Graves’ Disease

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Graves’ Disease (GD) is an autoimmune disease characterized by hyperthyroidism, ophthalmopathy, and dermopathy. The thyroidal component is driven by anti-thyrotropin receptor (TSHR) antibodies.
Robert J. Graves’
1797-1853

Caleb Hillier Parry
1755-1822

Karl Adolf von Basedow
1799-1854
• Parry CH. Collections from the unpublished medical writings. London: Underwoods, 1825:111

• Graves RJ. Clinical lectures delivered by Robert J. Graves, M.D. at the Mead Hospital during the session of 1834-5. London Med Surg J 1835; 7:516

• Basedow CA. Exophthalmos durch hypertropie des Zellgewebes in der Augenhohle. Wschr f d ges Heilkunde 1840;6:197-220
Epidemiology

• Incidence- 30-200 new cases per 100,000 per year
• Prevalence- 2.5 % of women and 0.23% of men
• GD is distributed relatively equally across races and around the globe
• Most common cause of hyperthyroidism in iodine sufficient areas

Tunbridge. Clin Endocrinol.1977
Vanderpump MPJ. Clinical Endocrinol 43:55-68, 1995
Symptoms of thyrotoxicosis

- Anxiety
- Irritability
- A fine tremor
- Sensitivity to heat
- Weight loss
- A rapid heartbeat
- Fatigue
- Difficulty sleeping
- Perspiration
- Brittle hair
- Light menstrual periods
- Frequent bowel movements
Thyroid Histology

- Normal: Papillary structures
- Graves': Diffuse hyperplasia
- Lymphocytic infiltration
Risk Factors

- Genetic
  - Monozygotic twins (35%) have a greater concordance rate than dizygotic twins (3%)
  - Susceptibility genes (CD40, CTLA-4, PTPN22) have been associated with GD
  - Increased frequency of HLA DR3 and DQA10501 haplotypes in GD

Brix TH. JCEM. 2001
Risk Factors

• Gender
  • Female to male ratio (8-10: 1)
• Age
  • low incidence in childhood
• Pregnancy
• Environmental factors associated with GD
  • Infection
  • Stress (emotional or physical)
• Medications
  • Iodine
  • Amiodarone

Pathogenesis

- GD is an autoimmune disease in which host susceptibility genes and environmental factors interact to initiate cellular and humoral immune responses against host antigens.

- The TSH receptor (TSHR) is an autoantigen in GD.

- Anti-TSHR antibodies (IgG class) stimulate the TSHR without modulation and cause hyperthyroidism.
Diagnosis

- Clinical
  - Goiter
  - Thyrotoxicosis
    - Symptoms
  - Ophthalmopathy
  - Dermopathy

- Biochemical
  - TSH, T3, T4, TSI (thyroid stimulating immunoglobulins)

- Nuclear Medicine
  - % Thyroidal Iodine uptake
  - Diffuse pattern of thyroidal uptake (scan)

Differential Diagnosis

- Other causes of hyperthyroidism
  - Toxic uninodular or multinodular goiter
  - Subacute thyroiditis
  - Silent thyroiditis
  - Struma Ovarii
  - Surreptitious Levothyroxine use
  - Toxic hyperplasia
Treatment of hyperthyroidism

• Reversible
  • Thionamides* (PTU, Methimazole)
  • B-blockers (Propranolol)
  • Corticosteroids
  • SSKI

• Definitive
  • Radioactive iodine therapy
  • Surgery

Remission of hyperthyroidism

- Remission can occur after thionamide therapy (12-18 months). Long term remission is rare with high % per year recurrence after discontinuation of thionamide therapy.
- Severity of hyperthyroidism, goiter size, higher T3, higher TSI are poor prognostic features for achieving remission.

Cooper DS. NEJM 2005;352:905-917
Graves’ Disease

Pregnancy

• Graves’ disease:
  • is uncommonly diagnosed during pregnancy
  • thyrotoxicosis often improves and autoimmune phenomenon often remit during pregnancy
  • commonly relapses or develops in the post-partum period in susceptible hosts
• High maternal TSI levels after 25 weeks of gestation are associated with increased risk of antibody transfer to fetus and the development of transient fetal thyroidal dysfunction

Chan GW. Nat Clin Pract Endocrinol 2007; 3:7; 470-78
Graves’ Disease
Children and the aged

- Children
  - The most common form of hyperthyroidism in children
  - TAO is extremely rare in children
  - Thionamide therapy is preferred
  - RAI therapy is controversial in children

- Aged
  - Often lack hyperkinetic symptomatology and present with myopathy, atrial fibrillation, heart failure
  - Apathetic hyperthyroidism (placid facies, withdrawn, depressed affect)

Rivkees SA. J Pediatr Endocrinol Metab 2006. 19;9:1095-111
GD Associated Manifestations
Thyroid Associated Ophthalmopathy (TAO)

• Pathogenesis*
  • TSHR and other antigens have been implicated
  • Uniqueness of orbital fibroblasts may underlie regional involvement

• Incidence
  • 20% of patients with GD develop clinically obvious ophthalmopathy

• Symptoms
  • Gritty, sandy sensation, Tearing
  • Retrobulbar pain and discomfort
  • Diplopia
  • Photophobia
  • Blurred vision

*Prabhakar BS et. al. Endocr Rev 2003. 24;6;802-25
*Khoo TK et. al. Thyroid 2007.17(10);1013-18
Who develops TAO?


Male Sex


Smokers


When?

85% within 18 months of thyrotoxicosis

TAO-Disease Course

Active Phase

Stable Phase

Immunomodulatory Therapy

Surgery

Disease

Time

18-24m

5-7yrs
Treatment of TAO

- **General**
  - Local/protective measures
  - Tinted spectacle lenses
  - Artificial tears/ointment
  - Nighttime eye patch/taping lids
  - Prisms
  - Smoking cessation*

Treatment of TAO

- Treatment of coexistent hyperthyroidism
- Immunomodulatory (most effective in active phase)
  - Steroid Therapy
    - PO, IV
  - Radiation Therapy
- Surgery (three step-reserved for stable disease)
  - Orbital decompression
  - Muscle surgery
  - Eyelid surgery

In a RCT, treatment with RAI alone led to development or worsening of:
ophthalmopathy (15%)
compared to methimazole (3%)
RAI + prednisone (0%)

Bartelena L. et al. *NEJM*
338:2;73-78.1998
Immunomodulatory therapy for Active TAO

- Steroid Therapy
  - Never tested for efficacy against placebo.
  - 60-90% response- Most efficacious early in disease process.
    - Rapid improvement (48hr) of inflammation, soft tissue changes, optic neuropathy ±
    - Proptosis, diplopia- less responsive
    - Relapse upon discontinuation-tapering/Side effect
  - Multiple routes (PO, IV, Local)
  - Can usually be safely with caution

Bartalena et. al. Endocrine Reviews. 2000
Immunomodulatory therapy for Active TAO

• Retrobulbar irradiation-for active TAO
  • Rationale-
    • Non-specific anti-inflammatory effects
    • Radio-sensitivity of lymphocytes
  • Efficacy
    • Improvement occurs in 1-4 wks, continues 1yr
    • Equally as effective as oral steroids (~65%) (Double blind, RCT, Prummel PF et al. Lancet. 1993)
GD Associated Manifestations
Dermopathy

- **Pathogenesis**
  - Unknown

- **Histology**
  - Glycosaminoglycan (hyaluronan) deposition in dermis

- **Diagnosis**
  - Often associated with severe TAO
  - Non-pitting edema
  - Peau d’orange texture
  - Friable, weepy skin (in the appropriate setting)

- **Therapy**
  - Local application of corticosteroids
  - Avoid trauma/biopsy
  - Does not improve with correction of hyperthyroidism

Other manifestations of GD

- Acropachy
  - Triad of:
    - digital clubbing
    - Soft tissue swelling of hands and feet
    - Peri-osteal new bone formation
Euthyroid Graves’ disease

- TAO consistent with GD in a patient with normal thyroid function
- DDX includes orbital or retro-orbital tumor, lymphoma. Helpful clues include:
  - History suggestive of previous hyperthyroidism
  - Measurement of TSI
  - Orbital MRI to exclude involvement of orbital muscle tendons
  - Orbital CT
## Differential Diagnosis

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