

Case: You admit a 67 year old man with severe decompensated CHF. He diureses well and responds to initial therapy in terms of oxygenation, but does not regain normal mental status as quickly. You send some labs to rule out reversible causes of altered mental status. TSH is elevated at 13. On further testing, free T4 is normal, but T3 is low.

Is this patient hypothyroid?

How will you manage him?

Sick Euthyroid Syndrome

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What is it?

- Any abnormal thyroid function test (TFT) in the setting of non-thyroidal illness (NTI) or systemic stress. Most commonly seen in seriously or critically ill patients. These changes can be detected as soon as two hours after onset of stress!
- Currently, the preferred term is “non-thyroidal illness syndrome” (NTIS) as some patients may, in fact, be hypothyroid
- The initial value that most commonly leads to further workup is an elevated TSH. Occasionally, the TSH can be low.

Are there any guidelines that can be employed in deciding when to check thyroid function in inpatients?

- There are no formal guidelines for use of TSH in inpatients. It is not unreasonable to check a TSH in an inpatient on thyroid replacement if there is a reason to do so, realizing that the values you obtain may be altered by illness.
- The American Thyroid Association recommends that adult outpatients be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter.
- Individuals at higher risk are: *Patients >60yo, female psychiatric patients, particularly if they are bipolar, dementia, hypercholesterolemia, sleep apnea, patients with autoimmune diseases (including T1 DM) or connective tissue disease, patients with a first degree relative with thyroid disease, postpartum women 4-8 wks after delivery, patients with goiter, nodular thyroid or Graves’ ophthalmopathy, psychiatric patients being treated with lithium, history of thyroidectomy or radioiodine therapy, history of high dose radiation to the neck, amiodarone therapy, suspected hypopituitarism, chronic autoimmune thyroiditis.*
- The most appropriate first test in inpatients is a TSH. Abnormal values can then be further investigated.
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What clinical scenarios have been described in NTIS?

The most common scenario is a low normal TSH with normal T4 and low T3.

- **Low serum total T3:** the most commonly identified abnormality (70% of patients in the hospital, mean value is 40% of normal).
- **Low serum total T3 and T4:** most common in critically ill patients in the MICU. Low total T4 is predictive of a bad outcome.
- **Low serum total T4:** seen with certain meds (dopamine and corticosteroids).
- **High serum total T4:** seen in situations where thyroid binding globulin is elevated (acute intermittent porphyria, chronic hepatitis, primary biliary cirrhosis). Free T4 is normal. Total T3 and T3 index are low. Reverse T3 is elevated.
- **High serum free T4:** seen with IV and subcutaneous heparin. Total T4 and the free T4 index are normal.

- **High serum total and free T4:** seen in treatment with amiodarone or iodinated contrast agents. These agents may precipitate hyperthyroidism, in the setting of thyroid nodules
- **In HIV:** multiple abnormalities have been described - increased T4 and TBG, decreased reverse T3, and normal T3 even in the setting of severe illness. T3 does decrease with PCP infection.

Other clinical pearls

- Dopamine (even short-term), dobutamine, octreotide and high dose glucocorticoids (>20mg/d prednisone, >100mg/d hydrocortisone, >4 mg/d dexamethasone) suppress TSH release. This, in the absence of T4 and T3 values, could mimic hyperthyroidism or mask true hypothyroidism.
- Furosemide and some NSAIDs displace T4 from binding proteins, decreasing serum T4 levels.
- Elevated thyroid hormone concentrations can be seen in up to 16% of psychiatric admissions (usually TSH). Most commonly seen in schizophrenia, affective psychosis, and amphetamine abuse. Rare beyond day 14 of admission.

Pathogenesis

- Multifactorial
- Includes decreased T4 to T3 conversion peripherally in illness, based on decreased activity of the enzyme 5'-MDI.
- Also related to alterations in serum binding of hormones. Albumin normally binds substances that compete with thyroid hormone for TBG, but in the setting of hypoalbuminemia, these competitors are able to displace thyroid hormone
- Cytokines such as TNF- α , IL1 and IL-6 and interferon-gamma have been shown to alter thyroid function.

Significance

- TFT abnormalities may confuse the diagnosis of true thyroid disease by causing an inappropriate diagnosis to be made or a true one to be missed.
- The changes seen in labs often have prognostic significance as well. Low T3 has been shown to be predictive of increased mortality in the setting of cirrhosis and CHF. Low T4 is also associated with increased mortality; a patient with low T4 and T3 is at the highest risk.

How can one diagnose thyroid disease in setting of acute illness?

- This can be challenging.
- Do not rely on results of one test alone in assessment for thyroid disease.
- Wait at least a week after resolution of a NTI to reassess thyroid status if an initially abnormal result was obtained.

Tips for hyperthyroidism

- TSH is almost uniformly undetectable in patients with hyperthyroidism, but only 7% of patients with NTI (unless they are being treated concurrently with steroids, dobutamine or dopamine)

Tips for primary hypothyroidism

- Hypothyroidism is a strong possibility if TSH is >25-30. (will be above 20 only 3% of the time in NTI)
- Subnormal free T4 in the absence of treatment with agents that suppress TSH (dopamine, corticosteroids, dilantin, carbamazepine) is strongly suggestive of hypothyroidism
- Presence of goiter and anti-thyroid antibodies (peroxidase, thyroglobulin) favor primary hypothyroidism
- Elevated rT3 in the setting of TSH >10 renders diagnosis of hypothyroidism unlikely.

Tips for secondary hypothyroidism

In NTI: TSH may be low, normal or minimally elevated.
Cortisol will be elevated or high normal.
Prolactin and LH/FSH should be normal.

In secondary hypothyroidism: Cortisol and gonadotropins will be decreased.
Prolactin will be increased.

Do these patients need to be treated with thyroid hormone?

- T4 replacement has demonstrated no benefit in studies
- T3 has shown some benefit and replacement doses have demonstrated no risk, but additional studies are needed.

Management

- Treat the underlying illness.
- Repeat studies at least a week after the acute insult has normalized.

Case follow up. While undergoing evaluation for altered mental status, the patient is found to have a UTI and is treated for the same. His mental status improves. The patient recovers from his CHF exacerbation and follow up with his PCP, who rechecks thyroid function tests one month after his hospitalization. These thyroid function tests are entirely within normal limits.

Clinical pearls

1. Do not assess thyroid function in an inpatient unless your suspicion for pathology is very high.
2. Never treat based on an abnormal TSH alone and do not treat unless you believe that thyroid pathology is contributing to the acute situation.
3. In the setting of significant acute or chronic illness, TSH can be normal, low or high.
3. A TSH of >25-30 is more convincing of hypothyroidism
4. There is not enough evidence at this time to support thyroid hormone replacement in the setting of non-thyroidal illness syndrome.
5. Allow at least 1 week to go by after resolution of an acute insult before rechecking thyroid function tests.

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