Thyroid Stimulating Hormone (Challenges)

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**TSH Structure**

- TSH (28-30 kDa) is a glycoprotein and consists of two subunits.
  - The α (alpha) subunit:
    - The gene is located on chromosome 6.
    - The α chain has a 92-amino acid sequence.
    - Nearly identical to hCG, LH, and FSH.
    - The α subunit is thought to be the effector region responsible for stimulation of adenylate cyclase (involved in the generation of cAMP).
  - The β (beta) subunit (TSHB):
    - The gene is located on 17.
    - The β chain has a 118-amino acid sequence.
    - Unique to TSH, and therefore determines its receptor specificity.
- TSH secreted throughout life, particularly reaches high levels during the periods of rapid growth and development.

**Hypothalamus-pituitary-thyroid-peripheral tissues axis**

- Effects
  - Target tissues: Heart, liver, brain, and muscle.
  - TH, T4, T3.
  - TSH, TSHR, and T3.
  - Proliferation.
  - T3.
  - T4.
  - Liver.

**TSH Source**

- Hypothalamus
  - Paraventricular nucleus
  - Supraoptic nucleus
  - median eminence
  - Portal vessels
  - Anterior lobe of the pituitary gland
  - Thymus gland
  - Posterior lobe of the pituitary gland
  - Parathyroid glands
  - Adrenal glands
  - Striated muscle
  - Brain
  - Spinal cord
Regulatory regions of hTSH β gene

Important TSH Assay Issues
1. TSH Diurnal Rhythm
2. TSH Variability
3. Log-linear Relationship
4. Equilibrium Time
5. Antibody Interference
6. Method Dependency
7. TSH Reference Intervals
8. Pregnancy
9. Drugs
10. NTI

TSH Diurnal Rhythm

TSH Variability
- Inter individual Variation: High 32%
- Intra individual Variation: Moderate 20%
- A wide population-based RI
- Serial determination in a person: ≥ 0.7 mIU/L
Log-linear Relationship

Sensitive Sensor

Equilibrium Time

Slow-back Sensor

Antibody Interference
False High TSH

TSH Assay Interference
(Heterophilic Antibodies Sources)

- Exposure to animals (e.g., animal technicians, veterinarians, animal handlers)
- Alternate animal contact therapy (e.g., thymic cells, sheep cells, embryonic cells)
- Exposure to animal products (e.g., food preparation)
- Special diets (e.g., cheese)
- Deliberate immunization (e.g., therapies, vaccinations, certain imaging treatments)
- Blood transfusions
- Autoimmune diseases
- Dialysis
- Patent medicines (OKT3)
- Maternal transfer
- Cardiac Myopathy
- G.I. Disease (E. Coli)
- Rheumatoid factors can also act as heterophilic antibodies

http://scantibodies.com/hbr.html
Antibody Interference
False LOW or High TSH

- TSH Auto Antibodies
- Measurement of Auto Abs

Method Dependency

- TSH Molecule Heterogeneity
- 10% Variation among assays
  - Same method for TSH monitoring
- Reference Interval also method dependent
  - Applied only for the same method

TSH Reference Intervals

- Higher prevalence of Abs for TSH 3.0 – 5.0 (Ab test)
- Progression to Overt Hypothyroidism
  - 2.5%/year if Ab-
  - 4.5%/year if Ab+
- Some proposed the upper cutoff= 3 or even 2.5 mIU/L
- 2004 Consensus: 0.45 – 4.5
- Still Controversial
- But Age Specific RI: for >70 years up to 6.0
- But Pregnancy RI according to ATA:
  - 1st T: 0.1 – 2.5
  - 2nd T: 0.2 – 3.0
  - 3rd T: 0.3 – 3.0
Pregnancy Induced TFTs Changed

Mother’s Thyroid Function

Fetal Thyroid Function

Weeks of Gestation

Non Thyroidal Illness (NTI)
Euthyroid sick syndrome

Some Examples
- Gastrointestinal diseases
- Pulmonary diseases
- Cardiovascular diseases
- Renal diseases
- Infiltrative and metabolic disorders
- Inflammatory conditions
- Myocardial infarction
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation

Drug Effects on TFTs

Table 1. Effects of some drugs on thyroid function tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Antithyroid hormone synthesis or release</td>
<td></td>
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<tr>
<td>Alkaline phosphatase</td>
<td>Inhibits TSH secretion</td>
</tr>
<tr>
<td>Methimazole, propylthiouracil, carbimazole, perchlorate</td>
<td>Increases TSH</td>
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<tr>
<td>Inhibits TSH secretion</td>
<td>Glucocorticoids, dopamine antagonists, anticoagulants</td>
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<tr>
<td>Inhibits T3 and T4 binding to transport proteins</td>
<td>Methimazole, ethylenediamine, thiocyanate, p-chlorophenylalanine</td>
</tr>
<tr>
<td>Increases TSH secretion</td>
<td>Chlorpromazine, imipramine, tricyclic antidepressants, estrogens</td>
</tr>
</tbody>
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In a case of Discordant or Anomalous Results
(Conclusion)

After review of the clinical context, the following steps are helpful in evaluating anomalous thyroid results:

a. Review of the medication history.

b. Confirmation of serum TSH by an alternative method that identifies the degree of TSH suppression.

c. Follow-up sampling to establish whether the abnormality is transient or persistent.

d. An alternative estimation of serum free T4, avoiding one-step methods that are known to frequently give spurious results, especially during critical illness.

e. Measurement of serum total T4 to establish whether the serum free T4 estimate is disproportionately high or low, due to a pre-analytical or method-dependent artefact.

f. Evaluation of the sample for possible heterophilic antibody interference; note that there are no established criteria that rule out such interference.

g. Investigation of propositus and family members for evidence of unusual binding abnormalities or hormone resistance.
Thank you for your Attention

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