THYROID EYE DISEASE:

Immunological Considerations

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GRAVES’ DISEASE

12th Century ACE Persian Physician
First account of neck swelling associated with exophthalmos

1786 Caleb Parry (Bath Medical Soc)
Read a paper presenting a 37 y/o female with goiter, exophthalmos, and lid retraction
Was published posthumously in 1825
GRAVES’ DISEASE

1835 Robert J. Graves (Dublin)
Described 3 cases with cardiac palpitations, goiter, 1 with exophthalmos, and lid retraction

His name was first associated with this disease in 1860 by Trousseau in France

1840 Carl Adolph von Basedow (Germany)
Published 4 patients with similar findings and reviewed the literature

His name was first associated with this disease in 1859 by Charcot
THE THYROID GLAND

acts on the anterior pituitary to synthesize and release thyroid stimulating hormone (TSH)

primary factor regulating growth and differentiation of thyroid follicular cells

binds to TSH receptors on thyrocytes

TRH

Hypothalmus

inhibition

cellular metabolism

growth & development

TSH

T4, T3

+
Immune-mediated disorders
Reactive immune cells are directed against “self-antigens”

Common auto-immune diseases are:

- type 1 diabetes
- rheumatoid arthritis
- multiple sclerosis
- Crohn’s disease
- lupus
- Graves’ disease
**STEPS IN CHRONIC AUTOIMMUNE DISEASE**

*Initial phase*: loss of specific self-tolerance

*Afferent phase*: recognition of self antigens by APCs, and transport to peripheral lymph nodes

*Activation phase*: T-cell activation and proliferation

*Effector phase*: T-cell migration to the target tissues, help other cells, and participate in inducing the inflammatory process
IMMUNE SELF TOLERANCE

Bone marrow

B cell

T cell

Thymus

B cell deletion

anti-self

some B- and T-cells with low specific affinity escape censorship

high ag affinity

T cell deletion

intra-marrow negative selection

intra-thymic negative selection
Initiation of Autoimmune Disease

- Thyrocyte: MHC I
- T cell: anti-self
- APC: MHC II
- T cell cross-reactive or native peptide epitope fragment
- Hi affinity receptor
- Low affinity receptor
- TCR
- Apoptosis
- Inflammation
- Activation proliferation
- T cell cross-reactive stimulation
Loss of Self-Tolerance

Viral infection or epitope immune activation
GRAVES’ DISEASE

A chronic organ-specific systemic disease

Autoimmune etiology

Primarily involves the thyroid gland

Secondarily involves other tissues
GRAVES’ DISEASE

Genetic Predisposition:

0.45% incidence of GD among all twins

0.16% incidence of GD among 1st degree relatives of affected twins

1.9% concordance rate among DIZygotic twins

25% – 35% concordance rate among MONOzygotic twins
Environmental Factors:

- Smoking
- Stress
- Exogenous Iodine intake
**GRAVES’ DISEASE**

**Smoking:**

- **Graves’ Disease:** smokers = 83%
- **Normal Controls:** smokers = 46%

N = 1730

- **Normal controls:** smokers = 30%
- **Graves’ Disease:** smokers = 48%
- **Graves’ Orbitopathy:** smokers = 64%

Vestergaard, 2002: Review of 25 studies

- **Graves’ Disease** = odds ratio: ever vs never smoker = 1.9
- **TED** = odds ratio: ever vs never smoker = 4.4
**GRAVES’ DISEASE**

**Smoking:**

*Improvement after steroids:* non-smokers = 64%

*Improvement after steroids:* smokers = 15%

*Improvement after RT:* non-smokers = 94%

*Improvement after RT:* smokers = 68%

Karadimas et al. 2003: 85 smokers with TED warned to quit, followed for 1 year; cessation rate = 0%
GRAVES’ DISEASE

Smoking:

*How does smoking influence the occurrence of GD?*

- unknown

- ?epiphenomenon related to stress

- smoke constituents can up-regulate expression of HLA-DR

- smoke constituents can increase specific cytokine secretion and adhesion molecule expression, implicated in GD
GRAVES’ DISEASE

Stress:

Relationship between stress and GD suggested since the early 19th C

Now supported by numerous studies

Risk of GD 6.3 X – 7.7 X greater for those with high scores on stressful life events (SLE) questionnaires than those with lower scores

Incidence of Graves’ disease higher under stressful situations, e.g. WWII in eastern Europe
GRAVES’ DISEASE

Stress:

How does stress influence the occurrence of GD?

- unknown

- may be related to the tight relationship between the hypothalamic – pituitary – adrenocortical axis and the autonomic NS and the immune system

- stress can activate this system resulting in secretion of cytokines which are implicated in GD
Environmental 

**Iodine:**

Areas with higher ingestion of Iodine = greater incidence of GD

Remission rate on therapy higher with low Iodine ingestion, lower with high Iodine ingestion

Relapses more common in patients ingesting higher levels of Iodine
Environmental Iodine:

How does exogenous Iodine influence the occurrence of GD?

- unknown
- in vitro, Iodine can stimulate lymphocyte activity
- Iodine increases anti-TSHR antibody titers in GD patients
GRAVES’ DISEASE

Demographics:

Childhood to old-age, but most commonly middle-aged adults
GRAVES’ DISEASE

Primary Target of the Immune Response:

Thyrotropin (TSHR) receptor antigen of the thyrocyte

Stimulating abs activate the cAMP cascade

Blocking abs block cAMP synthesis or prevent TSHR binding

Thyrocyte

T4, T3

cAMP

anti-self lymphocyte

may be stimulating or blocking

TSH receptor
GRAVES’ DISEASE

Immune Disease in the TSHR Ectodomain:

Thyroid-Associated Dermopathy = 8%
- “pre-tibial” inflammation
- glycosaminoglycan deposition
- edema
- nodular fibrosis

Phalangeal Acropachy = 1%
- soft-tissue swelling (clubbing)
- periosteal new bone formation

Thyroid Eye Disease (TED) = 30%-40%
- edema
- nodular fibrosis

[Images of medical conditions mentioned in the text]
GRAVES’ DISEASE

Secondary Targets in the Orbit:

Orbital fibroblast and pre-adipocyte fibroblast initiate homing of lymphocytes into the orbit

- presence of mRNA encoding exons 1-10 of human TSHR gene
- presence of a TSHR-like protein in fibroblasts of Graves’ patients
- absence of these proteins in normal orbits
Secondary Targets in the Orbit:

Relationship to eye muscle antigens (G2s, Fp)

Abs against eye muscle antigens seen in:

- 70% of patients with TED
- 7% of normal controls

Most likely secondary to muscle injury from orbital inflammation
Thyroid Eye Disease

Clinical Manifestations of TED:

**Subtypes**

*Congestive orbitopathy*
- diffuse orbital edema
- congested vascular tree
- relatively normal muscles

*Myopathic orbitopathy*
- enlarged extraocular muscles
- minimal congestive findings
Thyroid Eye Disease

Clinical Manifestations of TED:

- Conjunctival injection and chemosis
- Dry eyes
- Proptosis
- Eyelid injection
- Strabismus
- Compressive optic neuropathy
Thyroid Eye Disease

Conjunctival Injection and Chemosis:

Orbital congestion with increased venous pressure

Dilated anterior ciliary arteries

?Inflammatory involvement of conjunctival fibroblasts
**Dry Eyes**

TOA patients show significant ocular surface damage related to decreased tear secretion. Lacrimal acinar cells express TSH receptor antigens, and this may be a focus of inflammatory damage resulting in secretory impairment.
**Proptosis:**

Increased orbital fat volume from edema

Enlarged extraocular muscle volume

mild

moderate

globe prolaps
Thyroid Eye Disease

Eyelid Retraction:

- CT fibrosis
- Contraction of the levator muscle sheath
- Fibrosis of Müller’s muscle
- Shortening of fornix suspensory ligaments
Thyroid Eye Disease

**Diplopia:**

- Glycosaminoglycan deposition
- Fibrosis of EOM sheaths, perimysium, & suspensory fascia
Thyroid Eye Disease

**Compressive Optic Neuropathy:**

- Optic nerve compression by EOM’s
- Fibrosis of Annulus of Zinn
- Orbital congestion & fascial-compartment syndrome
- Short optic nerve
**Thyroid Eye Disease**

**Clinical Activity Index:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0 = none</th>
<th>1 = at rest</th>
<th>2 = with movement</th>
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<tbody>
<tr>
<td>Orbital pain</td>
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<td>Chemosis</td>
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<td>Eyelid edema</td>
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<td>Conjunctival injection</td>
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<td>Eyelid injection</td>
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<tr>
<td><strong>Total</strong></td>
<td>0</td>
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**Orbitopathy:**  
mild = 0-3  moderate = 4-5  severe = 6-8
Thyroid Eye Disease

Natural History of Clinical Activity:

- Clinical activity: 100%, 50%, 0%
- Disease severity: 100%, 50%, 0%
- Time: acute inflammatory phase, chronic fibrotic phase
Thyroid Eye Disease

Radiographic Findings:

- Increased fatty volume
- Enlarged EOM's
- Evaluated on coronal sections
Euthyroid Thyroid Eye Disease

Clinical manifestations of TAO

Radiographic evidence of orbitopathy

*No* evidence of clinical hyperthyroidism
Euthyroid Thyroid Eye Disease

Euthyroid TAO patients:

Tend to be slightly older than hyperthyroid TAO patients (56 yrs vs 52 yrs)

Tend to be less likely female compared to hyperthyroid TOA patients
Euthyroid Thyroid Eye Disease

TSHR blocking abs can be found in up to 29% of Graves’ patients.

Variable activity subtypes of TSHR abs

Diagram: cAMP
Thyrocyte
blocking anti TSHr lymphocyte
stimulating anti TSHr lymphocyte
Orbital TSH Receptor Epitope

Orbital Fibroblast

TSH epitope
receptor site

anti-TSHR T-Cell
T-Cell Homing Mechanisms

TSH epitope receptor site

TGF-1 receptor
upregulated 4-5 X
occupies same physical space as TSHR
T-Cell Homing Mechanisms

- TSH epitope receptor site
- T-cell traffic signalling
- Rantes IL-16
- Graves’ specific IgG
- TGF-1 receptor

Cell traffic and signalling involve various molecules and receptors, including the TSH epitope and IL-16.
Fibroblast-T cell Interaction

cytokines

transforming growth factors

inflammatory mediators
Fibroblast-T cell Interaction

- Increased blood flow
- Vascular dilatation
- Vascular permeability
- Tissue edema
- Valve incompetence, stasis
- Lymphatic relaxation

Inflammatory mediators:
- Prostaglandins
- Nitric oxide
- Histamine
- Proteases
- Collagenases

Fibroblast-T cell Interaction
augmented expression of TSHR; allows it to serve as an autoantigen
Adhesion Molecules

TNF-α

VCA M

selectins

ICA M
Glycosaminoglycan synthesis

Fibroblast-T cell Interaction

altered structure and distribution pattern

increased water binding and tissue edema

proptosis, enlarged EOMS, lid swelling

cytokines

INF $\gamma$

TNF $\alpha$

IL 1$\alpha$

IL 2, 6
Fibroblast-T cell Interaction

collagen synthesis

CT Fibrosis

eyelid retraction, EOM restriction

cytokines

INF $\gamma$
TNF $\alpha$
IL 1$\alpha$
IL 2, 6
Fibroblast-T cell Interaction

pre-adipocyte differentiation

cytokines

INFγ
TNFα
IL1α
IL2, 6

increased fat volume

proptosis
Fibroblast-T cell Interaction

- Transforming growth factors:
  - TGF-β
  - Platelet derived GF
  - Insulin-like GF

- T-cell proliferation

- Fibrosis

- EOM restriction

- Fibrosis
Thyroid Eye Disease

Rationale for Treatment:

Symptomatic therapy while disease is active

Medical treatment for significant congestion

Radiotherapy for severe congestion or early optic nerve compression

Emergency intervention for vision-threatening signs

Definitive surgical correction after disease stabilizes
Symptomatic Therapy

Artificial tears and punctal plugs for dry eyes
Fresnel prisms for diplopia
Botulinum toxin for lid retraction
Lateral tarsorrhaphy for proptosis and globe prolapse
Steroid Therapy

Indicated for acute congestive inflammatory orbitopathy and early compressive neuropathy

Pulsed IV steroids may be more effective

Improvement can be seen in motility and vision in up to 50%

However, steroids are not a long-term treatment option

Non-steroidal anti-inflammatory drugs (Voltaren 50mg bid) a better option
Radiation Therapy

Indicated for congestive orbitopathy and early compressive optic neuropathy

2000 cGy total, in 200 cGy fractions, sparing lens, lacrimal gland, and sella

No difference at 6 months between 1600 cGy vs 2400 cGy

Average dose to lens = 100 cGy

Risk for radiation-induced malignancy = 0.7%
Radiation Therapy

Produces favorable results in 50 – 60% of cases

Gorman, 2002: no benefit at 6 months

Poor results with longstanding inactive disease

Generally not very useful for diplopia or proptosis
Surgical Therapy

Requires stability of disease for best results

Staged Surgical Approach:

1. Orbital decompression
2. Strabismus surgery
3. Eyelid recession and blepharoplasty
Orbital Decompression

Indications:

- Compressive optic neuropathy
- Corneal exposure
- Orbital congestion
- Uncontrolled glaucoma
- Cosmetic improvement
Orbital Decompression

Transconjunctival approach to the orbital floor

Transcaruncular approach to the medial wall

Removal of extraconal and intraconal fat
Orbital Decompression
Strabismus Surgery

Indications:

Symptomatic stable diplopia

Cosmetic deformity
Eyelid Recession

**Indications:**

- Exposure keratopathy
- Subluxation of globe
- Cosmetic improvement
Upper Eyelid Recession
Lower Eyelid Recession

Disinsertion and recession of capsulopalpebral fascia

Placement of interpositional graft:
  hard palate mucosa
  auricular cartilage
  free tarsocconjunctival graft
  Medpor interpositional disk
Lower Eyelid Recession
Blepharoplasty

Excision of excess skin and fat
Usually combined with eyelid recession
Future Management Options

Immunomodulation of specific T cell receptors

Interference with target APC presentation of antigen: MHC expression, co-stimulatory molecule blockage

Specific cytokine/chemokine inhibition

Engineering of soluble human TSHR neutralizing antigens in the ectodomain