Diagnosis and Management of Hyperthyroidism

Ohio State Endocrine Update
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Conflicts of Interest

- Advisory Board: Veracyte
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Clinical Case

• 37 year old woman presents to primary care physician
  – Weight loss
  – Difficulty sleeping
  – Anxiety
• Symptoms for 6 weeks
• No eye complaints
• Family history of a “thyroid problem” in her sister
Clinical Case

- On exam:
  - Vitals: BP 132/54; Pulse: 106 (Regular); Temp: 99.1
  - No proptosis, mild conjunctival erythema, Lid Lag is present
  - Thyroid is mildly diffusely enlarged. There is no thyroid bruit. It is non-tender
  - Remainder of exam is normal except for a fine resting tremor on hand extension and rapid relaxation phases on reflexes
## Overt Symptoms of Thyrotoxicosis

<table>
<thead>
<tr>
<th>Symptoms: the top 5</th>
<th>Signs: the Top 5</th>
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<tbody>
<tr>
<td>Nervousness 99%</td>
<td>Tachycardia 100%</td>
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<tr>
<td>Diaphoresis 91%</td>
<td>Goiter 100%</td>
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<tr>
<td>Palpitations 89%</td>
<td>Tremor 97%</td>
</tr>
<tr>
<td>Fatigue 88%</td>
<td>Skin changes 97%</td>
</tr>
<tr>
<td>Weight loss 85%</td>
<td>Eye signs 71%</td>
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</table>
FIG. 1. A, Number of symptoms of hyperthyroidism reported by patients in the respective age groups, indicating that the majority of patients aged older than 61 yr reported a maximum of two symptoms.
Graves’ Orbitopathy and Dermopathy

Non Pitting Edema

Plaque

Nodular

Elephantiasis
Clinical Case

• Laboratories:
  – TSH: <0.004 mU/L
  – Free T4: 2.8 ng/dl (0.8-1.8)
  – Total T3: 4.8 ng/ml (0.6-1.81)
  – CBC is normal; Chemistries with mildly elevated alkaline phosphatase, otherwise normal
Thyrotoxicosis

- What is the differential diagnosis?
- Graves’ disease
- Painless Thyroiditis: Self Limited
- Toxic Nodular Thyroid Disease
- Subacute Thyroiditis: Painful & Self Limited
- Acute Thyroditis: Thyroid Abscess
- Exogenous Thyroid Hormone
- Other Rare Causes
Question 1. What initial diagnostic test you would recommend to best clarify this differential diagnosis?

A. Iodine uptake and scan
B. Thyroid Ultrasound
C. Thyroid Stimulated Immunoglobulin
D. Sedimentation Rate
Iodine Scan and Uptake

A. Normal  B. Graves' disease
C. Toxic mg  D. Toxic adenoma

Thyroiditis: Hyperthyroid Phase

Ananthakrishnan S and Lee SL.
4/26/2010
Thyroid Ultrasound

Normal Doppler

Graves’ Doppler


P. Nix, A. Nicolaides, A. P. Coatesworth
Thyroid Antibodies in Thyrotoxicosis

- **Graves’ Disease**
  - TSH Receptor Antibody
    - Sensitive but Not Specific
  - Thyroid Stimulating Immunoglobulin
    - Specific, but less sensitive
  - Anti-TPO and Anti-Tg
    - Sensitive but non-specific

- **TSI is Useful in Specific Situations:** Euthyroid Graves’ Orbitopathy; Pregnancy; Recent Iodine Exposure

- **Clinical Experience:** May all be negative in mild Graves’ disease
Clinical Case

• I-123 Scan and Uptake
  – Scan with diffuse uptake
  – 24 hour iodine uptake 39% (normal 10-30%)

–Diagnosis: Graves’ disease
Evaluation of Thyrotoxicosis

Serum TSH low: Repeat with a Free T4 & Total T3
NO RECENT IODINE EXPOSURE

Low Uptake:
- Painful: Subacute
- Painless: Viral
- Factitious: Serum Tg

High Uptake:
- Diffuse: Graves’

Nodular Uptake:
- Solitary Autonomous
- Toxic Multinodular
Treatment of Graves’ Disease

• Goals of Therapy
  – Symptomatic Control
    • Beta Blockers
  – Reduce moderate or severe levels
    • Co-morbidities
    • Atrial Arrhythmias
  – Definitive Cure
    • Goal to Cause Permanent Hypothyroidism
Question 2: Which of the following patients can be followed without thyroid-directed therapy?

A. TSH: <0.004; Free T4: 2.8 ng/dl (0.8-1.8); TT3: 4.8 ng/ml (0.6-1.8); High Uptake
B. TSH: <0.004; Free T4: 3.2 ng/dl; TT3: 1.8; Low or absent uptake
C. TSH: 0.28; Free T4: 1.3; TT3: 1.4; asymptomatic
D. TSH: 0.01; Free T4: 1.6; TT3: 1.6; asymptomatic
E. B and C above
Treatment of Graves’ Disease

- Beta Blockers
  - Reduce Heart Rate
  - Control Tremor
- Unless severe, selective once or twice daily beta blockers preferred (metoprolol, atenolol)
- At very high doses, propranolol can help block T4 to T3 conversion.
Question 3: Which of the following is true regarding antithyroid medications?

A. PTU is the agent of first choice in most outpatients.
B. Methimazole is the agent of first choice in most outpatients.
C. Methimazole must be dosed 2-3 times per day for efficacy in most patients.
D. Both PTU and Methimazole can be administered IV in emergencies.
Clinical Use of Anti-thyroid Medications: PTU and Methimazole

- Primary treatment for hyperthyroidism.
- Preparation prior to surgery or 131-I therapy.
• PTU and methimazole reach peak serum levels 1-2 hours after ingestion.

• PTU biologic effect lasts about 6-12 hours; dose 2-3 times per day (100-600 mg per day in divided doses).

• Methimazole biologic effect probably lasts about 12-24 hours; once daily dosing; likely more effective (10-40 mg per day once daily).
FIG. 1. Comparison of the efficiency of treatment with MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d in patients with GD in terms of normalizing serum FT4 levels.
Anti-Thyroid Medications for Primary Therapy

• Pearls
  – Benefit in treating patients for 12-18 months before discontinuation
  – Usually dose can be reduced after a few months of treatment
  – Patients with smaller goiter, lesser degrees of hypothyroidism, and women have greater chance of remission after treatment (~50%).
  – A percentage of pts in remission will recur over time, thus periodic TFTs are needed

Potential Adverse Effects of Antithyroid Agents

• **Minor**
  – Urticaria or macular skin rash 4-6%
  – Arthralgias 1-5%
  – Gastric distress; nausea 1-5%
  – Metallic taste <1%

• **Major**
  – Polyarthritis 1-2%
  – ANCA Positive Vasculitis <1% (PTU)
  – Agranulocytosis .1-.5%
  – Aplastic anemia <.1%
  – Immunologic Hepatitis .1-1% (PTU)
  – Elevated aminotransferase 30% (PTU)
Potential Adverse Effects of Antithyroid Agents

- **Major**
  - Cholestasis <1% (Tapazole)
  - Low prothrombin level <1% (PTU)
  - Autoimmune hypoglycemia <1% MMI
Potential Adverse Effects of Antithyroid Agents

• Agranulocytosis (ANC <500 cubic mm)
• .37% of patients taking PTU.
• .35% of patients taking methimazole.
• Usually occurs within first 90 days of treatment but can occur at anytime.
• More common in older patients and in those taking higher doses
Potential Adverse Effects of Antithyroid Agents: Agranulocytosis

- Possibly related to development of antineutrophil cytoplasmic antibodies.
- There is a controversy whether to routinely monitor CBC-differential.
- G-CSF may shorten the recovery time.
- Should not use alternative agent (PTU or Methimazole).

Potential Adverse Effects of Antithyroid Agents

- **Hepatotoxicity**
- 30% of patients treated with PTU will have non-progressive 1-2 fold elevations of serum aminotransferase levels.
- PTU associated hepatic necrosis is rare, typically occurs within 3 months of therapy, and manifests as markedly elevated aminotransferase levels.
- Mortality rate about 50%.
- Liver transplant recommended for hepatic necrosis.
- Routine monitoring of LFTs is often performed although not clearly preventive.
Potential Adverse Effects of Antithyroid Agents

- **Methimazole Hepatotoxicity**
- Methimazole typically causes a cholestatic process.
- May often recovery after discontinuation of Methimazole.
- **Routine Monitoring of LFTs is typically performed**
PTU-Related Hepatic Failure

• 33 published reports of severe PTU associated hepatic failure in adults and 14 in children.

• UNOS reported 16 liver transplants in adults and 7 in children between 1990-2007 related to PTU associated liver failure.
  – Average PTU dose was 300 mg daily
  – 6-450 days (median 120) of treatment.

• None due to methimazole.
Propylthiouracil-Induced Liver Failure
FDA ALERT June 4, 2009

- Recommendations and Information for Healthcare Professionals:
- Closely monitor patients on propylthiouracil therapy for signs and symptoms of liver injury, especially during the first six months after initiation of therapy.
- If liver injury is suspected, promptly discontinue propylthiouracil therapy and evaluate the patient for evidence of liver injury and provide supportive care.
• 643 neonates from mothers with Graves' disease were examined for major malformations to compare the influence of maternal hyperthyroidism vs. ingestion of methimazole (MMI) during the first trimester on the incidence of congenital malformations.
APLASIA CUTIS CONGENITA
MATERNAL HYPERTHYROIDISM AND FREQUENCY OF CONGENITAL MALFORMATION

- Group 1: mothers did not receive MMI and were hyperthyroid 6.0%
- Group 2: mothers did not receive MMI and were euthyroid 0.3%
- Group 3: mothers received MMI and were hyperthyroid 1.7%
- Group 4: Mothers received MMI and were euthyroid 0% malformations.

- CONCLUSION: Uncontrolled Hyperthyroidism poses a greater risk than MMI treatment

Methimazole-Related Congenital Abnormalities

- Cooper and Rivkees recommend that pregnant hyperthyroid women be treated with PTU in the first trimester, and then switched to methimazole in the second and third trimester, if antithyroid treatment is still required.
- There are no studies assessing this recommendation vs PTU alone during pregnancy.
- Cooper and Rivkees, JCEM 94: 1881, 2009.
Recommendations for Anti-thyroid Medications

- Methimazole is the first-line anti-thyroid drug for most adults and children.
- PTU should be used in the following:
  - Pregnant women in first trimester
  - Patients with life-threatening thyrotoxicosis who may benefit from the added T4-T3 blockade of PTU
  - Patients with allergy or intolerance to Methimazole.
I-131 Treatment

- Effective with a single dose in most patients depending on dose, cause, and degree of uptake
- Worsening of moderate/severe ophthalmopathy: Prednisone can prevent this in pts with significant basal eye disease.
- Increased risk of secondary cancers?
- **Goal of therapy is hypothyroidism**
  - Typically takes 6 weeks-6 months to develop; TSH rise will often lag
Pre-treatment prior to I-131 Therapy

• ATDs often used for a few months to lower thyroid hormone levels and improved symptoms before I-131
  – Reduce issues related to a transient rise in thyroid hormone levels that can occur after I-131
  – Commonly used in patients with co-morbidities, older patients, or very high thyroid hormone levels
• Stop ATDs 3-5 days prior to I-131 therapy
• Recent data suggest no impact on efficacy of I-131 therapy when MMI is used, but prior studies suggest that the dose may need to be a bit higher and that PTU may cause more resistance than Methimazole.

Cancer Mortality Following Treatment for Adult Hyperthyroidism

- 35,593 hyperthyroid patients treated between 1946 and 1964 in the original Cooperative Thyrotoxicosis Therapy Follow-up Study; 65% treated with $^{131}$I.
- There was a small excess of mortality from cancers of the lung, breast, kidney, and thyroid. Patients with toxic nodular goiter had an SMR of 1.16 (95% confidence interval [CI], 1.03-1.30). Radioactive iodine was not linked to total cancer deaths (SMR, 1.02; 95% CI, 0.98-1.07) or to any specific cancer with the exception of thyroid cancer (SMR, 3.94; 95% CI, 2.52-5.86).

Thyroid Surgery

Indications for surgery in Hyperthyroidism

- Large goiter with extreme hyperthyroidism or large compressive multinodular goiter that might not shrink quickly with therapy
- Severe Thyroid Orbitopathy
- Cold nodules/ suspicious nodules
- Patient Preference
- Pretreatment to normalize or reduce thyroid hormone levels
- Often includes 7 days of SSKI to reduce level and also thyroid vascularity
Clinical Case

- Pt was treated with a beta blocker for symptoms
- Opted for 18 month course of Methimazole
- Started on 20 mg/day; reduced to 5 mg/day
- FT4 and T3 normalized in 6 weeks; TSH normalized after 4 months
- Pt was unable to maintain a remission off of Methimazole after D/C
- Treated with I-131 and is on thyroid hormone for hypothyroidism
Summary

• Hyperthyroidism treatment depends on the cause and the severity of disease
• Initial work up to determine cause
• Treatment is predicated on:
  – Acute control of symptoms and levels
  – Long term goal of definitive treatment
• New data support that if ATDs used, Methimazole is the drug of choice other than in selected populations as described.