Update on the Management of Graves Disease

Fadi Nabhan, MD
Clinical Assistant Professor
Division of Endocrinology

Objectives

- Pathophysiology and Clinical Presentation
- Approach to Diagnosis
- Management
Robert Graves

- “violent and long continued palpitation in females….in one the beating of the heart could be heard from distance from the bed….enlargement of thyroid gland”

- “It was observed that….the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the lids were incapable of closing”
Graves Disease

- **Classic Triad:**
  - Thyrotoxicosis
  - Goiter
  - Eye Disease

Diagram:
- Activated T Cells
  - +
  - B Cells
- TSH R Abs
- TSH R
- Thyroid Follicular Cell
- Hyperthyroidism
- Hypertrophy
Genetic Factors

Environmental Factors

Immune Tolerance

Infection
Iodine Intake
Smoking
Stress

Mechanism of Disease

Epidemiology

- It affects 0.5% of the population

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- Iodine Sufficient Areas: 50-80% of all causes of Thyrotoxicosis

Epidemiology

- It affects 0.5% of the population
- Iodine Sufficient Areas: 50-80% of all causes of Thyrotoxicosis
- More Frequent in Women than Men 5:1
- Peak in the 5th and 6th decade but can occur at any age


Clinical Presentation
Clinical Presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
<td>80-95%</td>
</tr>
<tr>
<td>Palpitation</td>
<td>65-99%</td>
</tr>
<tr>
<td>Sweating</td>
<td>50-90%</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>40-90%</td>
</tr>
<tr>
<td>Wight loss</td>
<td>50-85%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>65-80%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45-80%</td>
</tr>
<tr>
<td>Oligomennorrhea</td>
<td>11%</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>10-65%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10-30%</td>
</tr>
</tbody>
</table>


Age Related Change in Graves Disease Hyperthyroid Symptoms

More Common In The Older

- Weight Loss
- Decreased Appetite
- Atrial Fibrillation
- Depression

Features of Goiter in Graves Disease

- Diffuse enlargement
- Non nodular
- Bruit

Graves Eye Disease

- 50% of patients.
- 3-4% have severe disease.
- Usually occur with hyperthyroidism or within 6-12 months of that
- Rarely can occur in absence of hyperthyroidism

Graves Dermopathy


Thyroid Acropathy

Thyroid Acropathy


Soft Tissue Swelling Periostitis

Differential Diagnosis
Thyrotoxicosis

Exogenous

Endogenous

Exogenous
Thyrotoxicosis

Endogenous

Extrathyroidal

Struma Ovarri

Exogenous

Struma Ovarri

Thyrotoxicosis

Endogenous

Extrathyroidal

Struma Ovarri

Thyroid
Thyrotoxicosis

Endogenous

Exogenous

Extrathyroidal

Struma Ovarri

Increased Production

Increased Release

Primary

Secondary

Thyroiditis

TSH Producing Tumors
Thyrotoxicosis

Endogenous

Exogenous

Extrathyroidal

Struma Ovarri

Increased Production

Increased Release

Thyroid

Primary

Secondary

Graves Disease
Toxic Nodular Goiter
Iodine Induced

TSH Producing Tumors

Laboratory Findings

- Suppressed TSH

- Elevated T4 and/or T3
**Approach to Diagnosis**

**Thyrotoxicosis**

Typical presentation of Graves disease

No need for further testing


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**Approach to Diagnosis**

**Thyrotoxicosis**

Clinically not diagnostic of Graves

Radioactive Iodine Uptake and Scan

Thyroid Radioiodine Uptake and Scan

Thyrotoxicosis

**HIGH UPTAKE**
- Graves Disease
- Toxic Nodular Goiter

**LOW UPTAKE**
- Thyroiditis
- Expanded Iodine Pool
- Surreptitious Thyroid Hormone Ingestion
- Ectopic Thyroid
Thyrotoxicosis

HIGH UPTAKE
- Graves Disease
- Toxic Nodular Goiter

Graves Disease--Thyroid Scan
**TSH Receptor Antibodies**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Graves Disease</th>
<th>Sensitivity Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation</td>
<td>3634</td>
<td>79.8 (52.2-94)</td>
</tr>
<tr>
<td>2nd generation</td>
<td>1451</td>
<td>96.4 (87-100)</td>
</tr>
<tr>
<td>3rd generation</td>
<td>1630</td>
<td>97.2 (95-100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Specificity Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd generation</td>
<td>1819</td>
<td>98.1 (90.3-100)</td>
</tr>
<tr>
<td>3rd generation</td>
<td>1976</td>
<td>99.2 (97.3-100)</td>
</tr>
</tbody>
</table>


**Approach to Diagnosis**

- **Thyrotoxicosis**
- Clinically not diagnostic of Graves
  - TSH Receptor Antibodies
  - OR?? Radioactive Iodine Uptake and Scan
Clinical Utility of TSH R Abs

- Radioactive iodine is contraindicated
- Prognostic marker for probability of Remission with use of antithyroid medication
- In pregnancy as a prognostic marker for fetal thyroid disease


Thyroid Ultrasound and color flow Doppler

- Hypoechoic
- Color flow Doppler is increased
Thyroid Ultrasound

- Normal Doppler
- Graves’ Doppler

*Brent G. N Engl J Med 2008; 358:2594-2605*

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Thyroid Ultrasound and color flow Doppler

- Hypoechoic
- Color flow Doppler is increased
- Should be done to evaluate cold nodules seen on iodine scan
Management

Approach to Management
Approach to Management

Control of Hyperthyroidism
Trying to Preserve Thyroid Function
With Aim at Remission

Anti Thyroid Drugs
Antithyroid Drugs

Actions

- Have been used since 1940s
- Inhibit thyroid hormone synthesis
- They may have clinically important immunosuppressive effects.

Antithyroid Drugs

- Which Drug?
- Dose
- Monitoring
- Duration of Treatment

Comparison between PTU and MMI

<table>
<thead>
<tr>
<th></th>
<th>PTU</th>
<th>MMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of Administration</td>
<td>Twice or three times daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Compliance</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Inhibits Conversion of T4 to T3</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## Comparison between PTU and MMI Side Effects

<table>
<thead>
<tr>
<th></th>
<th>PTU</th>
<th>MMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>5-20%</td>
<td>5-20%</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>0.2-0.5%</td>
<td>0.2-0.5%. Dose dependent</td>
</tr>
<tr>
<td>Hepatic Failure</td>
<td>&lt;0.1%</td>
<td>Cholestatics</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>ANCA +</td>
<td>Very rare</td>
</tr>
</tbody>
</table>
Therefore: Always use Methimazole except in limited situations.....

When Can PTU be used?

- PTU is drug of choice in first trimester

APLASIA CUTIS CONGENITA (Use of Methimazole)

When Can PTU be used?

- PTU is drug of choice in first trimester
- Treatment of thyroid storm
- Patients who are unable to tolerate MMI due to minor reactions and refuse to other modalities of therapy

Dose

Nakamura H. J Clin Endocrinol Metab. 2007 Jun;92(6):2157-62

Monitoring

- Baseline ling CBC and liver profile
  - A baseline absolute neutrophil count <500/mm3 or liver transaminase enzyme levels elevated > fivefold the upper limit of normal are contraindications to initiating therapy
Monitoring

- A differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis.

Monitoring

- No consensus concerning the utility of periodic monitoring of white blood cell counts and liver function tests.
**Monitoring Thyroid Function Tests**

- Assess thyroid function tests every 4 weeks until euthyroid.
  - TSH lags behind T4 changes
- Once the patient is euthyroid, check tests every 2-3 months.

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**Duration of Treatment and Probability of Remission**

Cooper DS. *J Clin Endocrinol Metab.* 2003 Aug;88(8):3474-81
Duration of Treatment and Probability of Remission

No difference if treatment exceeds 18 months

Factors that Increase Chance of Remission

- Disappearance of TSH-receptor antibodies during therapy
- Mild hyperthyroidism
- Smaller goiter

Cooper DS. J Clin Endocrinol Metab. 2003 Aug; 88(8): 3474-81
How Antithyroid Drugs Are Used

Methimazole 10-30 mg a day
Taper to maintenance 5-10 mg a day
Continue for about 18 months

Time

Taper further and then Stop if not Hyperthyroid

OR

Measure Receptor Abs and stop if negative

Time
Relapse

Repeat Antithyroid Drugs  RAI I-131  Surgery

May use low dose Methimazole long term?
Radioactive Iodine

- It has been used for treatment of hyperthyroidism for six decades
- Goal is to render patient hypothyroid
Radioactive Iodine Dose

- Administering a fixed activity (10-15 mCi)

  OR

- Calculating the activity based on the size of the thyroid and iodine uptake

- Fixed dose is easier and no definitive evidence of superiority of calculated dose
Success of Radioactive Iodine Treatment

- 80-90% after one dose
- Treatment can be repeated at a larger dose in patients who fail first dose

Chances of Success after Radioactive Iodine

- Severity of Hyperthyroidism
- Size of Goiter
Preparation of Radioactive Iodine Treatment

- Methimazole should be stopped about 3-7 days before I 131 Tx.
- Use of B Blocker around the treatment
- Negative pregnancy test within 48 hours of treatment

Post Radioactive Iodine Treatment

- Anti thyroid medication can be restarted in 3-7 days and then taper over 4-6 weeks
- Avoidance of pregnancy for 4-6 months
- Check Thyroid function tests every 4 weeks
Risk of Radioactive Iodine Treatment

- Worsening Hyperthyroidism

When to do Pre Treatment with Anti Thyroid Drugs

- Very symptomatic patient

- Have free T4 estimates 2–3 times the upper limit of normal

- Elderly and Co morbidities such as cardiovascular disease
Risk of Radioactive Iodine Treatment

- Worsening Hyperthyroidism
- Eye Disease

Changes in the Degree of Ophthalmopathy in Patients with Hyperthyroidism Who Were Treated with Radioiodine, Radioiodine and Prednisone, or Methimazole.

Changes in the Degree of Ophthalmopathy in Patients with Hyperthyroidism Who Were Treated with Radioiodine, Radioiodine and Prednisone, or Methimazole.

This is increased in SMOKERS!

Prevention of Ophthalmopathy around Radioactive Iodine Treatment

- Prednisone at 0.4–0.5 mg/kg/day (? 0.2 mg/kg sufficient)
- Started 1–3 days after radioactive iodine treatment
- Continued for 1 month
- Then tapered over 2 months
Surgery

- Normalize T4/T3 with antithyroid drugs
  - Consider using potassium iodide
  - Near-total or total thyroidectomy is the procedure of choice
  - Total thyroidectomy has a nearly 0% risk of recurrence
Surgical Complications

- Hypocalcemia (permanent <2%)
- Recurrent laryngeal nerve injury (permanent <1%)
- Post-operative bleeding
- Complications related to general anesthesia.

Approach to Management

- Control of Hyperthyroidism Trying to Preserve Thyroid Function With Aim at Remission
  - Anti Thyroid Drugs
- Definitive Treatment of Hyperthyroidism With Result in Hypothyroidism
  - Radioactive Iodine Or Surgery
Choice of Treatment

- Anti Thyroid Drugs
- I-131
- Or
- Surgery

High Probability of Remission

Low

Choice of Treatment

- Surgery
- I-131

Compressive Goiter
Severe Eye Disease?

High Surgical Risk
PATIENT PREFERENCE!!

Pattern of Therapy by Physicians

Survey of Endocrine Society, American Thyroid Association and AACE Members

730 Respondents
- ATDs: 53.9%
- I-131: 45%
- Surgery: 0.7%

Versus a similar study in 1991, there is greater use of ATDs and Lower Use of I-131

Burch HB, Burman KD, Cooper DS. J Clin Endocrinol Metab. 2012 97:4549-4558
Burch HB, Burman KD, Cooper DS. J Clin Endocrinol Metab. 2012 97:4549-4558

Potential Future Therapy
Hyperthyroidism
Hypertrophy

Adopted from Rebecca Bahn
THANK YOU!