Thyroid Eye Disease
Graves’ Orbitopathy
Graves’ Disease

James C. Fleming, MD, FACS
Philip M. Lewis Professor
Director, Department of Ophthalmology
Hamilton Eye Institute
University of Tennessee Health Science Center
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Premier Research – Phase II drug study for active thyroid eye disease
Epidemiology

- Incidence 0.4% in US
  - (1,000,000 diagnosed in one year)
- Female to Male Ratio About 5-6 to 1
- Age Usually 40s and 50s
- Most Common Orbital Disorder
  - (10 to 20% sight threatening disease)
- Most Common Cause of Exophthalmos
Historical Background

- Three people have been credited with describing the syndrome:
  - Caleb Parry – England
  - Robert James Graves – Ireland
  - Karl von Basedow - Germany

The association between thyroid disease and exophthalmos has been known for two centuries.
Graves’ Disease (Autoimmune Disorder)

- Fundamental cause
  Autoantibodies that bind to and stimulate the TSH receptor on the thyrocyte
  - This Ig G molecule is in the class of autoantibodies that activate the cell surface receptors

- Genetic predisposition

- Environmental factors (smoking)
The anti-TSH receptor T-cell interacts with the thyroid cell receptor, activating thyroid hormone production independent of the normal regulatory pathway.
Autoimmune Mechanisms “Unclear”

- Little direct evidence linking extra-thyroidal TSH-Receptor expression with Graves’ disease

- Autoantibodies from patients with Graves’ disease bind the Insulin-like growth factor 1 receptor (IGF 1 receptor) on the surface of fibroblast

TJ Smith. Autoimmunity. 2003;36:409
Thyroid eye disease
The orbit is a secondary target organ

- Orbital fibroblasts appear to be the prime targets of the autoimmune attack in the orbit
  - Retro-orbital preadipocyte fibroblasts
    - These cells undergo adipocyte differentiation (*increased orbital fat*)
    - T-cell mediated inflammatory response (*swelling and inflammation*)
    - T-cell mediators induce effector cell proliferation and elaboration of glycosaminoglycans (GAG) (*increased thickness of extraocular muscles and increased edema*)
Thyroid eye disease
The orbit is a secondary target organ

Dutton and Haik 2002
Thyroid Eye Disease
Clinical Features

- Eyelid retraction 91%
- Exophthalmos 63%
- Restrictive myopathy 42%
- Optic nerve dysfunction 6%
- Extraocular muscle enlargement 55%*
  * of those imaged

Euthyroid 7%

Bartley 1994
The Clinical Course
“Rundle’s Curve”

- Inflammatory phase
  - Acute
  - Subacute
    
    Active changes 6-24 months
    (This is quite variable)

- Chronic phase (fibrotic changes)
  - Proptosis change over 5+ years
    (Two long term studies)
    unchanged in 72%
    increased in 23%
    decreased in only 5%
The Clinical Course
“Rundle’s Curve”
The Literature : Risk Modifiers

Correlation does not equal Causality

Cigarette smoking*** confirmed multiple studies

- Selenium ?
- Thyroidectomy ?
- Statins ?
Risk Factors: Selenium

- Mean serum selenium levels were significantly lower in GO (1.10 ± 0.18 μm) than in GD (1.19 ± 0.20 μm) (P = 0.001). Mean selenium levels appeared to decrease in parallel with increasing severity of GO; selenium level was 1.19 ± 0.20 μm in GD, 1.10 ± 0.19 μm in moderate-to-severe GO and 1.09 ± 0.17 μm in sight-threatening GO (P = 0.003). Serum selenium levels remained significantly lower in GO after adjusting for age, smoking status, thyroidectomy, radioactive iodine treatment and residential location.

Serum selenium status in Graves’ disease with and without orbitopathy: a case-control study. 2014 (198 subjects)
Khong JJ1, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, Craig JE, Ebeling PR.
Risk factors: Statins

Data from 8404 beneficiaries in a large US managed care network who received a confirmed diagnosis of Graves' disease between 2001 and 2009

Patients who used statins for 60 days or more had a 40% reduced hazard for developing TAO (adjusted hazard ratio, 0.60; 95% confidence interval, 0.37 - 0.93).

Risk Factors- Thyroidectomy

- Data from 8404 beneficiaries in a large US managed care network who received a confirmed diagnosis of Graves' disease between 2001 and 2009. They found that 740 of these patients (8.8%) developed TAO.

- Patients with Graves' disease who underwent surgical thyroidectomy had 74% reduction in their hazard of developing TAO compared with patients who did not undergo the surgery (adjusted hazard ratio, 0.26; 95% confidence interval, 0.12 - 0.51).

Active Phase Disease Management

- **Medical Therapy**
  - Localized ophthalmic protective measures
  - Anti-inflammatory treatment
    - Corticosteroids
      - Oral
      - Orbital injection
    - Pulse IV steroid therapy **Therapy with statins represents a newly recognized risk factor for liver damage in patients undergoing treatment with high-dose intravenous methylprednisolone for active moderate to severe Graves' orbitopathy, independently of the dose administered,"
    - Immunosuppression ** (rituximab)
    - Targeted immunosuppression

- **Orbital Radiotherapy**
  - Controversy over benefit

- **Surgical intervention**
European Group On Graves' Orbitopathy (EUGOGO)


ITEDS: International Thyroid Eye Disease Society

Acute orbitopathy

- Severe Exposure
- Compressive optic neuropathy
- Globe prolapse
Acute Optic Neuropathy

- Patients improve with oral corticosteroids
  - Prednisone 1.0-1.5 mg/kg/day
  - Methylprednisolone pulse therapy 500mgMP over 3 days in 4 weekly cycles (6g total)**risk!
  - Surgical decompression
Optic Neuropathy

- Etiology – orbital congestion with compression of the optic nerve
Acute/Active Phase Disease Management

- Steroid therapy
  - Oral
  - Periocular
Radiation Technique

- Megavoltage radiation therapy (4-6 MeV)
  - High-energy linear accelerator
  - Well collimated beam
- 20 GY delivered to entire content of bony orbit
  - Fractionated over 10 days
Radiotherapy
Orbital Radiotherapy
“Controversial”

Prospective trials:

- Gorman CA et al. Ophthalmology. 2001 Sep;108(9):1523-34
Active Phase Management
Medical Recommendations

- Stop smoking !!!
- Documentation of location on Rundle’s curve
Chronic Congestive Phase
Cosmetic vs “Rehabilitation”

Treatment Decision Path
- Orbital surgery
- Strabismus surgery
- Eyelid surgery
Types of Decompression

- Naffziger 1931
- Dollinger 1911
- Sewall 1936
Evaluation of the Ophthalmopathy – CT scan

- Size and depth of orbit
- Size of muscles
- Size and position of sinuses
- Bone thickness
Rehabilitation surgery
Two subgroups

- Group I Proptosis with restrictive myopathy
  (clinically significant diplopia)
- Group II Proptosis minimal restrictive myopathy
Gradation of Floor and medial wall Lateral wall decompression

Strabismus surgery

Eyelid surgery

Treatment - Group I (type1) Proptosis with restrictive myopathy
Area of Floor / Medial Decompression
Floor Removal
Medial approach
3 Wall Decompression

- Strabismus surgery
- Malar augmentation
- Eyelid surgery
Group II  Minimal Myopathy (type 2)

Lateral Decompression

Possible Fat removal

Possible Malar augmentation

Eyelid surgery
Area of Lateral Decompression
Lateral Decompression
Lateral Decompression
Lateral decompression
Lateral Rim Modification
- Lateral wall decompression
- Orbital fat removal
Supplemental Procedures

- Preseptal fat may be removed to relieve orbital pressure and add to decompression effect
- Malar or orbital rim augmentation
Rim Augmentation
This is an Autoimmune Disease

The Future

My Prediction

- These patients will not require major surgical management of this disease
Immunotherapy: Block Specific Receptors (address the fundamental cause)

Phase II studies of Teprotumumab, a monoclonal antibody.

- Blocking autoantibodies that bind to and stimulate the TSH receptor on the orbital fibroblast
  - This Ig G molecule is in the class of auto antibodies that activate the cell surface receptors

- This is directed at the fibroblast activity

- Teprotumumab for Thyroid-Associated Ophthalmopathy.
Polling Questions

1. What is the usual age of onset of TED?
   a) 20-30
   b) 30-40
   c) 40-50
   d) 50-60
Polling Questions

2. TED is the most common orbital disorder?
   a) True
   b) False
Polling Questions

3. Thyroid eye disease affects the orbit by
   a) Increasing Orbital Fat
   b) Causing swelling
   c) Increasing the thickness of extraocular muscles
   d) All of the above
Polling Questions

4. Thyroid eye disease affect optic nerve dysfunction in
   a) 20%
   b) 6%
   c) 50%
   d) 63%
Polling Questions

5. Clinical course of TED is equal to “Rundal’s curve” lasting

a) 2 months
b) 6 months
c) 6-24 months
d) 36 months
6. What are the reported risk modifiers in TED?
   a) Low Selenium levels
   b) Thyroidectomy
   c) Statins
   d) All of the above
Thank You

Questions?