Case 1: Mary

Mary is a 27 year old who comes in to see you with a 2 week history of increasing anxiety, tremor, and heat intolerance. She has lost about 5 pounds during this time. She has no family history of thyroid problems or autoimmune diseases.

Her thyroid lab tests come back as follows: TSH 0.1 (normal = 4.5-5.0) and free T4 16.8 (normal = 4.6 – 12.0)

What is the best next step in evaluating Mary?

1. Check anti-peroxidase antibodies
2. Get a thyroid ultrasound
3. Order a thyroid scan and update
4. Check a T3 resin uptake
5. Start empiric propylthiouricil – no further testing is indicated

Evaluating hyperthyroidism

- Three most common causes of hyperthyroidism:
  - Graves’ disease
  - Thyroiditis
  - Autonomous nodule

- First step is a thyroid scan and uptake

Thyroid imaging studies

Indications:
- Hyperthyroidism: differentiate Graves’ Disease from autonomous nodule from early thyroiditis
- Nodular thyroid disease
- Neck mass of unclear source
Radiolabeled thyroid scans

- $^{99}$TcM preferred over $^{123}$I
  - $^{123}$I delivers a much higher radiation dose
  - $^{99}$TcM can be used in patients on thyroid suppressing drugs
- Look for either diffuse increase or decreases in uptake or for nodules
- Nodules: must be > 1 cm in diameter to show up

How about thyroid antibodies?

Three thyroid antigens to which Ab’s are directed:

- **TSH Receptor**: seen in 80-95% of patients Graves’ disease
- **Thyroglobulin**: seen in autoimmune thyroid diseases
- **Thyroid peroxidase**: involved in chronic lymphocytic (Hashimoto’s) thyroiditis

Ultrasound of the thyroid

- Most useful for follow-up of nodule found on examination or by scan
- Look to distinguish cystic from solid
- Uniform solid masses usually “burned out” nodule
- Hypoechoic mass more likely to be carcinoma

Other imaging tests

- **Thyroid CT**: used for evaluation of malignant thyroid disease; can assess thyroid size and evaluate mass, but no advantage over US
- **MRI**: Good resolution between thyroid, lymph tissue, and muscle; excellent for evaluation of tumor spread or poorly differentiate neck mass

Case 1: Part 2

- On exam, Mary has a slightly enlarged thyroid that is mildly tender.
- You send Mary for a thyroid scan and update the results come back as follows:
  - **Update**: decreased
  - **Scan**: mottled appearance

Based on the scan and uptake, what is the most likely diagnosis for Mary?

1. Graves’ disease
2. Multinodular goiter
3. DeQuervain’s thyroiditis
4. Suppurative thyroiditis
Interpreting thyroid scans

- Graves' disease: see diffuse increased uptake (entire gland more active)
- Nodular disease: focal area of increased uptake with reduced uptake in rest of gland
- Thyroiditis: patchy decreased uptake

Thyroiditis: 4 types

- DeQuervain’s/Subacute (granulomatous)
- Hashimoto’s (chronic lymphocytic)
- Silent
- Reidel’s stuma (chronic fibrocytic)
- Suppurative (acute bacterial infection)

Based on the history and scan, you diagnose Mary with DeQuervain’s thyroiditis. Your first line treatment should consist of which of the following:

1. Antibiotics
2. Methimazole
3. Ibuprofen
4. Prednisone

You see Mary back 1 week after her test results are back. Her symptoms have now totally resolved. She decided she does not want to take any ibuprofen and wants to know if she should do anything else?

What might you suggest?

Evelyn

Evelyn is a 72 year old who comes in to see you with a history of gaining weight over the past 6 months, increased fatigue, dry skin, and losing hair. She has Type 2 diabetes, hypertension, and hyperlipidemia. You check a TSH and find that it is 21.1 (normal 0.5 – 5) and her free T4 is 2.3 (normal 4.6 – 12.0)
What is your next step in evaluating Evelyn?
1. Get a thyroid scan
2. Check TSH antibodies
3. Check a thyroid peroxidase level
4. Check an ultrasound
5. Do nothing – just start thyroid replacement

Primary hypothyroidism
- Most common cause is Hashimoto’s
- Other causes:
  - Post-irradiation hypothyroidism (post Graves’ disease)
  - Post-surgical hypothyroidism
  - Iodine insufficiency
  - Idiopathic hypothyroidism

How do I evaluate hypothyroidism?
- You don’t
- Just treat it – doesn’t matter what caused it
- Exception: secondary hypothyroidism
  - If clinically hypothyroid, but TSH low then suspect secondary hypothyroidism
  - If have more than 1 pituitary-related dysfunction, assume they are all effected

How should I start thyroid replacement?
- For elderly patients and those with possible cardiac disease, start with 0.025 mg/D and increase every 6 to 8 weeks
- Monitor with TSH every 6 to 8 weeks Usual equivalent of thyroid made each day is 0.125 mg of T4

Where do I want to end up?
- Aim for full replacement of 0.10 mg to 0.15 mg a day
- One small study showed equally good results with bolus dose once a week with 7 times usual dose

Should you use a brand name?
- No benefit of brand name drugs over generic
- Study done with synthetic thyroxine and 4 generics showed no differences when patients were switched from one formulation to another over prolonged period of time
  (Dong et al. JAMA 1997; Rennie JAMA 2007)
Evelyn is put on thyroxine and titrated up to a dose of 113 micrograms over 6 months. On repeat testing, her TSH is now 2.1 (normal 0.5 to 5.0) and her free T4 is 7.3 (normal 4.6 – 12.0). Despite these normal labs, she says she still feels tired, though, and her memory is not what it used to be.

What is a reasonable next step in Evelyn’s management?

1. Check a thyroid ultrasound for an occult thyroid cancer
2. Start her on empiric paroxetine for unrecognized depression
3. Start her on a small dose of triiodothyronine (T3)
4. Increase her thyroxine to get her free T4 to the upper limits of normal

Adding T3 to thyroxine

• One study with small group of elderly patients showed partial substitution of T4 with T3 (Cytomel) at dose of 0.125 mg T3 for 0.05 mg. of thyroxine may improve mood and neuropsychological functioning
  (Bunevicius et al, NEJM, 1999)
• Second study suggested that best results obtained with slow release T3
  (Hennemann et al, Thyroid 2004)

Is T3 good for everyone?

• Two later controlled studies in total of 44 patients aged 29 – 65 showed no benefits of adding T3 to T4 therapy
  (Stegmund et al, Clin Endocrin 2004; Clyde et al, JAMA 2003)
• Analysis of T3 levels in 50 euthyroid patients with total thyroidectomies showed that normal T3 levels were achieved with T4 replacement only --- uncertain if there any value of additional T3
  (Jonklaas et al, JAMA 2008)

Evelyn reduces her thyroxine to 0.75 mg and starts triiodothyronine at a dose of 0.125 mg. Six weeks later her thyroid blood tests are still normal but her memory and energy level are much better. She is fine until 2 years later when she returns with atrial fibrillation, a tremor, accelerated hypertension with a wide pulse pressure and a TSH < 0.1.

Which of the following would most likely explain what happened?

1. She developed a multinodular goiter
2. She has nephrotic syndrome
3. Her anti-lipid medication was changed to clofibrate
4. She started some estrogen cream for her atrophic vaginitis
Thyroid and protein levels

- T4 is 97% protein bound and T3 is 99.7% protein bound

- Changes in health that cause alterations in serum protein levels will result in changes in thyroid levels – need to change replacement dose as well

Changes in serum proteins

- Increase protein levels – need more thyroxine
  - Pregnancy
  - Estrogen replacement
- Decreased serum protein – need to reduce thyroxine
  - Nephrosis
  - Cirrhosis
  - Protein malnutrition

Thyroid interaction with other drugs

- **Coumadin**: Coumadin increases effect of thyroid replacement

- **Insulin/oral hypoglycemic agents**: increased thyroid increases need for glycemic agents

- **Clofibrate**: may decrease hormone absorption

Sallie

Case 3

Sallie is an 87 year old woman who lives with her daughter and son-in-law. Her family brings her in because she is becoming more forgetful. A Mini-Mental Status exam shows a score of 25 and a blood test shows a TSH of 7.8 (normal 0.5 – 5.0) with a free T4 of 6.6 (normal 4.6 – 12.0).

What is the best way to characterize her lab test?

1. Subclinical hypothyroidism
2. Overt hypothyroidism
3. Normal for her age
4. Lab error
### Subclinical hypothyroidism (SCH)

- Many patients over age 65 have slight elevations in TSH (5 - 15 mU/ml) but normal T4 and T3
- More common in women and prevalence increases with age
- More common in whites; fairly uncommon in African-Americans and Asians
- About 50% of all patients have anti-Ty abs

### Subclinical hypothyroidism

- Is it a variant of normal, a pre-disease state, or actual disease: what's the natural history?
- Research all over the place: good evidence for each of the three possibilities above

### SCH: pre-disease?

- About 10% of patients with subclinical hypothyroidism develop overt hypothyroidism within 3 years
- Patients with positive thyroid antibodies most likely to become symptomatic

### SCH: normal variant?

- Data from nationally representative sample (NHANES II) shows no difference between folks with SCH (n=218) and euthyroid control (n=8,300)
  - (Hueston et al, Annal Fam Med 2004)
- Also no increase in inflammatory markers of heart disease (CRP and Hcy) in these folks
  - (Hueston et al, Clinical Endocrin 2005)

### SCH: cause of heart disease

- Two population-based studies
  - Busselton Heart Study of ~2,000 people in West Australia
  - Health, Aging, and Body Composition Study of ~2,800 people in Memphis and Pittsburgh
- Both studies identified people with SCH and no heart disease and followed them for 4 – 20 yrs

### Brusselton Study

- 119 people with SCH followed for 20 yrs
- Increase in cardiac events found (HR 1.7, 95% CI 1.2-2.4)
- Difference found only after 12 years and only in people with TSH>10.
- No increase risk of death (HR 1.5, CI 1.0 -2.4)
## Health, Aging Study
- Older people enrolled (70-79)
- Followed for 4 years
- 338 (12%) with SCH
- Found increase in CHF with SCH (HR 2.33, CI 1.10-4.96)
- No increase in CV events, stroke, or CV-related mortality

(Rondondi et al, Arch Intern Med 2005:165:2460)

## What is a reasonable next step in treating Sallie?
1. Start a low dose of thyroxine and increase slowly if improving
2. Do not start treatment but continue to monitor TSH levels annually
3. Do nothing and reassure Sallie’s family that this is probably secondary to ageing

## Does treatment make a difference?
- Cochrane review April 2008
- 14 studies done looking at thyroid replacement in SCH (total N=350)
  - 7 studies on symptoms, mood, quality of life found no statistical difference with treatment
  - 1 study showed an improvement in cognitive function
  - 6 studies on LDL found “trend” towards improvement but not statistically significant

(Herrick, American Family Physician, 2008)

## What's the natural history of SCH in the elderly?
- Leyden-85-Plus trial
  - Looked at 599 residents of Leyden, Netherlands over age 85
  - Did thyroid assessment at baseline and followed people for 5 years
  - Assessed performance of ADLs, depressive symptoms, and cognitive function

(Gussekloo J et al. JAMA 2004)

## Leyden-85-plus results
- 9% of patients over 85 had SCH
- No baseline difference in performance, cognition, or depression in patients with elevated TSH compared to those with normal TSH
- In 5 years of observation, no association of SCH with decline in performance, cognition, or increased depression

## More interesting results
People with SCH actually had:
- Lower decline in dependency on instrumental ADLs over time compared with normal TSH people
- Greater survival over the 5 year period than people with normal TSH
What’s the take home?

- Appears to be little risk to being having either subclinical hypothyroidism or mild overt hypothyroidism if you are old
- Replacement not only might be unnecessary, could be detrimental to your health

Any questions?