Funny thyroid function tests - avoiding the pitfalls…

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cambridge University Hospitals NHS Foundation Trust
Each year, Clinical Biochemistry at Addenbrooke’s receives >100,000 requests for thyroid function tests

What percentage of these return abnormal results?

A  <1%
B  1-5%
C  6-10%
D  11-15%
E  16-20%

Answer: D (11-15%)

Interpretation of the majority of abnormal TFTs is straightforward - BUT occasionally…

‘Anomalous TFTs’
‘Discordant TFTs’
‘Funny TFTs’
‘Perplexing TFTs’
‘Puzzling TFTs’
‘Weird TFTs’
What constitute ‘anomalous TFTs’?

Most easily considered in terms of two broad categories:

1. TFTs discordant with the clinical picture
2. TFTs discordant with each other

‘Anomalous TFTs’
‘Discordant TFTs’
‘Funny TFTs’
‘Perplexing TFTs’
‘Puzzling TFTs’
‘Weird TFTs’

thyrotoxic
dysfunctional
hypothyroid
euthyroid
Required knowledge for resolving ‘anomalous TFTs’

1. Physiology of the HPT axis and factors that govern thyroid hormone action at a tissue and cellular level

2. Principles underpinning laboratory measurement of T4, T3 and TSH; potential mechanisms of assay interference

3. Conditions associated with ‘anomalous TFTs’

‘Anomalous TFTs’
‘Discordant TFTs’
‘Funny TFTs’
‘Perplexing TFTs’
‘Puzzling TFTs’
‘Weird TFTs’
Thyroid hormone action and regulation
Thyroid hormone action and regulation

- T3 $\leftarrow$ T4

- T3 $\leftarrow$ T4
t

- TRH

- SA

- TSH

- T3 $\leftarrow$ T4

- TBG/Albumin/Prealbumin

- T3

- T4

- Deiodinase

- MCT8

- T3

- T4

- T4

- RXR

- TR

- CoA

- +++

- +ve

- DNA

- TRE

- Thyroid hormone action and regulation
Thyroid function test patterns

- subclinical hyperthyroidism
- recent Rx for hyperthyroidism
- drugs (e.g. steroids, dopamine)
- NTI

- subclinical hypothyroidism
- poor compliance with thyroxine
- malabsorption of thyroxine
- drugs (e.g. amiodarone)
- assay interference
- NTI recovery phase
- TSH resistance

Thyrotoxic
FT4/FT3 ↑
TSH ↓

‘Normal’
FT4/FT3 ↔
TSH ↔

Hypothyroid
FT4/FT3 ↓
TSH ↑

- central hypothyroidism
- isolated TSH deficiency
- assay interference

Illustrative cases
Case 1 – initial presentation

35-yr-old woman

PC  Tiredness

HPC  6 month history of:
• tiredness
• difficulty losing weight

PMH  Palpitations (normal ECG)

DH  Iron / multivitamins

O/E  P=60 bpm SR; no goitre

Clinical impression: ‘? thyroid’
Question 2

Which is the most appropriate next step in management?

A  Arrange $^{99m}$ technetium thyroid scintigraphy

B  Arrange contrast-enhanced MR scan of pituitary

C  Check serum alpha subunit (ASU) level

D  Commence antithyroid drug (ATD) therapy

E  Seek laboratory advice on further investigation

Answer: E
### Case 1 – further investigations

<table>
<thead>
<tr>
<th></th>
<th>Assay 1</th>
<th>Assay 2</th>
<th>Assay 3</th>
<th>Assay 4</th>
<th>Assay 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FT4 (pmol/L)</strong></td>
<td>5.0 (8.0–21.0)</td>
<td>4.2 (9.0–20.0)</td>
<td>18.0 (12.0–22.0)</td>
<td>21.4 (10.0–24.0)</td>
<td>42.5 (11.0–22.0)</td>
</tr>
<tr>
<td><strong>TSH (mU/L)</strong></td>
<td>&gt;100 (0.2–4.5)</td>
<td>&gt;100 (0.4–4.0)</td>
<td>&gt;100 (0.3–4.5)</td>
<td>&gt;100 (0.3–5.0)</td>
<td>&gt;100 (0.35–5.5)</td>
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</tbody>
</table>
FT4/FT3: ‘1-step’ competition assays

- $T_3/T_4$
- $T_3/T_4$ binding Ab
- endogenous $T_3/T_4$
- competing labelled $T_3/T_4$

Enhancement Solution

Fluorescence Measurement

variant albumin

Diagram:
- Schematic representation of the assay process.
- Red circles represent endogenous $T_3/T_4$.
- Yellow stars represent competing labelled $T_3/T_4$.
FT4/FT3: ‘2-step’ assay

FT4/FT3: ‘2-step’ assay

FT4/FT3: ‘2-step’ assay

FT4/FT3: ‘2-step’ assay

FT4/FT3: ‘2-step’ assay
Case 1 – further investigations

<table>
<thead>
<tr>
<th>FT4 (pmol/L)</th>
<th>Assay 1</th>
<th>Assay 2</th>
<th>Assay 3</th>
<th>Assay 4</th>
<th>Assay 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>4.2</td>
<td>18.0</td>
<td>21.4</td>
<td>42.5</td>
<td></td>
</tr>
<tr>
<td>(8.0–21.0)</td>
<td>(9.0–20.0)</td>
<td>(12.0–22.0)</td>
<td>(10.0–24.0)</td>
<td>(11.0–22.0)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TSH (mU/L)</th>
<th>Assay 1</th>
<th>Assay 2</th>
<th>Assay 3</th>
<th>Assay 4</th>
<th>Assay 5</th>
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<tbody>
<tr>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td></td>
</tr>
<tr>
<td>(0.2–4.5)</td>
<td>(0.4–4.0)</td>
<td>(0.3–4.5)</td>
<td>(0.3–5.0)</td>
<td>(0.35–5.5)</td>
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</tr>
</tbody>
</table>

→ Choose your ‘friends’ carefully (laboratory!)
Case 1 – further investigations

**Equilibrium Dialysis**

- Serum
  - T3/T4 binding antibodies
  - binding proteins

- Dialysate
  - Free T4/T3

**Radiolabelled T4 binding**

- Control serum: <15%
- Patient serum: <15%

**Anti-iodothyronine antibodies**

Detected

**Table:**

<table>
<thead>
<tr>
<th>FT4 (ng/dL)</th>
<th>Equilibrium dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.4 (0.8-2.7)</td>
</tr>
</tbody>
</table>

**Conclusion:** Primary autoimmune hypothyroidism FT4 assay interference (anti-T4/T3 antibodies)
Case 1 – follow-up

3 years later ... referred back by GP:

Serial TFTs:

<table>
<thead>
<tr>
<th>Time</th>
<th>TSH 0.35–5.5</th>
<th>FT4 11.5–22.5</th>
<th>Thyroxine (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>2.5</td>
<td>15.8</td>
<td>125</td>
</tr>
<tr>
<td>12 months</td>
<td>1.9</td>
<td>16.2</td>
<td>125</td>
</tr>
<tr>
<td>24 months</td>
<td>25.5</td>
<td>16.4</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>28.5</td>
<td>17.0</td>
<td>125</td>
</tr>
<tr>
<td>27 months</td>
<td>39.4</td>
<td>18.5</td>
<td>150</td>
</tr>
<tr>
<td>30 months</td>
<td>37.9</td>
<td>20.3</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td>50.2</td>
<td>23.8</td>
<td>175</td>
</tr>
</tbody>
</table>
Question 3

Which is the most appropriate next step in management?

A  Arrange contrast-enhanced MR scan of pituitary
B  Arrange thyroxine absorption test
C  Arrange triiodothyronine (L-T3) suppression test
D  Screen for malabsorption disorder
E  Seek laboratory advice on further investigation

Answer: E
TSH assay interference - negative
TSH assay interference - positive
### Case 1 – further investigations

#### FT4 (pmol/L)

<table>
<thead>
<tr>
<th>Dilution study</th>
<th>Assay 1</th>
<th>Assay 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>23.8 (11.5–22.7)</td>
<td>26.0 (9.0–20.0)</td>
</tr>
<tr>
<td>1:2</td>
<td>26.0 (9.0–20.0)</td>
<td>29.0 (12.0–20.0)</td>
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<tr>
<td>1:4</td>
<td>29.0 (12.0–20.0)</td>
<td>34.0 (15.0–22.0)</td>
</tr>
<tr>
<td>1:8</td>
<td>34.0 (15.0–22.0)</td>
<td>39.0 (17.0–24.0)</td>
</tr>
<tr>
<td>1:16</td>
<td>39.0 (17.0–24.0)</td>
<td>47.0 (19.0–28.0)</td>
</tr>
</tbody>
</table>

#### TSH (mU/L)

<table>
<thead>
<tr>
<th>Dilution study</th>
<th>Assay 1</th>
<th>Assay 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>50.2 (0.35–5.5)</td>
<td>0.06 (0.4–4.0)</td>
</tr>
<tr>
<td>1:2</td>
<td>0.06 (0.4–4.0)</td>
<td>0.12 (0.4–4.0)</td>
</tr>
<tr>
<td>1:4</td>
<td>0.12 (0.4–4.0)</td>
<td>0.24 (0.8–8.0)</td>
</tr>
<tr>
<td>1:8</td>
<td>0.24 (0.8–8.0)</td>
<td>0.48 (2.4–24.0)</td>
</tr>
<tr>
<td>1:16</td>
<td>0.48 (2.4–24.0)</td>
<td>0.96 (4.8–48.0)</td>
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</table>

### Assay interference

#### No interference

<table>
<thead>
<tr>
<th>Dilution study</th>
<th>TSH</th>
<th>TSH x dilution</th>
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<tr>
<td>1:1</td>
<td>27.50</td>
<td>27.50</td>
</tr>
<tr>
<td>1:2</td>
<td>14.00</td>
<td>28.00</td>
</tr>
<tr>
<td>1:4</td>
<td>6.88</td>
<td>27.52</td>
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<tr>
<td>1:8</td>
<td>3.35</td>
<td>26.80</td>
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<td>1:16</td>
<td>1.64</td>
<td>26.24</td>
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</table>

#### Assay interference

<table>
<thead>
<tr>
<th>Dilution study</th>
<th>TSH</th>
<th>TSH x dilution</th>
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<tr>
<td>1:1</td>
<td>13.30</td>
<td>13.30</td>
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<tr>
<td>1:2</td>
<td>3.75</td>
<td>7.50</td>
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<td>1:4</td>
<td>0.96</td>
<td>3.83</td>
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<td>1:8</td>
<td>0.26</td>
<td>2.08</td>
</tr>
<tr>
<td>1:16</td>
<td>0.07</td>
<td>1.04</td>
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</table>

### Screening for TSH assay interference:

- TSH dilution studies
- Gel filtration chromatography
- (Comparison across assays)
Case 1 – further management

<table>
<thead>
<tr>
<th></th>
<th>TSH (0.35–5.5)</th>
<th>FT4 (11.5–22.5)</th>
<th>Thyroxine (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>2.5</td>
<td>15.8</td>
<td>125</td>
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</tr>
<tr>
<td>30 months</td>
<td>37.9</td>
<td>20.3</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td>50.2</td>
<td>23.8</td>
<td>175</td>
</tr>
<tr>
<td>36 months</td>
<td>0.9</td>
<td>17.9</td>
<td>125</td>
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</tbody>
</table>

**Conclusion:** Stable primary hypothyroidism
TSH assay interference
Case 1 – several years later…

51-yr-old woman

<table>
<thead>
<tr>
<th>PC</th>
<th>Profound tiredness</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td>6 month history of:</td>
</tr>
<tr>
<td></td>
<td>• tiredness &amp; fatigue</td>
</tr>
<tr>
<td></td>
<td>• marked sleepiness</td>
</tr>
<tr>
<td>PMH</td>
<td>As previously; &amp; depression</td>
</tr>
<tr>
<td>DH</td>
<td>Thyroxine 275 mcg/day</td>
</tr>
<tr>
<td></td>
<td>Citalopram 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>HRT (combined) patch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TSH</th>
<th>&gt;100 mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>1.3 pmol/L</td>
</tr>
<tr>
<td>Anti-TPO</td>
<td>65 U/L</td>
</tr>
<tr>
<td>TRAb</td>
<td>0.2 U/L</td>
</tr>
</tbody>
</table>

O/E  P=60 bpm SR; no palpable goitre; BMI 33.5 kg/m²
Myxoedematous facies, slow-relaxing reflexes
Question 4

Which is the most likely explanation for the failure to respond to supraphysiologic thyroxine therapy?

A  Elevated thyroid hormone binding capacity
B  Increased deiodination of T4 to rT3 (reverse T3)
C  Increased metabolism of thyroxine
D  Malabsorption of thyroxine
E  Non-concordance with thyroxine therapy

Answer: E
Case 1 – several years later…

47-yr-old woman

PC  Profound tiredness

HPC  6 month history of:
   • tiredness & fatigue
   • marked sleepiness

PMH  As previously; & depression

DH  Thyroxine 275 mcg/day
    Citalopram 40 mg/day
    HRT (combined) patch

O/E  P=60 bpm SR; no palpable goitre; BMI 33.5 kg/m²
     Myxoedematous facies, slow-relaxing reflexes

<table>
<thead>
<tr>
<th></th>
<th>TSH (0.4–4.0)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;100 mU/L</td>
<td></td>
</tr>
<tr>
<td>FT4</td>
<td>1.3 pmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Coeliac serology: negative

‘Malabsorption screen’: negative
Case 1 – review of recent TFTs

<table>
<thead>
<tr>
<th></th>
<th>TSH (0.4–4.0 mU/L)</th>
<th>FT4 (9.0–20.0 pmol/L)</th>
<th>Thyroxine (mcg/day)</th>
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<tbody>
<tr>
<td>12 month period with previous GP</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;0.1</td>
<td>22.4</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>0.94</td>
<td>-</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>8.8</td>
<td>6.1</td>
<td>175</td>
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<td>'Lost to follow up'</td>
<td></td>
<td></td>
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<tr>
<td>12 month period with current GP</td>
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<tr>
<td>0.12</td>
<td>23.3</td>
<td>250</td>
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</tr>
<tr>
<td>15.1</td>
<td>20.5</td>
<td>250</td>
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<tr>
<td>&gt;100</td>
<td>1.3</td>
<td>275</td>
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</tr>
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</table>
Consider Assay Interference

Consider TH malabsorption

Consider increased metabolism/excretion/binding capacity

Consider Compliance

- **Dietary factors**
  - Fibre
  - Espresso Coffee

- **GI Disorders**
  - Coeliac disease
  - Lactose intolerance
  - Achlorhydria

- **Binding capacity**
  - Oral E2 therapy
  - SERMs
  - Mitotane

- **Investigations**
  - Prescription history
  - L-T4 absorption test
  - Supervised dosing

- **Drugs**
  - Cholestyramine
  - FeSO₄
  - Sucralfate
  - Aluminium hydroxide
  - Calcium carbonate
  - Sevelamer HCl
  - PPIs
  - Orlistat

- **Metabolism**
  - Carbamazepine
  - Phenytoin
  - Phenobarbitone
  - Rifampicin
  - Imatani

- **Weekly Dosing** may be a treatment option

**Anomalous TFTs in patients receiving L-T4 therapy**
Case 1 – supervised thyroxine administration

Do not underestimate the ingenuity of your patients!
SUPERVISED THYROXINE ABSORPTION TEST


Pre-test:
• Exclude:
  – confounding dietary factors/medications
  – conditions associated with thyroxine malabsorption (e.g. coeliac disease, achlorhydria, lactose intolerance)
  – overt non-compliance (e.g. failure to collect regular thyroxine prescription)
  – assay interference
• Check no contraindications to high-dose thyroxine therapy (consider performing ECG)

On day of the test:
• Ensure patient:
  – has fasted from midnight
  – empties bladder immediately prior to dosing (to allow continuous observation for 60 min post-dosing)
• Under direct supervision, administer the equivalent of one week’s cumulative thyroxine dose [e.g. 1.6 × body weight (kg) × 7 mcg] in liquid (preferred option) or tablet form (with dose rounded to nearest 50 mcg)
• Follow immediately with 200mL water orally, and observe patient for 60 min (keep fasted during this time)
• Collect blood samples for measurement of FT4, FT3 and TSH at 0, 30, 45, 60, 90, 120, 240 and 360 min
**SUPERVISED THYROID ABSORPTION TEST**

**Post-test:**
- Continue weekly supervised (observed for 60 min) administration of the same dose of thyroxine for a further 5 weeks
- Collect blood samples for measurement of FT4, FT3 and TSH at 0 and 120 min at weeks 2, 3, 4, 5 and 6

**Interpretation and follow-up:**
- TSH normalization → non-compliance; explore patient perspective; consider continued weekly dosing
- Inadequate FT4 rise post-thyroxine administration → institute further investigations for malabsorption
- Consistent rises in FT4 post-thyroxine, but no change in TSH levels → consider dose adjustment and/or further investigations into disorders of TH metabolism/excretion
Case 2 – initial presentation

24-yr-old woman

PC  Galactorrhoea

HPC  8 month history of:
  • bilateral galactorrhoea
  • secondary amenorrhoea

PMH  Thyroidectomy (Graves’ – aged 20y)

DH  Thyroxine 250 mcg/day

O/E  P=64 bpm SR; no thyroid remnant; galactorrhoea; normal VF and VA

Clinical impression: Microprolactinoma
Case 2 – pituitary MRI
Question 5

Which treatment is most likely to produce shrinkage of the pituitary mass and restoration of normal pituitary function?

A  dopamine agonist  
B  fractionated radiotherapy  
C  somatostatin analogue  
D  thyroxine  
E  transsphenoidal hypophysectomy  

Answer: D
Case 2 – radiological follow up

Serial pituitary MRI:

Presentation  + 6/12  + 70/12

Conclusion: Erratic compliance with TH replacement leading to reversible thyrotroph hyperplasia
Case 3 – initial presentation

7-yr-old girl

PC  PV bleeding

HPC  4 day history of PV blood loss
     6 month history of weight gain

O/E  Early puberty
     Breast development stage 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>TSH</td>
<td>&gt;150 mU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>1.7 pmol/L</td>
</tr>
<tr>
<td>LH</td>
<td>&lt;0.2 U/L</td>
</tr>
<tr>
<td>FSH</td>
<td>7.9 U/L</td>
</tr>
<tr>
<td>E2</td>
<td>180 pmol/L</td>
</tr>
</tbody>
</table>
Case 3 – management

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At presentation</th>
<th>After 75 mcg levothyroxine per day for 4/52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>675 mU/L</td>
<td>85 mU/L</td>
</tr>
<tr>
<td>TSH (0.4–4.0)</td>
<td>&gt;150 mU/L</td>
<td>4.1 mU/L</td>
</tr>
<tr>
<td>FT4 (11.5–20.7)</td>
<td>1.7 pmol/L</td>
<td>15.4 pmol/L</td>
</tr>
<tr>
<td>LH</td>
<td>&lt;0.2 U/L</td>
<td>0.2 U/L</td>
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<tr>
<td>FSH</td>
<td>7.9 U/L</td>
<td>0.3 U/L</td>
</tr>
<tr>
<td>E2</td>
<td>180 pmol/L</td>
<td>-</td>
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</tbody>
</table>
Algorithm for discordant TFTs


**Step 1:** Re-evaluate clinical history

- **Age**
- **Pregnancy changes**
- **Thyroxine therapy**
- **Confounding medications**
- **Non-thyroidal illness (NTI)**

**Step 2:** Re-assess thyroid status

- ? hyperthyroid
- ? euthyroid
- ? hypothyroid

**Step 3:** Decide which TFT is most likely to be discordant

**Step 4:** Exclude TH &/or TSH assay interference

**Step 5:** Investigate for rare genetic/acquired disorders of HPT function

Consider:
- neonatal period
- elderly

Consider:
- ↓TSH (1st trimester; 2° to ↑hCG)
- ↑TT4 & ↑TT3 (from 1st trimester; 2° to ↑TBG)
- changes in FT4 & FT3
- pregnancy RR

Consider:
- confounding dietary factors or medications
- malabsorption syndromes
- altered TH metabolism
- non-compliance
- other factors (see Table 2)

Consider:
- amiodarone
- furosemide
- heparin
- corticosteroids
- dopamine
- others (see Table 3)
**Case 4 – initial presentation**

26-yr-old woman

<table>
<thead>
<tr>
<th>PC</th>
<th>Galactorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td>12 month history of:</td>
</tr>
<tr>
<td></td>
<td>• bilateral galactorrhoea</td>
</tr>
<tr>
<td></td>
<td>• oligomenorrhoea</td>
</tr>
<tr>
<td>O/E</td>
<td>P=64 bpm SR;</td>
</tr>
<tr>
<td></td>
<td>small smooth goitre</td>
</tr>
<tr>
<td></td>
<td>bilateral galactorrhoea</td>
</tr>
<tr>
<td></td>
<td>normal secondary sexual characteristics</td>
</tr>
<tr>
<td></td>
<td>normal VF and VA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>1037 mU/L</td>
</tr>
<tr>
<td>TSH</td>
<td>2.9 mU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>29.2 pmol/L</td>
</tr>
</tbody>
</table>

No assay interference
No drug therapy
No intercurrent illness

**Clinical impression:** Microprolactinoma
Thyroid function test patterns

- FT4/FT3 ↔ TSH
- Thyrotoxic
  - FT4/FT3 ↑
  - TSH ↓
  - ‘Normal’
  - FT4/FT3 ↔
  - TSH ↔
  - Hypothyroid
  - FT4/FT3 ↓
  - TSH ↑

- Normal
- FT4/FT3 ↔
- TSH ↔

- FT4/FT3 ↓
- TSH ↓*

- FT4/FT3 ↑
- TSH ↑*

- FT4/FT3 ↑
- TSH ↔ or ↑

- FT4/FT3 ↓
- TSH ↔ or ↓*

- subclinical hyperthyroidism
- recent Rx for hyperthyroidism
- drugs (e.g. steroids, dopamine)
- NTI

- subclinical hypothyroidism
- poor compliance with thyroxine
- malabsorption of thyroxine
- drugs (e.g. amiodarone)
- assay interference
- NTI recovery phase
- TSH resistance

- assay interference; FDH
- thyroxine replacement therapy (including poor compliance)
- drugs (e.g. amiodarone, heparin)
- NTI (incl acute \( \Psi \) disorders); neonatal period
- TSH-secreting pituitary adenoma
- Resistance to thyroid hormone (RTH)
- Disorders of thyroid hormone transport or metabolism
Human thyroid hormone receptors & RTH

• Members of the steroid nuclear receptor superfamily

![Diagram showing chromosomes 17 and 3, DNA, T3, and hTRα1, hTRβ1, hTRα2, hTRβ2]

**RTHα (THRA)**
- First described in 2012
- A small number of cases reported to date

**RTHβ (THRB)**
- First described in 1967
- ~1 in 40,000 live births
- >150 different heterozygous mutations

Resistance to thyroid hormone (RTH) – TRβ
Case 4 – initial presentation

26-yr-old woman

PC  Galactorrhoea

HPC  12 month history of:
• bilateral galactorrhoea
• oligomenorrhoea

O/E  P=64 bpm SR;
small smooth goitre
bilateral galactorrhoea
normal secondary sexual characteristics
normal VF and VA

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin (&lt;=620)</td>
<td>1037 mU/L</td>
</tr>
<tr>
<td>TSH (0.4–4.0)</td>
<td>2.9 mU/L</td>
</tr>
<tr>
<td>FT4 (9.0–20.0)</td>
<td>29.2 pmol/L</td>
</tr>
</tbody>
</table>

No assay interference
No drug therapy
No intercurrent illness

Clinical impression: Microprolactinoma
Case 4 – pituitary MRI

T1WI: no gadolinium

T1WI: no gadolinium: fat suppression
### Case 4 – further investigations

<table>
<thead>
<tr>
<th>TRH stimulation test</th>
<th>CASE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td><strong>TSH</strong> <em>(0.4–4.0)</em></td>
</tr>
<tr>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td>20’</td>
<td>23.8</td>
</tr>
<tr>
<td>60’</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>SHBG</strong> <em>(18–114 nmol/L)</em></td>
<td>26</td>
</tr>
<tr>
<td><strong>α-subunit</strong> <em>(0.4–1.0μg/L)</em></td>
<td>0.45</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TSHoma stimulation test</th>
<th>TSH <em>(0.4–4.0)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td><strong>TSH</strong></td>
</tr>
<tr>
<td>0</td>
<td>3.4</td>
</tr>
<tr>
<td>20’</td>
<td>4.0</td>
</tr>
<tr>
<td>60’</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>SHBG</strong> <em>(15–55 nmol/L)</em></td>
<td>131</td>
</tr>
<tr>
<td><strong>α-subunit</strong> <em>(0.4–1.0μg/L)</em></td>
<td>1.44</td>
</tr>
</tbody>
</table>

**Conclusion:**
1. Prolactinoma &
2. Resistance to thyroid hormone (*THRB*)
Case 4 – follow-up pituitary MRI (18 months of DA)

T1WI: no gadolinium

T1WI: with gadolinium
## Cases 4 & 5 – comparison of further investigations

<table>
<thead>
<tr>
<th>TRH stimulation test</th>
<th>CASE 4</th>
<th>CASE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH (0.4–4.0 mU/L)</td>
<td>TSH (0.4–4.0 mU/L)</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td><strong>TSH</strong></td>
<td><strong>Time</strong></td>
</tr>
<tr>
<td>0</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>20’</td>
<td>23.8</td>
<td>20’</td>
</tr>
<tr>
<td>60’</td>
<td>17.0</td>
<td>60’</td>
</tr>
<tr>
<td><strong>SHBG</strong></td>
<td>26</td>
<td><strong>SHBG</strong></td>
</tr>
<tr>
<td>(18–114 nmol/L)</td>
<td></td>
<td>(10–57 nmol/L)</td>
</tr>
<tr>
<td><strong>α-subunit</strong></td>
<td>0.45</td>
<td><strong>α-subunit</strong></td>
</tr>
<tr>
<td>(&lt;1.0 IU/L)</td>
<td></td>
<td>(&lt;3.0 IU/L)</td>
</tr>
<tr>
<td><strong>THRB gene</strong></td>
<td><strong>I353M</strong></td>
<td><strong>THRB gene</strong></td>
</tr>
</tbody>
</table>
Case 5 – pituitary MRI

T1 SE non-contrast

T1 SE gadolinium
Case 5 – volumetric MRI

SPGR MRI - coronal

SPGR MRI - axial
Case 5 – SPGR MRI (coronal) pre- & post-SSA

Pre-SSA

On SSA & L-T4

6 months off SSA

<table>
<thead>
<tr>
<th></th>
<th>TSH</th>
<th>FT4</th>
<th>FT3</th>
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</thead>
<tbody>
<tr>
<td>Pre-SSA</td>
<td>7.7</td>
<td>23.5</td>
<td>7.3</td>
</tr>
<tr>
<td>On SSA &amp; L-T4</td>
<td>1.6</td>
<td>14.2</td>
<td>3.9</td>
</tr>
<tr>
<td>6 months off SSA</td>
<td>12.4</td>
<td>20.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Pre-SSA</td>
<td>On SSA &amp; L-T4</td>
<td>6 months off SSA</td>
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<tr>
<td>--------</td>
<td>--------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>7.7</td>
<td>TSH</td>
<td>12.4</td>
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<tr>
<td>FT4</td>
<td>23.5</td>
<td>FT4</td>
<td>20.3</td>
</tr>
<tr>
<td>FT3</td>
<td>7.3</td>
<td>FT3</td>
<td>7.3</td>
</tr>
</tbody>
</table>
Case 5 – TSHoma

**Presentation**

- SE MRI
- $^{11}$C-Methionine PET-SPGR MRI

**On SSA**

- SPGR MRI
Investigation of hyperthyroxaemia with non-suppressed TSH

Elevated T4/T3 with detectable TSH

- Confirm elevated free T4/T3 by equilibrium dialysis/‘two-step’ method
  - Confirm linearity of TSH assayed in dilution
  - Exclude confounding drug therapy / intercurrent illness

Check:
- Affected relatives?
- α-subunit:TSH ratio
- SHBG
- Pituitary MRI/CT
- TRH response
- T3 suppression
- SRL response
- THRBP gene analysis

Yes
- Normal
- Normal
- No adenoma
- Normal/exaggerated
- Yes
- No
- Mutation in >90%

No adenoma
TSH-secreting pituitary adenoma

Resistence to thyroid hormone

TFT Pitfalls – traps for the unwary..!

Pre-laboratory

Paying insufficient attention to the clinical context...

- Age
- Pregnancy changes
- Thyroxine therapy
- Confounding medications
- Non-thyroidal illness (NTI)

Laboratory

Failing to recognise limitations of commonly used T4/T3/TSH assays

- Assay interference:
  - Heterophile Ab
  - Anti-animal Igs
  - Anti-iodothyronine Ab
  - FDH

Post-laboratory

Limited experience of dealing with rarer genetic or acquired HPT disorders

- Resistance to thyroid hormone
- Disorders of TH transport
- Disorders of TH metabolism
- TSHomas
Acknowledgements

Addenbrooke’s Hospital
Carla Moran
Olympia Koulouri
Nadia Schoenmakers
Anne McGowan
Sue Oddy
David Halsall
Krish Chatterjee

Referring Clinicians/Laboratories

Cambridge National TFTs Referral Service

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Krish Chatterjee: kkc1@medschl.cam.ac.uk

http://www.sas-centre.org/centres/hormones/cambridge.html
Further reading

What should be done when thyroid function tests do not make sense?
Gurnell, Halsall & Chatterjee
Clinical Endocrinology (2011) 74: 673–678

How to interpret thyroid function tests
Koulouri & Gurnell

Pitfalls in the measurement and interpretation of thyroid function tests
Koulouri, Moran, Halsall, Chatterjee & Gurnell

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