Thyroid disorder for Resident

Chaicharn Deerohanawong M.D.
Diabetes and Endocrinology Unit
Department of Medicine
Rajavithi Hospital, Ministry of Public Health
Topics

- Abnormal thyroid function test
- Euthyroid sick syndrome
- Difficult cases of thyrotoxicosis
- Amiodarone induce thyroid disorder
- Monitor thyroid function after treatment thyroid disorder
- Subclinical thyroid disorders
## Usual Interpretation of TFT

<table>
<thead>
<tr>
<th>FT4 (T4)</th>
<th>FT3 (T3)</th>
<th>TSH</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>สูง</td>
<td>สูง</td>
<td>ต่ำ</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>ต่ำ</td>
<td>ต่ำ</td>
<td>ต่ำ</td>
<td>Secondary hypothyroidism</td>
</tr>
<tr>
<td>หรือ ปกติ</td>
<td>หรือ ปกติ</td>
<td>หรือสูงเล็กน้อย</td>
<td></td>
</tr>
<tr>
<td>ต่ำ</td>
<td>ต่ำ</td>
<td>สูง</td>
<td>Primary hypothyroidism</td>
</tr>
</tbody>
</table>
Unusual Thyrotoxicosis

• T3 toxicosis
  - early or mild thyrotoxicosis
  - toxic multinodular goiter
  - iodine deficiency area

• T4 toxicosis
  - idodine induce thyrotoxicosis
  - thyrotoxicosis in severe med illness
  - thyroiditis
Unusual Thyrotoxicosis

- Thyrotoxicosis with normal or elevated TSH
  - Lab TSH error
  - TSH producing tumor
  - Selective pituitary resistance to thyroid hormone
Hyperthyroixinemia with non-suppressed TSH

- Clinical thyrotoxicosis
- Rare
  - TSH producing tumor
  - Thyroid hormone resistance

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>TSH-omas</th>
<th>RTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial cases</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CT scan or MRI lesions</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>High $\alpha$-subunit</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>High $\alpha$-subunit/TSH ratio</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Elevates TSH after TRH</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>$T_3$ suppression test</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Unusual Thyrotoxicosis

- Thyrotoxicosis with low iodine uptake
  - Subacute thyroiditis
  - Painless thyroiditis
  - Iodine induced thyrotoxicosis
  - Factitious thyrotoxicosis
  - Struma ovarii
  - Metastatic functioning thyroid CA
A 30 years old woman presents with palpitation for 2 weeks. Her thyroid gland diffuse enlarge 30 gm. Her TFT has increase T3 and T4 and TSH 0.10

What is the likely cause of hyperthyroid in this patient?

What questions that we should ask more in this patient?
Answers

- Painless thyroiditis
  History of postpartum, bruit of thyroid gland, consistency of gland

- Subacute thyroiditis
  Fever, pain at the thyroid gland
# Graves’ vs Painless thyroiditis

<table>
<thead>
<tr>
<th></th>
<th>Graves’</th>
<th>Painless T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Onset</td>
<td>Vary</td>
<td>&lt; 2 months</td>
</tr>
<tr>
<td>2. Ophthalmopathy</td>
<td>10%</td>
<td>NO</td>
</tr>
<tr>
<td>3. Bruit of thyroid</td>
<td>+ / -</td>
<td>-</td>
</tr>
<tr>
<td>5. I 131 uptake</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>6. Doppler USG (blood flow)</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>7. TSH R Ab</td>
<td>+ / -</td>
<td>-</td>
</tr>
</tbody>
</table>
Euthyroid Hyperthyroxinemia

- Abnormal thyroid binding protein
- Acute psychiatric illness
- Antibody to thyroid hormone
- Gen thyroid hormone resistance syndrome
- Sick euthyroid syndrome
- Drugs
<table>
<thead>
<tr>
<th>Increases Serum TBG</th>
<th>Decreased Serum TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiology</strong></td>
<td></td>
</tr>
<tr>
<td>Pregnancy, new born</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Androgens, anabolic steroids</td>
</tr>
<tr>
<td>Opiate</td>
<td>Glucocorticoids (large doses)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>L-Asparaginase</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Nicotinic acid</td>
</tr>
<tr>
<td>Clofibrate</td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td></td>
</tr>
<tr>
<td><strong>Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Acromegaly (active)</td>
</tr>
<tr>
<td>Acute viral hepatitis</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Chronic active liver disease</td>
<td>Severe systemic illness</td>
</tr>
<tr>
<td>Estrogen producing tumors</td>
<td></td>
</tr>
<tr>
<td>Hydatidiform mole</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
<td></td>
</tr>
<tr>
<td>Familial TBG excess (x-linked)</td>
<td>Familial TBG Deficiency</td>
</tr>
</tbody>
</table>
Euthyroid Hyperthyroxinemia

- Abnormal thyroid binding protein
- Acute psychiatric illness
TFT changes in acute psychiatric illness

- 16% increased thyroid hormone with raised or normal TSH
- Found in schizophrenia, affective psychosis, and amphetamine abuse
- Rarely persists beyond 14 days
- Unknown mechanism

Trends in Endocrinol Metab 1997;8:282-7
Euthyroid Hyperthyroxinemia

- Abnormal thyroid binding protein
- Acute psychiatric illness
- Antibody to thyroid hormone
- Gen. thyroid hormone resistance syndrome
- Sick euthyroid syndrome
Sick Euthyroid Syndrome

- TBG ↓
- Circulating binding inhibition
- TSH ปกติ ↓ ต่ำ ดูง
Sick Euthyroid Syndrome

\[ T_4 \xrightarrow{5'-\text{deiodinase}} T_3 \xrightarrow{5-\text{deiodinase}} \text{Reverse } T_3 \]

\[ T_2 \xrightarrow{5'-\text{deiodinase}} \]
Sick Euthyroid Syndrome

Low T3 with

- Normal T4
- Low T4
- High T4

TSH may be low, normal or high (<15mIU/L)
Change in Thyroid Tests in The course of NTI
Euthyroid Hyperthyroxinemia

- Abnormal thyroid binding protein
- Acute psychiatric illness
- Antibody to thyroid hormone
- Gen thyroid hormone resistance syndrome
- Sick euthyroid syndrome
- Drugs
## Drugs affecting TFT

<table>
<thead>
<tr>
<th>Effect</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>May cause hypothyroidism</td>
<td>Lithium, iodine (all forms, including kelp, contrast media, etc.), interleukin-2, interferon-alpha</td>
</tr>
<tr>
<td>May cause hyperthyroidism</td>
<td>Iodine, interleukins, interferons</td>
</tr>
<tr>
<td>Reduce conversion of $T_4$ to $T_3$</td>
<td>Glucocorticoids, iodine, propythiouracil, beta-blockers, amiodarone</td>
</tr>
<tr>
<td>Suppress thyroid stimulating hormone</td>
<td>Dopamine, dobutamine, glucocorticoids, phenytoin, bromocriptine, octreotide</td>
</tr>
<tr>
<td>Increase clearance of $T_4$</td>
<td>Carbamazepine, phenytoin, rifampin, phenobarbitol</td>
</tr>
</tbody>
</table>
**Drugs affecting TFT (2)**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce binding of T&lt;sub&gt;4&lt;/sub&gt; to thyroid-binding globulin</td>
<td>Salsalate, salicylates, nonsteroidal anti-inflammatory drugs, furosemide, heparin</td>
</tr>
<tr>
<td>Cause increased thyroid-binding globulin</td>
<td>Estrogens, tamoxifen, methadone, heroin, 5-fluorouracil, clofibrate, perphenazine, mitotane</td>
</tr>
<tr>
<td>Reduce thyroid-binding globulin</td>
<td>Androgens, glucocorticoids, aspariginase</td>
</tr>
<tr>
<td>Influence absorption of thyroxine</td>
<td>Cholestyramine, aluminum hydroxide, ferrous sulfate, sucralfate, cation exchange resins</td>
</tr>
</tbody>
</table>
Amiodarone induced thyroid dysfunction

• Euthyroid: FT4 may be elevated
  FT3 may be reduced
  TSH normal

• Thyrotoxicosis: FT4 elevated, TSH low,
  FT3 may be high normal

• Hypothyroid: TSH high
  FT4 may be low normal
# Amiodarone induced thyrotoxicosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 thyrotoxicosis</th>
<th>Type 2 thyrotoxicosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Excess iodine</td>
<td>Destructive, inflammation</td>
</tr>
<tr>
<td><strong>Thyroid Ab</strong></td>
<td>Often present</td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>IL – 6</strong></td>
<td>normal</td>
<td>high</td>
</tr>
<tr>
<td><strong>%Iodine uptake</strong></td>
<td>Low but may be normal</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td><strong>Doppler USG</strong></td>
<td>Hypervascular</td>
<td>Reduced flow</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>High dose PTU (K perchlorate)</td>
<td>Steroid</td>
</tr>
</tbody>
</table>
TFT for Diagnosis and Follow-up Treatment of Thyrotoxicosis

• **Diagnosis**
  – $FT_4$, TSH or
  – $FT_3$, TSH
  – Critical illness: $FT_4$, $FT_3$, TSH

• **Follow-up treatment**
  – $FT_3$, $FT_4$ in early treatment
  – $FT_4$, TSH if suspect of overtreatment
  – $FT_3$ if suspect of relapse
**DURING TREATMENT OF HYPERTHYROIDISM**

<table>
<thead>
<tr>
<th>TSH, FT₄, FT₃</th>
<th>FT₄, FT₃</th>
<th>FT₄, FT₃</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperthyroid</strong></td>
<td><strong>Transition</strong></td>
<td><strong>Euthyroid</strong></td>
</tr>
</tbody>
</table>

- TSH, FT₄, FT₃
- FT₄, FT₃
- FT₄, FT₃

**Normal range**

- TSH
- FT₄
- FT₃

TSH require several months to return to normal after euthyroid
ผู้ป่วยหญิง อาชุ 54 ปี มาตรวจด้วยเรื่องเหนื่อยง่าย ตรวจพบมี heart rate 122 / นาที AF, thyroid gland diffuse enlarge 40 grams, no bruit

ผลการตรวจฮอร์โมน

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FT₃</td>
<td>20.75</td>
<td>pg/ml (2.57-4.43)</td>
<td></td>
</tr>
<tr>
<td>FT₄</td>
<td>7.12</td>
<td>ng/dL (0.932-1.71)</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.005</td>
<td>mIU/L (0.27-4.20)</td>
<td></td>
</tr>
</tbody>
</table>
# Follow-up treatment

<table>
<thead>
<tr>
<th>Month</th>
<th>$\text{FT}_3$ (pg/ml)</th>
<th>$\text{FT}_4$ (pg/ml)</th>
<th>TSH (U/mL)</th>
<th>MMI (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20.75</td>
<td>7.12</td>
<td>0.005</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>6.41</td>
<td>1.04</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>
## Follow-up treatment

<table>
<thead>
<tr>
<th>Month</th>
<th>FT₃ (pg/ml) (2.57-4.43)</th>
<th>FT₄ (0.932-1.71)</th>
<th>TSH (0.27-4.20)</th>
<th>MMI (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20.75</td>
<td>7.12</td>
<td>0.005</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>6.41</td>
<td>1.04</td>
<td>0.005</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>3.28</td>
<td>0.52</td>
<td>3.87</td>
<td></td>
</tr>
</tbody>
</table>
Laboratory Diagnosis of Hypothyroidism

- Earliest change of TFT in previous Graves’ disease with ablative treatment:
  - decreased $\text{FT}_4$, then increased TSH
- Earliest change of TFT in previous euthyroid patient:
  - increased TSH
Monitoring Treatment of Hypothyroidism

- **Central hypothyroidism**: FT4
  
  **Aim**: FT$_4$ in upper third of normal range

- **Primary hypothyroidism**: TSH (± FT4)
  
  **Recommendation**: FT$_4$, TSH if suspected of noncompliance with T$_4$ treatment

  **Noncompliance**: normal FT4 + high TSH
  
  or high FT$_4$ + high TSH
Screening TSH for thyroid disease

- **TSH alone:**
  - Normal TSH → euthyroid status

- **Misleading**
  - Low TSH, but not thyrotoxicosis
  - Normal TSH, but not euthyroid
  - High TSH, but not primary hypothyroidism
Low TSH but not thyrotoxicosis

- Pregnancy first and early second trimester
- Euthyroid sick syndrome
- Euthyroid Graves’ disease
- Remission phase of Graves’ disease
- On eltroxin suppressive therapy
- Long standing MNG with autonomous function of gland
- Drugs
- Secondary hypothyroidism
Conditions with TSH alone might be misleading

**Common**
- Recent treatment of thyrotoxicosis
- Pituitary disease
- Non-thyroidal illness
- Drugs

**Rare**
- TSH-secreting pituitary adenoma
- Thyroid hormone resistance
Option to consider in interpreting thyroid function

1. Repeat laboratory test (consider laboratory error, wrong patient, etc)
2. Clinical correlation/status
3. Patient occupation, past medical history, family history
4. Medications
5. Consider alternate tests
6. Consider common etiologies first
7. Endocrine consult
• FT3 normal in pregnancy period

• First trimester to early second trimester
  – TSH ปกติ หรือ ↓

• Third trimester
  – FT₄ ปกติ หรือ ↓
Transient Hyperthyroxinemia in Hyperemesis Gravidarum:

- Hyperemesis gravidarum, early pregnancy
- Palpitations, sinus tachycardia, goiter +/-
- No clinical evidence of Graves’ disease
- No ophthalmopathy
- No family history of thyroid disease
- Thyroid antibodies are negative
- Common in Asian women
- Excessive hCG stimulation results in transiently elevated $T_4$, $FT_4$ and low TSH
- Supportive treatment

Subclinical Thyroid Disorders

• Subclinical hyperthyroidism
  TSH low and normal FT4, FT3
• Subclinical hypothyroidism
  TSH high and normal FT4, FT3
Fact

- Subclinical thyroid disease: common
- Associated with complications??
  Fair to good evidence
  only TSH < 0.1 (osteoporosis, atrial fibrillation)
  or >10 (hypercholesterolemia, atherosclerosis)
- Benefit from treatment: in some selected patients
- Screening for general population: not recommend
- Aggressive case findings: Reasonable
Treatment Subclinical Hyperthyroidism

- Persistent TSH < 0.1 mIU/L + ≥ 1 risk factor
  - age > 60 yr
  - menopausal woman with osteoporosis
  - tachyarrhythmia eg. AF
  - patient with heart disease
  - RAIU high
Treatment Subclinical Hyothyroidism

- Persistent TSH > 10 mIU/L + Positive thyroid auto Ab
- TSH > upper limit in pregnant woman or woman who plan to pregnant
The Adrenal Incidentaloma
For Internist

Chaicharn Deerochanawong M.D.
Professor of Medicine, Rangsit Medical University
Diabetes and Endocrinology unit, Department of Medicine
Rajavithi Hospital, Ministry of Public Health
Adrenal Incidentaloma

- Definition
- Rule out functioning tumor
- Benign vs Malignant
  - Imaging Phenotype
  - Effect of Size
  - Role for FNA Biopsy
Definition

- An adrenal mass discovered **serendipitously** by radiologic examination

- In the absence of symptoms or clinical findings suggestive of adrenal disease

- and $\geq 1$-cm in diameter
What to do?
Prevalence by Age -- Autopsy Data

Kloos et al., *Endo Rev* 16:460, 1995
Most = Nonfunctioning Cortical Adenomas

In a recent review* (9 studies with 1800 patients) the overall mean % of dx were:

**Malignant = 3%**
- Primary adrenal carcinoma 2%
- Metastases 1%

**Benign = 97%**
- Nonfunctioning 90%
- Subclinical Cushing syndrome 6%
- Pheochromocytoma 3%
- Primary aldosteronism 1%

*Cawood et al. Eur J of Endo 2009;161:513-527*
Adrenal Incidentaloma

- Definition
- Rule out functioning tumor
- Benign vs Malignant
  - Imaging Phenotype
  - Effect of Size
  - Role for FNA Biopsy
Incidentally Discovered Adrenal Mass

History and physical exam
Hormonal testing:
- 1-mg DST
- 24-hr urine fractionated metanephrines and catecholamines
- If hypertensive, PAC/PRA ratio

Confirmatory testing
Adrenal Incidentaloma

- Definition
- Rule out functioning tumor
- Benign vs Malignant
  - Imaging Phenotype
  - Effect of Size
  - Role for FNA Biopsy
Suspicious Imaging Phenotype:
- large (> 4-cm)
- irregular margins
- inhomogeneous
- dense/vascular
- precontrast HU > 20
- <50% contrast washout at 10 min
Benign Imaging Phenotype:

- small (< 3-cm)
- smooth margins
- homogeneous
- "hypodense"
- < 10 HU precontrast

Benign
Hounsfield Unit (HU)

More lipid
Benign

+60 HU

ACCa
Met
Pheo
Lipid-poor adenoma

-20 HU
## Adrenal Incidentaloma -- Size Factor

### Accuracy in diagnosis of ACCa

* $N = 1,004$ incidentalomas (36 ACCa):*

<table>
<thead>
<tr>
<th></th>
<th>$&gt; 4$-cm</th>
<th>$&gt; 5$-cm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>88%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>75%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Positive PV</strong></td>
<td>44%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Negative PV</strong></td>
<td>97%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Adrenal Incidentaloma -- Size Factor

Risk of Malignancy

Unnecessary Surgery

Adrenal Mass > 4-cm and Young Age
CT-Guided FNA Biopsy

Always exclude pheochromocytoma before adrenal bx!!!
CT-Guided FNA Biopsy

What it CAN tells us:

- Infection: eg. TB, Fungus
- Metastatic disease
- Lymphoma

What it CAN’T tell us:

- It cannot distinguish between primary adrenal cortical benign vs malignant—hopefully with advances in histopathology, this will be possible in the future
Incidentally Discovered Adrenal Mass

History and physical exam
Hormonal testing:
• 1-mg DST
• 24-hr urine fractionated metanephrines and catecholamines
• If hypertensive, PAC/PRA ratio
Incidentally Discovered Adrenal Mass

History and physical exam
Hormonal testing:
• 1-mg DST
• 24-hr urine fractionated metanephrines and catecholamines
• If hypertensive, PAC/PRA ratio

Confirmatory testing

Imaging phenotype

Suspicious imaging phenotype:
• nonenhanced CT attenuation >10 HU
• CT contrast medium washout <50% at 10 min

Consider:
• FNA biopsy if metastatic disease or infection suspected
• Surgery
• Close follow-up (e.g. repeat imaging at 3 months)
Incidentally Discovered Adrenal Mass

History and physical exam
Hormonal testing:
• 1-mg DST
• 24-hr urine fractionated metanephrines and catecholamines
• If hypertensive, PAC/PRA ratio

Imaging phenotype

Benign imaging phenotype:
• nonenhanced CT attenuation <10 HU
• CT contrast medium washout >50% at 10 min

Consider:
• Repeat imaging at 6, 12, and 24 months
• Repeat hormonal testing annually x 4 years
• Surgery if ≥4-cm in diameter
Incidentally Discovered Adrenal Mass

History and physical exam
Hormonal testing:
• 1-mg DST
• 24-hr urine fractionated metanephrines and catecholamines
• If hypertensive, PAC/PRA ratio

Imaging phenotype

Benign imaging phenotype:
• nonenhanced CT attenuation <10 HU
• CT contrast medium washout >50% at 10 min

Consider:
• Repeat imaging at 6, 12, and 24 months
• Repeat hormonal testing annually x 4 years
• Surgery if ≥4-cm in diameter

This is where all of the uncertainty and debate lie