Session 5: Thyroid Disorders: From the Obvious to the Obscure

Learning Objectives

1. Describe the spectrum of the signs and symptoms of thyroid disease - from subclinical hypothyroidism to life-threatening thyrotoxicosis.
2. Understand the diagnostic and management considerations for special patient populations commonly seen in primary care practice.
Session 5

Thyroid Disorders: From the Obvious to the Obscure

Faculty

James V. Hennessey, MD
Associate Professor of Medicine
Harvard Medical School
Director, Clinical Endocrinology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Dr James Hennessey is currently an associate professor of medicine at Harvard Medical School and director of clinical endocrinology at the Beth Israel Deaconess Medical Center, Boston, Massachusetts. He completed his subspecialty training in endocrinology and metabolism at the Walter Reed Army Medical Center, where he conducted research in thyroxine bioequivalence.

Dr Hennessey served as the chief of endocrinology at USAF Medical Center Wright-Patterson, Ohio and later joined the faculty of Wright State University School of Medicine as director of Clinical Clerkships. He later served again at Wright-Patterson Medical Center during Operation Desert Storm. He completed his Air Force career as state surgeon of the Rhode Island National Guard. He was associate director for clinical education in the division of endocrinology and associate professor of medicine at Brown Medical School, Providence, Rhode Island, prior to his move to Boston.

A focus of Dr Hennessey’s career has been the clinical education of students, residents, and fellows in endocrinology and metabolism. He is an active member of the American Association of Clinical Endocrinologists (AACE), the American Thyroid Association (ATA), The Endocrine Society, and the American College of Physicians (ACP); he is a former governor of the Rhode Island chapter of the ACP.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr Hennessey is a consultant for AbbVie and Akrimax Pharmaceuticals.
SESSION 5
2:15–3:15pm
Thyroid Disorders: From the Obvious to the Obscure

SPEAKER
James V. Hennessey, MD

Learning Objectives

• Describe the spectrum of the signs and symptoms of thyroid disease – from subclinical hypothyroidism to life-threatening thyrotoxicosis

• Understand the diagnostic and management considerations for special patient populations commonly seen in primary care practice

Goiters and Nodules

• Goiter definition: enlargement of the thyroid gland which causes swelling in the neck
  – Endemic goiter; enlargement a response to a lack of iodine
  – Sporadic goiter; hyperplastic or neoplastic overgrowth
    • Toxic nodular goiter; autonomous thyroid hormone production
    • Exophthalmic goiter (Graves’ disease) associated with hyperthyroidism

• Thyroid Nodule: area of different contour or consistency on palpation with differing echotexture on sonographic examination

Thyroid Nodule Prevalence

• By age 30, ~20% of the population has a thyroid nodule (women>men)

• Likely hood of malignancy is higher in the extremes of age (<20 years, >70 years)

• Lifetime likelihood of a nodule is ~ 60%

Thyroid Cancer Risk: Multinodular (MNG) versus Single Nodule (SN) Goiter

Squares/horizontal lines: Odds ratio/95%CI; diamonds: pooled odds ratio

Presenter Disclosure Information

The following relationships exist related to this presentation:

► James V. Hennessey, MD, is a consultant for Abbott Laboratories and Akrimax Pharmaceuticals.

Off-Label/Investigational Discussion

► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Mazzaferi EL. NEJM. 1993;328:553-559.

Risk Factors for malignancy: Patient History

- Surgical diagnosis of thyroid cancer in contralateral lobe
- Ionizing Irradiation (XRT) as child/adolescent
- Calcitonin > 100 pg/mL
- PET positive thyroid nodule
- Low dietary iodine intake
- Thyroid cancer in first degree relative


Thyroid Nodule Laboratory Diagnosis

- TSH
  - Suppressed C/W thyrotoxicosis
  - Malignancy unlikely
  - Elevated C/W hypothyroidism

RADIONUCLIDE SCANNING

Indication:
- Thyrotoxic nodule identification (TSH < normal)
- 99mTc (False +s), 131-I (Rads) or 123-I (Std)

Thyroid Ultrasound

Indication: normal to ↑ TSH
- Defines a distinct nodule vs. abnormal parenchyma
- Role to guide FNA (cystic, posterior)
- MNG nodule selection
- Useful in f/u of low risk patient, incidentaloma

- MRI / CT SCANNING
  - Offer little in pre-operative diagnosis
  - Contrast administration may delay Dx &/or Rx

Who Should Be Biopsied?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>&gt; 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>AND iso- or hyperechoic</td>
<td>≥ 1-1.5 cm</td>
<td>C</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WITH suspicious feature</td>
<td>≥ 1.5-2.0 cm</td>
<td>B</td>
</tr>
<tr>
<td>W-OUT suspicious feature</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥ 2.0 cm</td>
<td>C</td>
</tr>
<tr>
<td>Purely Cystic nodule</td>
<td>Not indicated</td>
<td>E</td>
</tr>
</tbody>
</table>

B= Recommend fair evidence, C= Recommend expert opinion, E= Recommend against

High Risk Features and Biopsy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Size Threshold</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications</td>
<td>≥ 1 cm</td>
<td>B</td>
</tr>
<tr>
<td>High-Risk History*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With suspicious feature</td>
<td>&gt; 5 mm</td>
<td>A</td>
</tr>
<tr>
<td>W-out suspicious feature</td>
<td>&gt; 5 mm</td>
<td>I</td>
</tr>
<tr>
<td>Abnormal Cervical LN</td>
<td></td>
<td>All</td>
</tr>
</tbody>
</table>

+ FHx Thy Ca (1°), Hx XRT/Irrad. (child), Surg. Dx Thy Ca, PET pos, nodule, Calcitonin > 100 pg/ml, RET pos, MÉN, FMTC

A= Strongly recommend  B= Recommend fair evidence, I= Neither for or against


FNA Malignancy Prediction with Bethesda System

<table>
<thead>
<tr>
<th>Category</th>
<th>Malignant risk</th>
<th>What next?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>1-4+%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>Clinical F/U</td>
</tr>
<tr>
<td>Atypical</td>
<td>5-15%</td>
<td>Re-do (U/S)</td>
</tr>
<tr>
<td>Follicular Neoplasm</td>
<td>15-30%</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Suspect malignancy</td>
<td>60-75%</td>
<td>Total Tx</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Total Tx</td>
</tr>
</tbody>
</table>

FNA = fine needle aspiration


Thyroid Nodule Work-up

Adapted from Cooper, et al. Thyroid. 2006;16(2):1-33.

Case 2

72-year-old man presents with worsening palpitations over 2 months
- ROS: 14 lb. weight loss over last 6 months, recent insomnia
- PE:
  - BP 152/84, Pulse 112 BPM, irregular
  - Eyes: alert stare present
  - Thyroid: Palpable 3.5 cm left nodule, freely movable
  - Cor: Irregularly irregular rhythm, no M/G/R
  - Lungs: bibasilar rales
  - LE: 1+ edema

What additional work-up is needed?

ECG Results:
- Atrial fibrillation with ventricular response of 110 BPM

Lab Results:
- TSH <0.05 (0.4-4.2 mIU/mL)
- FT4 2.1 (0.8-1.8 ng/dL)
- TT3 345 (80-200 ng/dL)

Thyrotoxicosis (T-Tox)

Definition: Thyroid hormone (TH) excess (+/- symptoms)
- Without regard to source
  - Preformed TH passively released from the thyroid
  - Exposure to extra thyroidal sources of TH
    - Exogenous and endogenous
- Hyperthyroidism
  - Thyroid hormone production by the thyroid
    - Thyroid stimulated by trophic factors
    - Constitutive activation of thyrocytes
      - Autonomous excessive TH synthesis and release

Thyrotoxicosis Classification and Etiology

- **Classification**: all may have signs & symptoms
  - **Overt T-Tox**: ↓TSH, ↑FT4, ↑T3
  - **Subclinical T-Tox**: ↓TSH, normal FT4 and T3

- **Etiology**:
  1. **Graves’ disease (GD)**, autoimmune, stimulating TSH-receptor antibodies (TRAbs)
  2. **Toxic Nodular** disease, growth and autonomy
     - Multinodular (TMNG) or Adenoma (TA)
     - TAs have somatic TSH receptor activating mutations
  3. Both susceptible to iodine induced T-Tox
  4. TMNG Incidence increases with age and in Iodine deficiency

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Thyrotoxicosis Etiology Continued

3. **Painless and Subacute Thyroiditis (SAT)**
   - Inflammation of thyroid tissue → TH release
   - Painful SAT: post viral → fever, thyroid pain
   - Painless SAT underlies 10% “hyperthyroidism”
     - Occurs postpartum (PPT), with lithium, cytokines (Interferon alpha), and 5-10% of amiodarone T-Tox
     - Results in changing Thyroid function abnormalities
     - May spontaneously resolve to euthyroidism

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Excess Thyroid Hormone Manifestations

- Increased thermogenesis and metabolic rate
- Reduced cholesterol and vascular resistance
- Profound effects on cardiovascular system
  - a fibrillation, embolic events, CV collapse, death
- Other complications of untreated thyrotoxicosis
  - Weight loss, anxiety, osteoporosis
- Signs & symptoms (S/S) of overt and subclinical
  - Similar, differing only in magnitude
  - Only moderate correlation elevation of TH and S/S
- Elderly may exhibit fewer hyperadrenergic signs
  - “apathetic” with depressed mood and more arrhythmias

Clinical Evaluation

- Comprehensive H&P, VS: PR, BP, RR, BMI
  - Thyroid: +/- tender, symmetry, nodularity
  - Gen PE: Pulmonary, Cardiac, Neurologic
    - +/- Edema, eye signs, pretibial myxedema
- Biochemical evaluation:
  - TSH most sensitive and specific (intact pituitary)
  - Otherwise reflex FT4 and TT3 for suppressed TSH

Determination of Etiology

- **Radioactive Iodine uptake (RAIU)**
  - Should be performed when the clinical presentation is not diagnostic of Graves’
    - Exception
      - Pregnancy
      - Obvious signs and symptoms of Graves’ disease
  - Radioactive iodine thyroid scan
  - Should be added in the presence of thyroid nodularity

Hyperthyroidism-Differential Diagnosis

- **Graves’ Disease**
- **hCG mediated**
- **Hot Nodule**
- **Multinodular Goiter**

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Management of Hyperthyroidism

- **Symptomatic Management:**
  - Beta-adrenergic blockade
    - For elderly, resting HR >90, coexistent CV Disease
    - All with symptomatic thyrotoxicosis
  - **Thyroid storm:** Rare life-threatening syndrome of exaggerated clinical manifestations of thyrotoxicosis
    - Antithyroid drugs to decrease TH production
    - Systemic support for hyperthermia and hypovolemia
    - Beta blockers tissue effects of excess circulating TH
    - Identify and treat precipitating illness
- **Directed Interventions based on Etiology**

Who Should be Treated?

- **Overt hyperthyroidism due to Graves’**
  - Treatment with any of the following
    - 131-I, antithyroid medication (ATD), thyroidecomy
- **Overt hyperthyroidism due to TMNG/TA**
  - Treatment with any of the following
    - 131-I, thyroidecomy, ATD (occasionally)
- **Subclinical hyperthyroidism?**

Subclinical Thyrotoxicosis Rx?

<table>
<thead>
<tr>
<th>Factor</th>
<th>TSH (&lt;0.1 mU/L)</th>
<th>TSH (0.1 – 0.5 mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65 with comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Menopausal</td>
<td>Consider treating</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Hyperthyroid symptoms</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65, asymptomatic</td>
<td>Consider treating</td>
<td>No</td>
</tr>
</tbody>
</table>

Antithyroid Drug Comparison – MMI and PTU

<table>
<thead>
<tr>
<th>Feature</th>
<th>Methimazole</th>
<th>Propylthiouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>Inhibits intra-thyroidal hormone synthesis</td>
<td>Yes</td>
</tr>
<tr>
<td>Impact on peripheral thyroxine to T3 conversion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Indications</td>
<td>Graves’ disease with hyperthyroidism or toxic multinodular goiter for whom surgery or radioactive iodine therapy is not an appropriate treatment option</td>
<td>Yes</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Congenital defects especially in first trimester (category D)</td>
<td>Liver toxicity in adults, children, and in utero</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis</td>
<td>Agranulocytosis</td>
</tr>
</tbody>
</table>

PTU Black Box Warning

**WARNING:** Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthioracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthioracil should be reserved for patients who can not tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

Because of the risk of fetal abnormalities associated with methimazole, propylthioracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy.

Anti-Thyroid Drug Recommendations

- **PTU** not be considered 1st line ATD therapy
  - MMI preferred in children and adults
- **PTU** may be considered over MMI:
  - **1st Trimester of pregnancy**
    - Until more is known with potential MMI embryopathy
    - Consider switch to MMI in 2nd and 3rd to ↓ risk liver dz
  - **In Thyroid Storm**
    - Advantage T4→T3 conversion inhibition
    - Reaction to MMI (NOT AGRANULOCYTOSIS) in whom 131-I or surgery are not possible

When to Refer

• Patients with persistent TSH suppression
  – To determine etiology of finding
  – To determine indications for treatment
• Adults: overt & subclinical hyperthyroidism
• Children/Adolescents with hyperthyroidism
• Patients with thyrotoxicosis during pregnancy
• Patients with GD and ophthalmopathy


Case 3

• A 36-year-old woman with complaints of
  – Inability to lose weight
  – Dysphoria
  – Cold intolerance over 6 months
• Saw OB/GYN 2 months ago who ordered “lab tests” but patient did not follow up
• PE: BP:136/88, P 68,
• Hgt: 5’4”, Wgt 186 lb., (BMI 32 kg/m²)
  – 25-35 gram firm thyroid
  • No nodules palpable
  • Obese abdomen without striae


But What is an Upper Normal TSH?

NHANES III: 4.12 mU/L (Thyroid risk free)¹
NHANES III: Age adjusted (Thyroid risk free)²

<table>
<thead>
<tr>
<th>Age group</th>
<th>97.5 centiles</th>
<th>% &gt; 4.5 mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 years</td>
<td>3.56 mIU/liter</td>
<td>2.4%</td>
</tr>
<tr>
<td>70–79 years</td>
<td>5.9 mIU/liter</td>
<td>9.9%</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>7.49 mIU/liter</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Not all elevations of TSH levels = Hypothyroidism!!!!

¹. Hall and others 2002 JCEM 87:489-99
². Surks  et al. 2007JCEM 92: 4575–4582

Hypothyroidism

Overt: Elevated TSH, low FT4
Obvious but non-specific symptoms
Cardiovascular manifestations
  ↑ CVD risk, Hypertension, Hyperlipidemia, CHF
Pulmonary, Musculoskeletal, Neurologic and Psychiatric
Skin/connective tissue, Renal/electrolyte abnormalities
Gastrointestinal/liver, Hematologic and Hemostatic
Pituitary and adrenal dysfunction
Subclinical: Elevated TSH, normal FT4
Little to no symptoms
milder metabolic changes

Hypothyroid Etiology

• Iodine deficiency (most common world wide)
• Chronic autoimmune thyroiditis (Hashimoto’s)
  – More frequent in women than men
  – Increases in frequency with age
• Iatrogenic
  – 131-I or surgical treatment of hyperthyroidism
  – After external beam irradiation of the thyroid
  – Drugs: thionamides, lithium, amiodarone, interferon-alfa, interleukin 2, tyrosine kinase inhibitors (sunitinib)
• Central hypothyroidism: insufficient active TSH
  – Tumors: pituitary, hypothalamus
  – Infiltrative, inflammatory, surgical, irradiation

Reported Symptoms and TSH Levels

Who to Treat

- TSH > 10 mlu/ml considered for Rx
  - Due to risk of CHF and CV mortality
- TSH > upper “normal” & < 10 mlu/ml
  - Treatment based on individual factors
  - Symptoms c/w hypothyroidism
  - Positive TPO antibodies
  - ASCVD, CHF or risk of same
- Thyroid hormones should NOT be used to treat “hypothyroid symptoms” without biochemical confirmation of hypothyroidism

Which patients with a “normal” TSH should be considered for treatment?

- Women who are pregnant
  - 1st Trimester TSH > 2.5 mIU/L
  - 2nd Trimester TSH > 3.0 mIU/L
  - 3rd Trimester TSH > 3.5 mIU/L
- Women of child bearing age who are pregnant or planning pregnancy
  - Including those with assisted reproduction
  - When there are positive TPO-abs, or history of miscarriage or previous hypothyroidism, TSH > 2.5

Thyroid Hormone Therapy Considerations

- In 2004, the FDA approved generic substitution for branded levothyroxine products.
- ATA, TES, AACE opposed decision, as the evaluation process allows products differing by 12.5% or more in bioavailability to be designated as interchangeable.
- ATA, TES, AACE Recommend that we should:
  - Alert patients that preparations may be switched at pharmacy
  - Encourage patients to ask to remain on the same preparation at every pharmacy refill
  - Make sure that patients understand the need to have their TSH retested and dosing readjusted every time their levothyroxine preparation is switched

Thyroid Hormone Therapy Targets

- Therapy Targets for LT4 Replacement
  - Replacement Doses: 1.6-1.7 mcg/kg/day (0.8 mcg/lb.)
    - Lower start doses: elderly, symptomatic CAD (12.5-15 mcg/d)
    - Initial full replacement for younger and without cardiac symptoms
  - Best outcomes when taken fasting, with water only, 30-60 minutes before breakfast or at bedtime 4 hours after last meal
  - Check TSH 4-8 Weeks after start, change of dose or product
    - Titrates TSH into the “normal range”
    - Pregnancy
      - 1st Trimester < 2.5 mIU/L
      - 2nd Trimester < 3.0 mIU/L
      - 3rd Trimester < 3.5 mIU/L

http://www.thyroid.org/thyroxine-products-joint-position-statement/
When to Refer for Hypothyroidism

- Children and infants
- When difficult to render and maintain euthyroidism
- Pregnancy and pre-pregnancy planning
- Patients with cardiac disease
- Presence of goiter, nodule or other structural issue
- Presence of pituitary or adrenal disease
- Unusual constellation of thyroid function tests
- Unusual causes of hypothyroidism


Questions

?