Thyroid Disease

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Lilly – HypoCCS Study Investigator
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OBJECTIVES

At the conclusion of this presentation, participants will know the differential diagnosis and have a logical approach to the investigation of patients with:

a) Signs and symptoms of hypothyroidism
b) Signs and symptoms of hyperthyroidism
c) Single or multiple thyroid nodules
Thyroid

- Develops from endodermal epithelium in the foregut
- Migrates from the base of the tongue to the neck
Thyroid

- 15-20 grams in size in adults; huge potential for growth
Thyroid

- Isthmus over the second or third tracheal ring
- Right lobe often slightly larger than the left
\( T_3 \) triiodothyronine

- half-life 0.75 days
- Relative potency 1.0
- Only 20% of \( T_3 \) is secreted by the thyroid
- \( T_3 \) is 99.7% protein bound
- metabolism of \( T_3 \) is through deiodination
- 5' deiodination inactivates \( T_3 \)

\( T_4 \) thyroxine

- half-life 6.7 days
- Relative potency 0.3
- 100% secreted by the thyroid
- \( T_4 \) is 99.98% protein bound
- metabolism of \( T_4 \) is through deiodination
- 5' deiodination converts \( T_4 \) to inactive reverse \( T_3 \)
Control of Secretion of $T_3$ and $T_4$

- When $T_3$ and $T_4$ levels drop, hypothalamus releases TRH.
- TRH causes the pituitary to secrete TSH (and Prolactin)
- TSH, half-life 30 minutes, stimulates $T_3$, $T_4$ synthesis, thyroid enlargement
- TSH is inhibited by:
  - Dopamine/Dopamine agonists
  - Phenytoin
  - Somatostatin and analogues
  - High dose glucocorticoids
- TSH is stimulated by:
  - GLP-1
  - alpha adrenergic agonists
- TSH shares an alpha subunit with FSH, LH and hCG

As a result
- gestational hyperthyroidism
- physiologic hyperthyroidism of pregnancy
- trophoblastic tumors may cause hyperthyroidism

- TSH range 0.4 – 4.2 mU/L; tends to rise with age
What can go wrong with thyroid function?

• Hyperthyroidism

• Hypothyroidism

• Development of thyroid enlargement, diffuse or nodular
Hyperthyroidism

- A 33 year old woman presents with fatigue, palpitations, tremor and weight loss.

Most likely diagnoses:
- Graves’ Disease (50-80%)
- Toxic adenoma or toxic multinodular goitre
- Thyroiditis – silent, subacute

Less likely:
- Over replacement
- Thyrotoxicosis factitia
- Drug induced: lithium, interferon, amiodarone
- Struma ovarii
- Metastatic thyroid cancer
Features of Hyperthyroidism

- Palpitations
- Tachycardia
- Atrial fibrillation
- Congestive heart failure
- Increased calcium excretion
- Demineralization of bone
- Weight loss
- Proximal muscle weakness
- Heat intolerance
- Emotional lability
- Increased renal blood flow, GFR
- Increased RBC mass
- Nervousness
- Lid retraction
- Hair loss
- Soft, friable nails
- Menstrual irregularities
Graves’ Disease

- Auto Immune Thyroid Disease
- May show antibodies against TPO, thyroglobulin and TSH receptor
- History tends to be chronic, > 3 months
- May be associated with other auto immune diseases – pernicious anemia, DM Type I, ITP, vitiligo, myasthenia gravis, Addison’s disease, RA, SLE
- Specific clinical findings – orbitopathy, pretibial myxedema
- High radioiodine uptake
- Diffuse Goitre
Toxic Nodular Thyroid Disease

- Palpable thyroid nodule(s)
- Nodular disease on ultrasound
- Focal increased uptake on nuclear medicine scan
- History tends to be chronic, >3 months
- Typical patients are > 50
Follicular adenoma
“Hot” Nodules
Treatment of Hyperthyroidism

Graves’ Disease

- anti thyroid drugs (PTU, methimazole), β blockers
- radioactive iodine
- surgery

P.T.U. now not used as first line in adults or children (rare cause of hepatic failure)
Still used in the first trimester of pregnancy
Also used in thyroid storm because of blockage of T4 → T3 conversion

Methimazole can be prescribed once a day, but is generally prescribed 20 to 30 mg per day initially, (10 mg bid or tid)

Antithyroid drug therapy for 12-18 months if no permanent remission, radioiodine

Radioiodine – need to wait until rendered euthyroid by antithyroid drugs

Surgery – not much used in North America
Treatment of Hyperthyroidism

Thyroid adenoma or Multinodular goitre

Surgery

Radioactive iodine

After radioactive iodine patients will probably not be hypothyroid
Treatment of Hyperthyroidism

• **Thyroiditis**

  $\beta$ blockade ± antithyroid drugs

  Steroids

  Pain relief – NSAIDS

  Await spontaneous resolution

  May have transient/permanent hypothyroidism
Patients likely to relapse after Antithyroid Drug Therapy for Graves’ Disease

1. Previous cause of ATD therapy with recurrence
2. Long history of symptoms
3. Young, male
4. Family history of autoimmune thyroid disease
5. Cigarette smoking
6. Presence of ophthalmopathy
7. Pronounced hyperthyroidism at the beginning of therapy
8. High ATD dose at the end of therapy
9. Pronounced TSHRAb titre
10. Large goitre
11. Increase in size of goitre
12. Nodular goitre, or high intrathyroid flow on Doppler

Overall recurrence rate 50-60%
• 43 year old woman presents with fatigue, weight gain, constipation and cold intolerance.

• Most likely diagnosis: Hashimoto’s Disease
  Rule out: - subacute/silent thyroiditis
  - Pituitary Disease

? Duration of symptoms, Associated Pituitary Symptoms
? Previous thyroid disease, Radioiodine therapy or surgery
? TSH level
? Drugs
? Goitrogens
? Pain
Causes of Hypothyroidism

- **Congenital**

- **Acquired**
  - iodine deficiency
  - Hashimoto’s disease
  - Drugs (eg lithium, Iodine)
  - Post surgery
  - Goitrogens (cabbage, turnips, rutabaga)
  - Thyroid infiltration (sarcoidosis, scleroderma)

- **Central**
  - Pituitary
  - Hypothalamic
Replacement Therapy for Hypothyroidism

- Normally 20% of $T_3$ is secreted directly from the gland;
  80% is converted from $T_4$

- Therefore in patients on $T_4$ replacement:
  - Levels of $T_4$ are higher than normal if $T_3$ is maintained at the normal level

Feedback inhibition of TSH relies on $T_3$ and $T_4$
T₃ Replacement Therapy

• T₃ is rapidly absorbed, with a peak at 2 to 4 hours

• Short half-life, 0.75 days (T₄ 6.7 days)

• Therefore fluctuations in biologic activity over the course of the day

• T₄ considered safer for long term regular replacement

• No advantage to T₃/T₄ mixtures on meta analysis
Dessicated Thyroid

- Animal preparations contain higher ratios of $T_3:T_4$ than the human thyroid
- May lead to supraphysiologic $T_3$ concentrations soon after administration
- Batch to batch variation
- Not recommended
Special Considerations in Thyroid Hormone Dosing

Dose needs to be increased:

1. In pregnancy (especially the first trimester), increase dose 25-30%

2. Where absorption is interfered with by medications:
   - iron (ferrous sulphate)
   - calcium (carbonate)
   - cholestyramine
   - sucralfate
   - aluminum hydroxide
   - espresso coffee
Dose needs to be increased:

3. In GI Disorders
   - celiac disease
   - small bowel resection
   - bypass procedures
   - impaired gastric secretion (atrophic gastritis)

4. Where metabolism is increased by drugs (P450)
   - estrogen
   - phenytoin
   - carbamazepine
   - rifampin

5. Where there is interference with deiodination
   - cirrhosis
   - amiodarone therapy
Special Considerations in Thyroid Hormone Dosing (cont’d)

Dose needs to be decreased:

In patients over 65, with decreased thyroid hormone clearance

In women receiving androgen therapy for breast cancer
Thyroiditis

• Subacute, infectious
  – Viral, bacterial

• Silent

• Post Partum (often confused with PP blues)
  – Auto immune

Hyperthyroidism self-limited, may be followed by hypothyroid phase
Total duration ≤ 3 – 4 months
Other Agents Causing Thyroiditis

- Most cases are related to activation or exacerbation of auto-immune disease
  - IL-2
  - Interferon - alpha
  - GM – CSF

Can precipitate silent thyroiditis
Amiodarone-Induced Thyroiditis

- 62 year old man
- Hyperthyroid
- On Amiodarone therapy

RAIU 4 hours <1%
56 year old woman presents with a palpable 2 cm right sided nodule.

? Sudden onset associated with pain – likely to be hemorrhage into a cyst

Otherwise, majority of thyroid nodules are asymptomatic and only 5-10% are malignant.

? Single or multiple nodules
? Male vs Female
? Young vs Old
? Solid vs Cystic
? Hot vs Cold
? Mobile vs Fixed
? Hoarseness, Dysphagia
? Lymphadenopathy
? History of radiation exposure
Evaluation of Thyroid Nodules

- Anatomical evaluation – ultrasound, solid vs cystic
- Functional evaluation – nuclear medicine – hot vs cold
- Histological evaluation – FNA if nodule > 1 cm

Unless associated with other features suspicious for malignancy, nodules < 1 cm should be re-examined in 6-12 months, to see if there has been interval change.
Follicular neoplasm
“Cold” Nodule
FNAB of Papillary Thyroid Cancer
Lithium Therapy

• Lithium, like iodine, inhibits thyroid hormone release

• High doses inhibit organification

• Some patients develop a goitre (up to 40%) and hypothyroidism (20%)

• Some may develop silent thyroiditis, even Graves’ Disease

• Lithium may be used to make radioactive treatment more effective
Amiodarone and Thyroid Function

- Amiodarone has significant iodine content and some structural similarity to $T_4$
- Inhibits deiodination of $T_4 \rightarrow T_3$
- Therefore relatively increased $T_4$ concentrations to maintain normal $T_3$
- May interfere with $T_3$ binding to receptors
- Iodine normally causes an initial inhibition of iodine processing and then an escape (Wolff-Chaikoff)
- In some patients on amiodarone:
  - prolonged inhibition without escape leads to goitre formation and hypothyroidism
- Many of these patients have auto immune thyroid disease
Amiodarone and Hyperthyroidism

- In some patients, hyperthyroidism may develop

- Amiodarone-induced thyrotoxicosis
  
  - Type I – Jod-Basedow effect
    - Development of Graves’ Disease in pre-disposed individuals (more common in Europe, iodine deficiency predisposes)
  
  - Type II
    - direct cytotoxic effect of iodine causing thyroiditis (more common in North America – no iodine deficiency)
Tyrosine Kinase Inhibitors (e.g. Sunitinib)

Used for

- Renal cell carcinoma
- Gastro intestinal stromal tumors

Causes follicular cell apoptosis and thyroid destruction

Thyroid function must be monitored in patients on Tyrosine Kinase Inhibitors

Hence use of these agents to slow the progression of thyroid cancer
Use of Radioactive Iodine Treatment

1. For treatment of hyperthyroidism (Graves’, nodular disease)
   - generally considered safe

2. For treatment of thyroid cancer
   - The risk of a secondary primary malignancy may be slightly increased
   - Risks may outweigh benefits when the cumulative dose rises above 37 GBq I$^{(3)}$
Thyroid Cancer
Thyroid Disease
Take Home Points

1. T₄ has long half life – do not test too often.

2. Do not overreact to subtle changes in TSH

3. Check T₃, T₄ in conjunction with TSH

4. Increase dose L-thyroxine in pregnancy

5. Watch fetus carefully in patients who have had Graves’ Disease

6. Watch Iron, calcium supplements in patients on T₄

7. Do not use T₃ or dessicated thyroid for routine replacement

8. Patients on replacement T₄ following thyroid cancer removal need TSH completely suppressed
References


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