean 1.3 yrs (range 0.2 – 16 yrs), but mean clinical activity score was 6.4
5. 5 parameters: fat + muscle volume, fat volume, muscle volume, proptosis measured by CT, monocular range of motion, lid fissures
6. There was no significant difference between treated and non-treated parameters at 6 months and 12 months, therefore, no difference between radiation therapy and natural history of disease
7. Fluorescein angiogram at study entrance and study exit, 4 patients with radiation retinopathy
8. We see no role for XRT

9. **Opposing view from European studies – potential benefit with diplopia**