THYROID EYE DISEASE: THERAPY IN THE ACTIVE PHASE

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BACKGROUND INFORMATION

• Synonyms: Grave’s ophthalmopathy, Graves’ orbitopathy, dysthyroid orbitopathy, thyroid associated ophthalmopathy, infiltrative ophthalmopathy, thyroid eye disease (TED)
• First described: sixth century affected the founder of Zen Buddhism and Kung Fu—Bodhidharma
• Modern description of hyperthyroidism, diffuse goiter and exophthalmos: Parry 1825, Graves 1835, von Basedow 1840
• Most frequently (80%) associated with hyperthyroidism, euthyroidism 10%, hypothyroidism 5%
• Ocular signs (lid retraction, lid lag) can be seen in other types of hyperthyroidism: thyroid cancer or thyroid inflammatory disease.

IMMUNOPATHOGENESIS

TED distinct autoimmune disorder separable from Grave’s hyperthyroidism
• Circulating T cells (directed against antigen on thyroid follicular cells) recognized antigens on orbital fibroblasts (extraocular myocytes)
• Activated CD4 T cells and local fibroblasts—release of cytokines
• Expression of immunomodulatory proteins (72-kd heat-shock protein, HLA-DR)
• Stimulation of GAGs and proliferation of fibroblasts
• Accumulation of GAGs and edema in orbital connective tissue

Shan and Douglas: JNO 34(2);177-185, 2014
Bahn and Heufelder: NEJM 329;1468-1475, 1993
PATHOLOGY
Clinical manifestations: mechanical effects of orbital volume increase
Accumulation of GAGs in orbital connective tissue
Edema, inflammation and fibrosis in the endomysial connective tissue investing extracapsular muscle fibers
Late stage: fibrosis and atrophy of extracapsular muscles due to chronic compression of muscle fibers

DIAGNOSIS
• Clinical Manifestations (including increase IOP with upgaze)
• Orbital ultrasound (computed tomography/magnetic resonance imaging)
• Endocrine dysfunction
• Thyrotropin receptor antibodies (thyroid stimulating immunoglobulins)


CLINICAL MANIFESTATIONS
• SOFT TISSUE
• OCULAR MOTILITY
• OPTIC NERVE

8/2/2014
CLINICAL MANIFESTATIONS: SOFT TISSUE

Eyelid retraction (most common)
Proptosis: 60%
Lid lag

CLINICAL MANIFESTATIONS: OCULAR SURFACE

Conjunctival injection
Keratitis

CLINICAL MANIFESTATIONS: OCULAR MOTILITY

CLINICAL MANIFESTATIONS: OPTIC NEUROPATHY

CLINICAL MANIFESTATIONS: OPTIC NEUROPATHY

DIFFERENTIAL DIAGNOSIS

- Non-specific orbital inflammation (orbital pseudotumor)
- Inflammatory orbital inflammation: sarcoidosis, Wegener’s, amyloidosis
- Orbital neoplasms: lymphoma, breast carcinoma
- Infectious orbital cellulitis
- Orbital vascular malformations
- Carotid-cavernous sinus fistula
- Orbital cysts

TREATMENT

1. How active and severe is the TED?
2. What TED risk factors can be modified or treated?
3. What is the best management strategy for the Graves' hyperthyroidism?
4. What is the optimum treatment for the TED?
**RISK FACTORS**

Effect of Abnormal Thyroid Function on the Severity of Graves' Ophthalmopathy

- Many clinicians have the impression that treatment of Graves' disease improves ophthalmopathy. This idea is not supported by clinical data.

**TREATMENT**

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**HYPERTHYROID TREATMENT**

- Antithyroid drugs: No influence on TED natural history
- Possible TED improvement due to restoration of euthyroidism

- Thyroidectomy: No influence on TED natural history in the short term
- Possible beneficial long-term effect due to thyroid ablation

- Radioactive Therapy: Short-term: possible TED progression
  - Long-term: possible beneficial effect due to thyroid ablation

  *This effect can be prevented by concomitant glucocorticoid administration at moderate doses*

**RADIOACTIVE IODINE TREATMENT: RISK FACTORS FOR WORSENING/PROGRESSION**

- Cigarette smoking
- Pre-existing TED
- Severe pre-treatment hyperthyroidism
- High serum TSH-receptor antibody levels
- High serum TSH levels

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TREATMENT

- Supportive
- Corticosteroids
- Selenium
- Orbital radiation therapy (ORT)
- Orbital decompression

TREATMENT FREQUENCY

- NO: no treatment
- SG: systemic glucocorticoids
- OR: orbital radiotherapy
- OD: orbital decompression
- RS: rehabilitative surgery

SUPPORTIVE TREATMENT

- Therapeutic measure: Sign and/or symptom
- Sunglasses: Photophobia
- Artificial tears and ointment: Foreign body sensation
- β-Blocking eye drops: Eyelid retraction; increased intraocular pressure
- Nocturnal taping of the eyes: Lagophthalmos
- Prisms: Mild diplopia
- Botulinum toxin: Eyelid retraction


CORTICOSTEROID TREATMENT

• Despite being the most often used and most frequently studied therapy for TED, the precise dosage, duration, preparation and route (intravenous [iv], oral [po] or periocular) of administration of corticosteroids a matter of opinion and debate.

• Corticosteroids: first-line treatment for patients with active moderate-to-severe TED and dysthroid optic neuropathy.

• Response rate: po corticosteroids less than iv corticosteroids (60% vs 80%, respectively).

• Pooled data: iv corticosteroids compared to po corticosteroids fared better in terms of double vision, ocular motility and proptosis.

• To date there have been only 4 randomized clinical trials that have compared the efficacy of po corticosteroids to iv corticosteroids.


• Extensive review of the literature (non-randomized studies, RCTs, consensus statements, systematic reviews and meta-analyses) recommended a 12 week course of iv methylprednisolone (.5 grams/week for 6 consecutive weeks followed by .25 grams/week for 6 consecutive weeks, not to exceed a total of 8 grams) for active moderate-to-severe TED.


• Multi-center, randomized, double-blinded trial (EUGOGO) accessed the efficacy and safety of 3 different cumulative doses (2.25 gm, 4.98 gm and 7.47 gm) of iv methylprednisolone over a 12 week period of time in active moderate-to-severe TED. 7.47 gm group had the greatest CAS positive short-term response. Benefit did not persist at 24 weeks and was associated with a slightly higher rate of adverse events compared to the lower doses.


SELENIUM

Selenium – nonmetallic trace element.

Selenoproteins important in cell development and proliferation, oxidative stress protection and production of T3.

Thyroid gland contains the largest amount of selenium and needed for proper functioning.

STUDY CHARACTERISTICS

Over 5 years, 159 mild GO patients randomized

3 groups:
oral sodium selenite 100µ g BID
oral pentoxifylline 600 mg BID
oral placebo BID.

Intention to treat analysis for all patients seen at the 3 month visit.

90% (137/152) patients completed the 12 month study.

PRIMARY OUTCOMES
ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>Selenium (N=73)</th>
<th>Mimoso (N=72)</th>
<th>Portacel/Sciten¹ (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ Four patients left the study during the first month and were not included in the final analysis.

Potential concerns of selenium supplementation: diabetes mellitus and glaucoma.

ORBITAL RADIATION TREATMENT

- Overall response rate of 60%.
- Debate on the role of ORT in TED.
- Impediment to a general consensus: paucity of RCTs, non-standardized clinical measures and outcomes, conflicting study results and heterogeneity of study design and diverse patient populations enrolled.
- ORT: second-line treatment for active moderate-to-severe TED.
- 5 RCTs compared ORT to corticosteroids in various combinations.
- 3 RCTs compared ORT to sham: 2 for moderate-to-severe TED and 1 for mild TED.

SURGICAL TREATMENT

Clinical Radiology 2014 69 7–18

Surgical or medical decompression as a first-line treatment of optic neuritis in Graves’ ophthalmopathy: a randomized controlled trial


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Very severe and active GO patients

<table>
<thead>
<tr>
<th>treatment</th>
<th>surgery</th>
<th>steroids</th>
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</thead>
<tbody>
<tr>
<td>responders</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>non-responders</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

8/2/2014
RITUXIMAB

- Human/murine chimeric monoclonal antibody
- Targets CD20 (transmembrane protein expressed on the surface of pre-B and mature B lymphocytes, but not on stem cells, pro-B lymphocytes or plasma cells).
- Blocks activation and differentiation of B-cells leading to specific elimination of B cells without affecting their regeneration from stem cells and the production of immunoglobulins from plasma cells.

TREATMENT ALGORITHM FOR TED

“One of the most wonderful things in nature is a glance of the eye…”

--Ralph Waldo Emerson