Thyroid Eye Disease: Managing the Thyroid Patient

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Graves’ disease is named for the doctor who first described it in Ireland—Robert J. Graves. He noticed it in a patient in 1835. The disease is also referred to as Basedow’s disease—named after a German, Karl Adolph van Basedow, who described the disease in 1840. He didn’t know that Graves had described the same disease just a few years earlier. The term Basedow’s disease was commonly used in continental Europe; in the United States, it’s usually called Graves’ disease.
GRAVES DISEASE

- most common form of overt hyperthyroidism
- autoantibodies are directed against the thyroid-stimulating hormone (TSH) receptor.
- The disease is classically characterized by the triad of goiter, exophthalmos, and pretibial myxedema.
- Risk factors for Graves disease include:
  - family history of hyperthyroidism
  - other autoimmune disorders
  - high iodine intake
  - Stress, illness, trauma
  - use of steroids
  - smoking
Thyroid Associated Orbitopathy (TAO)

- Most common cause of unilateral or bilateral exophthalmos (adults)
- Commonly occurs between 25-50 years of age
- Women 4X more often affected than men
  - 16/100,000 vs 4/100,000
- Exophthalmos, eyelid retraction, diplopia (restrictive myopathy), occasional compressive optic neuropathy
- Vision threatened by corneal exposure or compressive optic neuropathy
TAO Epidemiology

- MOST COMMON CAUSE OF ADULT PROPTOSIS (unilateral or bilateral)
- Women 4 - 6x > men
- Median age of dx 43y/o
TAO Pathology

- Lymphocytic and Plasmacytic infiltration
- Activated Fibroblasts
- Increase orbital volume and pressure due to 5-fold increase in tissue osmotic load from increased glycosaminoglycans (GAGs)
- Smoking
  - Decreases T-suppressor lymphocyte activity
  - Less control of T-helper cells directed against antigens
TAO Histopathology

- Retrobulbar fat and connective tissue fibroblast stimulation, GAG deposition, edema
- Extraocular myositis with edema, muscle necrosis, lymphocytic infiltration
TAO Diagnosis

- Clinical findings most important
- Thyroid problem runs separate course from orbit problems, thyroid levels may be high, normal or low (high most common)
- CT scan shows enlarged EOM’s (I’M SLO)
- Muscle tendons usually preserved, giving fusiform appearance of muscle on scan
Proptosis, edema, lid retraction, lid lag, glabellar furrows

Corneal exposure, chemosis

EOM restrictive myopathy with noncomitant diplopia

Increased IOP (>8mm in upgaze)

Pretibial edema

Thyroid problem runs separate course from orbit problems, thyroid levels may be high, normal or low (high most common)
Diagnostic Studies

- TSH or serum TSH are highly sensitive
- Free T4 index, serum T3, antithyroid antibodies are now considered less useful
- TSH receptor assays
  - TRAb (thyroid receptor ab), TBII (TSH-ginding inhibitor immunoglobulin), LATS (long-acting thyroid stimulator)
- IgG binding assays
  - TSI (thyroid-stimulating immunoglobulin)
- Thyroid peroxidase studies are useful to associate eye findings with abnormal thyroid
  - Thyroid peroxidase test (antimicrosomal ab test)
  - Antithyroglobulin test (antithyroid ab test)
Clinically

- Those with Graves
  - 90% hyperthyroid
  - 1% hypothyroid
  - 3% hashimoto thyroiditis
  - 6% euthyroid
Clinically

- Eyelid retraction 90%
- Exophthalmos 60%
- Lid lag 50%
- EOM myopathy 40%
- Diplopia 17%
- Optic nerve 6%
- Classic findings 5%
- Myasthenia < 1%
Clinical Course

- In 60% patients, eye disease occurred within 1 yr of diagnosed thyroid disease

- Those with no abnormal thyroid function or regulation with eye findings, risk of developing thyroid disease 25% at one year, 50% at five years
Clinical Course

- Acute episodes occur lasting from 3 months to 1 year
- Average 1-3 acute episodes during course of disease
- Proptosis, diplopia, retraction often persist after acute phase
- Smoking predisposes or worsens the orbitopathy
Numerous eponymous signs are associated with thyroid-associated orbitopathy, including the following:

- Dalrymple sign (upper eyelid retraction with temporal flare)
- von Graefe sign (lid lag on downgaze)
- Older monikers:
  - Vigouroux sign (eyelid fullness)
  - Stellwag sign (incomplete and infrequent blinking)
  - Grove sign (resistance to pulling down the retracted upper lid)
  - Joffroy sign (absent creases in the forehead on superior gaze)
  - Möbius sign (poor convergence)
  - Ballet sign (restriction of one or more extraocular muscles)
von Grafe Sign

Dalrymple Sign
# ‘NO SPECS’ Classification

Werner 1969, 1977

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<td>EOM</td>
</tr>
<tr>
<td>5</td>
<td>Corneal</td>
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<tr>
<td>6</td>
<td>Sight/optic nerve</td>
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Newer Classifications

Newer classification system:
- Clinical Activity Score (CAS) – used mainly in Europe
- Vision, Inflammation, Strabismus, Appearance (VISA) – used mainly in North America

Complex, but based on indicators of signs of activity and the degree of severity, more accurate

Both use scoring systems to grade severity

Not interchangeable, use one best suited to your scope of practice
Exophthalmometry
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CT / MRI

- CT better for surgical planning of decompression
- MRI better for optic nerve compression
- Imaging reveals thickened EOM bellies with tendon sparing (fusiform enlargement)
- MR, IR, IO most often involved
- Dilated SOV or apical crowding seen
EOM
TAO Therapy Goals

- Monitor visual function
  - Va, VF, Color Vision, IOP, Hertels, etc

- Manage comfort
  - Corneal lubrication, hydration

- Decrease orbital congestion
  - Systemic steroids, radiotherapy, newer therapies

- Expanding orbital volume
  - Surgical decompression
TAO Medical Treatment - Basics

- Topical lubrication, patching, moisture chambers to protect exposed cornea, prisms
- Systemic corticosteroids during acute phase
- Immunosuppressives have been used successfully, but increased potential side effects
- Patient education of disease course, no cure, but usually acute disease is self-limiting
- Sleep head elevated
- STOP SMOKING ! STOP SMOKING !
TAO Therapy
Work Closely with IM, Endocrinology

- If IM or endocrinology treats with radioactive iodine (RAI), studies show it is beneficial to treat concurrently with steroids:
  - 0.5 mg/kg/day up to 2 months post-treatment
Thyroid Ophthalmopathy
Medical Treatment – PO vs IV

- **STEROIDS**
  - PO prednisolone Indications: Optic neuropathy, Inflammatory soft tissue changes, progressive strabismus
  - PO: 0.5-1.0 mg/kg/day prednisolone. Usually given as tapering dose once or twice daily for several months
    - Retrospective studies show 60% short-term benefit in reducing inflammatory signs; no proof of ultimate reduction in strabismus (diplopia) or ocular restriction
  - Side Effects: Cushing’s disease (moon-face, weight gain, acne, adrenal insufficiency), diabetes, insomnia, mood disturbances, osteopenia, necrosis of femoral head, susceptibility to infections
**STEROIDS**

- **IV methylprednisolone**
  - Indications: Same as oral prednisone,
  - IV:
    - 1 gm MP alternate days for 3 sessions; repeat cycle every 3 – 6 weeks PRN.. or:
    - 500 mg MP weekly for 4 weeks, then 250 mg weekly for 16 weeks:
      - maximum dose 8.0 gms, monitor liver and cardiac function
  - IV seems to be better tolerated with less systemic side effects, 85% effective in reducing inflammatory signs

- **Side-effects:** Fewer than oral prednisone; however, electrolyte disturbances and cardiac arrhythmias have been reported; monitoring is important; liver toxicity and death have been reported in cumulative dosing over 9 gms MP.
Thyroid Ophthalmopathy
Medical Treatment

New medical therapy horizons:

- **Rituximab (Rituxin)**
  - several individual and small case-series showing benefit in patients with severe TED poorly responsive to corticosteroid therapy from use of this B-cell lymphocyte depleting biologic agent. At least two randomized, controlled trials are underway to assess effectiveness of this agent.

- **Octreotide, pentoxifylline, nicotinamide, plasmapheresis, IV immunoglobulin** are all mainstream treatments, but have shown some promise in reducing TAO symptoms.
Thyroid Ophthalmopathy
Medical Treatment

- New medical therapy horizons:
  - Others
    - **Azathioprine:** Inhibitor of DNA synthesis, immunosuppressive
      - **Indications:** May allow weaning of corticosteroids for long-term therapy and may reduce ultimate complications of proptosis, and motility problems in TED. Currently being studied for its benefits in combination with Radiotherapy by British CIRTED trial.
      - **Side-effects:** Nausea, fatigue, hair loss, rash. Bone marrow suppression and possible secondary infections. Human carcinogen. May interact with allopurinol (gout therapy)
    - **Selenium:** This toxic non-metallic element is a component of an antioxidant enzyme.
      - Occurs naturally in soil and is required in trace quantities through food supplies (garlic, red meat, fish, grains) to help regulate the immune system. A recent EUGOGO prospective randomized trial showed significant benefit when selenium supplements were taken for one year in reducing lid retraction and improving quality of life in patients with mild, non-inflammatory orbitopathy (Appearance/exposure changes).
Thyroid Ophthalmopathy
Radiation Therapy

- Radiation therapy controversial, but has been shown to be beneficial in ACUTE phase (within 7 mo of dx)
- 1500 – 2000 cGy fractionated over 10 days
- Takes weeks to help, must treat concurrently with systemic steroids (similar to I-131)
- presumed to work by directly targeting lymphocytes and fibroblasts
Thyroid Ophthalmopathy
Radiation Therapy

- **Indications:**
  - **Optic neuropathy:** RT may sufficiently reduce the width of distended ocular muscles near the orbital apex to prevent the need for surgery in patients with optic neuropathy. RT may also be useful in preventing progressive expansion of muscles and recurrence of vision loss following surgical orbital decompression in patients with compressive optic neuropathy.
  
  - **Inflammation/congestion:** RT may help reduce inflammatory changes on the surface of the eye and on the eyelids in approximately 60% of patients. A randomized controlled prospective trial found RT was equally helpful as oral prednisone in reducing inflammatory periocular soft tissue changes. The benefit of prednisone was more rapid, but the benefit of RT appeared to be longer lasting. Prednisone combined with RT appeared to be more beneficial than treatment with prednisone alone.
  
  - **Strabismus / motility:** Two randomized controlled studies from the Netherlands found that patients with TED treated with RT ultimately had better ocular excursions than patients treated with sham (no) RT.
  
  - **Appearance / exposure:** Radiotherapy appears to have little benefit in reducing ultimate proptosis or lid retraction in patients.
Modern linear accelerator radiotherapy units have an excellent safety record. Several large reviews demonstrate no increased risk of cataract and no reports of radiation induced tumors. Because of a small theoretical lifetime risk of developing tumors, RT is usually avoided in people less than 35 years old.

There have been reports of a slight increased risk of retinal vascular disease in patients with diabetes or hypertension, and RT is often avoided in patients with diabetes.

RT may cause some temporary redness and hair loss in the temple area near where the beam is focussed. Orbital inflammation may temporarily be worsened during the two week therapy and oral prednisone is be given to help reduce this effect.
Thyroid Ophthalmopathy Surgical Treatment

- ~ 5% of TAO patient will require surgery
- No cookbook approach, tailor to each patient’s needs
- Usual approach is:
  - Decompression
  - Strabismus
  - Retraction repair
  - Other
Thyroid Ophthalmopathy
Surgical Treatment

- Orbital decompression surgery
  - Medial wall
  - Floor
  - Lateral wall
    - Controversial, tailor approach per surgeon experience and patient need
- Strabismus surgery
- Upper eyelid recession surgery
- Lower eyelid elevation / spacers
Diplopia

- TRO causes scarring in EOM
  - Inferior and medial rectus muscles
- Unequal scarring causes diplopia
- Diplopia is very troubling to patient
Diplopia Treatment

- Opaque tape (Scotch tape) on inside of one glasses lens
- Fresnell prisms
- Steroids if used early
  - My experience has not been encouraging
- Surgery if stable for 3 - 6 months
Eyelid Retraction

- TRO causes scaring of eyelid muscles
- Scaring causes shortening of the muscles
- Upper and lower eyelids can be effected
- Contributes to discomfort and “stare”
- Can be very variable
Eyelid Retraction Treatment

- Wait for stability in most cases
- Steroids and radiation minimally effective
- Upper eyelid surgery
  - Remove and stretch scarred muscles
- Lower eyelid surgery
  - Recess scarred muscles
  - Place graft to help push eyelid upward
    - ECG, TarSys, AlloDerm, etc
Upper Lid Recession
Lower Lid Recession

Ear cartilage graft
Exophthalmos

- Not directly related to optic nerve problems
- Can cause severe disfigurement
- Can be a cause of corneal exposure and vision loss
- Caused by fluid accumulation in EOM and orbital fat
- Worst vision loss often seen in patients with minimal exophthalmos
Exophthalmos Treatment

- Wait for stability in most cases
- Steroids
  - Questionable value
- Radiation
  - Questionable value
- Surgery--Orbital decompression
There does not need to be exopthalmos for vision loss to occur!!!
Vision Loss

- Compression of the optic nerve
- Corneal changes due to exposure from exophthalmos and eyelid retraction
Optic Nerve

- Visual changes are great source of patient concern

Evaluation
- Visual acuity
- Marcus-Gunn swinging flashlight
- Color Vision
  - An early sign of compression
- Visual field examination

- Optic nerve compression can happen in the absence of exophthalmos
Optic Nerve Compression

- Bony orbit narrows posterior
- Optic nerve exits through narrowest part
- EOM surround this choke point
- Swollen EOM put pressure on optic nerve
- Causes color vision and visual acuity loss
Optic Nerve Compression Treatment

- Must relieve pressure on optic nerve
- Steroids can be effective
- Orbital decompression
  - Removes bone in posterior orbit
- Radiation
- Optic nerve sheath fenestration less helpful
Orbital Decompression

**INDICATIONS:**
- Progressive proptosis
- Optic neuropathy
- Optic nerve compression
- Orbital inflammation/pain
- Exposure keratopathy
- Cosmetic deformity
Orbital Decompression

- 2 wall
  - 3-7 mm globe position change
- 3rd wall
  - Add 3-4 mm
- 4 wall
  - Up to 14-17 mm
Orbital Decompression

- Usually 2 walls, medial wall and floor most common
- Leave bony strut between two to reduce potential for post op strabismus
- Lateral wall not helpful for apex, but may help for proptosis
- My approach is ENT does transnasal medial wall decompression and I do transconj floor – excellent results
- Fat decompression described, but controversial
Orbital Decompression

- 70% have residual diplopia needing correction-
  - EOM Imbalance
  - ION damage - rare
  - Maxillary sinusitis - rare
Cosmetic Concerns

- Fluid accumulation in eyelid skin and fat
- Conservative skin removal if at all
- Fat herniation in upper and lower eyelids
  - Same as typical cosmetic complaints
  - Occurs earlier and more severely in TRO
- Treatment is surgical excision
  - More difficult to achieve a perfect result
Special Concerns

- TAO and pregnancy: if compressive optic neuropathy, IV steroids best until delivery, then surgery. If emergent due to visual loss, risks to fetus parallel those of abdominal surgery.
The End

- Thank you
- Fill out evaluation
- Enjoy your day