Current PSYCHIATRY

Psychiatric illness or thyroid disease?

Don't be misled by false lab tests

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Thyroid dysfunction is often in the differential diagnosis of psychiatric disorders. The author reviews the practical aspects of workup, diagnosis, and patient management, and addresses how to distinguish findings of a true thyroid illness from false readings.

Psychiatrists commonly order thyroid testing and are often the first to confront abnormal thyroid test results. As thyroid testing has become more sophisticated and sensitive (*Box 1*), the interpretation and management of abnormal or slightly abnormal results has become increasingly complex. What's more, older individuals, hospitalized patients, and those with psychiatric illness often present with subtle laboratory abnormalities.

Hyperthyroidism and hypothyroidism are highly prevalent disorders, especially in women and the elderly. Thyroid dysfunction is the second most common endocrine disorder after diabetes among elders. In the three cases that follow, some of the problems and solutions in dealing with thyroid testing are presented.

Case 1: Depression and thyroid abnormalities

J.R., 67, has a history of hypertension. She was referred for evaluation of depressive symptoms. She reports 3 months of increasing fatigue, lethargy, and poor motivation. Her weight has increased by 10 pounds over this period. Her physical exam, ECG, and chest x-ray are normal. She is well groomed and slightly overweight. Her medications have not changed recently and include hydrochlorothiazide 25 mg/d and an aspirin a day.

J.R. reports no history of treatment for psychiatric illness, denies current use of alcohol, tobacco, or illicit drugs, exhibits no abnormal movements or psychomotor changes, and her speech is articulate. Her mood is depressed, and her affect is restricted. She is not suicidal or homicidal, and her exam reveals no psychotic features.

Challenge Patients with thyroid abnormalities often present with psychiatric complaints. Classically, hypothyroidism can present like a depressive episode with similar symptoms of fatigue, anhedonia, weight gain, and sleep disturbance. Patients with hypothyroidism, however, may have physical complaints as well, which should alert the clinician to an underlying thyroid disorder. Typical physical complaints include hair loss, weight gain, dry skin, cold intolerance, constipation, muscle cramps, and joint pains. Women may also

Box 1

SCREENING FOR HYPOTHYROIDISM AND HYPERTHYROIDISM

An elevated or decreased TSH suggests thyroid dysfunction and should always be evaluated.

A low free T4 confirms the diagnosis of hypothyroidism. A low total T3 or free T3 is not always present but is associated with severe forms of hypothyroidism. The hallmark of hyperthyroidism is an elevated free T4 level or free T3 level or both. In a primary thyroid disorder, the TSH is below 0.1 U/L or undetectable.

Here is a description of these tests and what they mean:

- TSH (thyroid-stimulating hormone) is a pituitary hormone that acts on the thyroid gland to increase thyroid hormone secretion. Measurement of TSH is the most sensitive test to screen for hypothyroidism and hyperthyroidism as long as a second-generation assay is used (0.05 mIU/L). Thyroid testing should always begin just with the TSH test. Ordering a free T4 test at the same time is redundant and costly.
- T4 (thyroxine) is best and most accurately measured in its unbound free form. Of all the tests that measure thyroxine, free T4 most accurately reflects unbound thyroid hormone, which is physiologically active. Also, several variables (e.g. pregnancy, disease states, medications) alter total T4 levels by increasing or decreasing thyroid binding hormones. A free T4 test should always follow an abnormal TSH.
- T3 (triiodothyronine) is produced in the thyroid and in peripheral tissues via the enzymatic conversion of T4. Like T4, it is bound and unbound in the serum by thyroid binding globulin, and either form can be measured. T3 should be measured when the TSH is abnormal but the free T4 is within normal limits.
- T3 resin uptake is used to calculate indirectly free T4 and should only be ordered if a free T4 test is unavailable.
- Thyroid antibody tests can help uncover the underlying cause of thyroid dysfunction. These tests lack sensitivity and specificity and should not be used to rule out cancer. Thyroid peroxidase antibodies (antithyroglobulin) and antimicrosomal antibodies are associated with Hashimoto's thyroiditis and Graves' disease. Thyroid-stimulating immunoglobulin (TSI) or thyroid-stimulating hormone receptor antibodies are almost always unique to Graves' disease.
- A radioactive iodine uptake thyroid scan (RAIU) is the best test to determine the cause of hyperthyroidism. Uptake is elevated in most common conditions causing hyperthyroidism, but the pattern of uptake differs. In the context of hyperthyroidism, absent uptake should raise a red flag for nonfunctioning nodules that can be either benign or malignant. A thyroid scan is unhelpful and should not be ordered in working up hypothyroidism.
- Thyroid ultrasound can characterize gland size and nodularity but cannot distinguish benign from malignant masses.
- Fine-needle aspiration biopsy (FNAB) is the best test to distinguish benign and malignant nodules.

complain of menstrual disturbances such as menorrhagia, and may have trouble with fertility.

What makes the diagnosis difficult and often missed is that some patients have hypothyroidism with minimal or no symptoms. This is especially true in elders because many of the signs and symptoms of hypothyroidism are attributed to "normal" aging. In one recent review of women older than 70 who were screened in an office-based setting, 2% were diagnosed with unsuspected overt hypothyroidism.[1] Because classical exam and laboratory findings associated with hypothyroidism tend to present later in the disorder, many patients with thyroid dysfunction have "normal" exams.

Exam findings associated with a hypo-functioning thyroid may include an enlarged thyroid gland (goiter) or non-palpable gland, non-pitting edema (myxedema), sinus bradycardia, decrease in body temperature, and delayed relaxation of the deep tendon reflexes. Secondary laboratory abnormalities associated with hypothyroidism include normacytic anemia and elevated lipoproteins. Without specific thyroid testing, a "normal" physical does not rule out thyroid dysfunction.

Hyperthyroidism can also manifest as a depression in elders, known as "apathetic hyperthyroidism." Patients report decreased cognition, depression, and fatigue, and often experience unexplained weight loss, muscle weakness, or atrial fibrillation. Therefore, elderly patients presenting

with depression may have a hyper- or hypo-functioning thyroid.

Case 1 concluded The treating psychiatrist diagnosed the patient with major depression. In addition to treatment with an antidepressant, the patient underwent laboratory testing, including a complete blood count, metabolic panel, and TSH (thyroid stimulating hormone). Test results were normal except for a TSH of 64 mU/L, consistent with hypothyroidism. The patient was referred to her primary care physician to begin thyroid hormone replacement.

Comment Although psychiatric symptoms may be caused by clinically important thyroid dysfunction, thyroid function testing may uncover abnormalities of questionable clinical significance. The prevalence of abnormal thyroid hormone levels in hospitalized psychiatric patients ranges from 3% to 32%.[2] High thyroid levels (free T4 index and total T4) are associated with acutely psychotic patients such as those with schizophrenia, affective psychosis, and amphetamine abuses. Most studies show that these changes are transient and often normalize with correction of the psychiatric condition, usually within 10 days. Many researchers believe these findings are consistent with euthyroid sick syndrome (*Box 2*).[3]

Depressed patients and those with bipolar disorder often present with altered measures of the hypothalamic-pituitary-thyroid (HPT) axis. These abnormalities include mildly elevated or depressed T3, T4 and TSH levels and are not indicative of true thyroid dysfunction (*Table 1*). It has been debated whether these patients differ in prognosis from psychiatric patients without such abnormalities, although data in depressed patients suggest equivalent outcomes.[4] Furthermore, there is no clear evidence that thyroid supplementation benefits depressed patients with mildly elevated TSH with normal T4 and T3 values.[5]

The prevalence of thyroid disorders in the general population depends largely on the age, sex, and iodine consumption of the population studied. Women in general face a greater risk of overt thyroid dysfunction than do men, and elders face a greater risk than do the young. High dietary iodine consumption is associated with autoimmune hypothyroidism, especially in the aged. Iodine deficiency facilitates the development of hyperthyroidism secondary to toxic nodular goiter.

A number of other risk factors should also clue the clinician to thyroid dysfunction (*Table 2*).

Table 1

INTERPRETING TEST RESULTS

Cause	TSH	Free T4	Free T3
Hypothyroidism	Increased	Decreased	Normal or decreased
Hypothyroidism	Decreased	Increased	Increased
Subclinical hypothyroidism	Increased	Normal	Normal
Subclinical hypothyroidism	Decreased	Normal	Normal
Euthyroid sick syndrome	Normal or decreased	Normal or decreased	Decreased
Hypothalamic pituitary disorder	Decreased	Decreased	Normal or decreased
Hypothalamic pituitary disorder	Increased	Increased	Normal or decreased

Case 2: Subclinical thyroid abnormalities

S.J., 34, has a history of panic disorder that has been well controlled with a selective serotonin reuptake inhibitor (SSRI). He is referred to a primary care physician for an annual physical exam. His blood pressure is elevated as it has been on several occasions over the past year. His physical exam is otherwise normal. Laboratory and ECG test results are normal, except for an elevated TSH at 12 mU/L. Follow-up free T4 and free T3 tests are within normal limits. S.J. agrees to eat less salt to address his hypertension.

Challenge An elevated or decreased TSH with a normal thyroxine level (*Table 1*) is referred to as a "subclinical" thyroid disorder, which is more common than overt thyroid disorders. Women and elders are at greatest risk for subclinical hypothyroidism. In patients older than 60, the rate can be as high as 17% in women and 15% in men.[6] The rate largely depends on the number of patients receiving exogenous thyroid hormone—16% in populations including individuals

Table 2

WHEN TO CONSIDER THYROID DYSFUNCTION

- Women >age 50
- History of autoimmune disorder (i.e., type 1 diabetes mellitus, collagen vascular disease)
- Thyroid nodule or mass present on physical exam
- History of supervoltage x-ray therapy to the neck
- Laboratory evidence of subclinical thyroid dysfunction with a positive antithyroid antibody test
- Long-term use of drugs affecting thyroid function (e.g., lithium carbonate)
- Personal or family history of thyroid dysfunction
- History of infertility

receiving exogenous thyroid hormone and as low as 0.6-1.1% in populations without such patients.[1] Chronic subclinical hypothyroidism or mild thyroid failure is the most common condition found in thyroid function screening.

Although patients with subclinical abnormalities appear to be symptom-free, there are clinical implications for these patients. Subclinical hyperthyroidism in the elderly increases the risk for atrial fibrillation and osteoporosis. Postmenopausal women with chronically low TSH measures have lower bone density, especially in cortical bone (e.g., the forearm and hip). Subclinical hypothyroidism is associated with lipid abnormalities and progression to overt hypothyroidism. More recently it has become apparent that this "subclinical" syndrome is not as symptom-free as once assumed, with dry skin, cold intolerance, and easy fatigability more common than in euthyroid patients.[7]

Case 2 concluded Three months later, repeat testing reveals a negative thyroid antibody test, a TSH elevated to 9 mU/L, and a free T4 and fasting lipid profile within normal limits. S.J. and his physician discuss the pros and cons of thyroid replacement and decide to retest his thyroid function in 6 months with a repeat TSH.

Comment Should individuals with subclinical disorders be treated? How frequently should their thyroid function tests be monitored? The answers vary greatly among clinicians.

Some experts argue that treatment improves behavioral function and decreases lipid levels. Some clinicians take a "wait and see" approach because values can normalize in approximately 10% of patients.[6,8] Others treat based on presence of symptoms and risk of progression to overt thyroid failure (*Table 2*). If treatment is elected, only partial supplementation is usually needed. Most clinicians will start with a dose of 25 ug/d of T4 with adjustment every 6 to 8 weeks until the TSH is normalized.

Unless subclinical hyperthyroidism is secondary to over-replacement with exogenous thyroid hormone, this condtion can be more difficult to treat than subclinical hypothyroidism. Antithyroid therapy should be discussed with patients who have symptoms suggestive of hyperthyroidism, osteoporosis, recurrent atrial fibrillation, or thyroid gland nodules. Consultation with an endocrinologist can help clarify the risks and benefits and determine the specific antithyroid treatment appropriate for each patient.

Case 3: Medications and thyroid abnormalities

R.K., 56, has a long history of bipolar disorder. Upon presenting to his psychiatrist for routine follow-up, he reports a lack of energy but denies other symptoms of mania or depression. He periodically leaves work early or takes a short nap in his office to combat the fatigue. He feels that this may simply be part of "getting old." He denies any new medical problems and has seen his family physician in the last year. He states that he has been compliant with his medications, lithium and olanzapine. He appears slightly withdrawn and blunted but otherwise there are no abnormal features.

His lithium level, thyroid function, or kidney function had not been checked for 7 months. Subsequent testing reveals an elevated TSH (50 mU/L), a normal kidney profile, and a lithium level in the therapeutic range.

Challenge In psychiatric settings, lithium carbonate is the drug most commonly associated with decreased thyroid function. Lithium interferes with both thyroid hormone syn-

thesis and secretion. One-half of those taking lithium chronically develop goiter, and 40% develop subclinical or overt hypothyroidism.[9-11]

Many patients treated with lithium test positive for antithyroid antibodies. It is unclear if this finding represents a chronic autoimmune thyroiditis or is secondary to lithium treatment itself. In any case, patients taking lithium face an increased risk of thyroid failure. Other risk factors for thyroid failure include female gender and duration of treatment. Lithium dosage does not seem to be related to risk.

Clinicians differ on the frequency of thyroid monitoring for patients taking lithium. For patients without a history of thyroid dysfunction, annual TSH testing is likely sufficient.

Other medications affecting thyroid hormone production include methimazole, propylthiouracil, and iodide-containing drugs and dyes. Methimazole and propylthiouracil are given to patients intentionally with overt hyperthyroidism and interfere with hormone synthesis. Patients receiving medications or dyes containing iodide may also be susceptible to hypothyroidism. These agents are partially deiodinated after they are given and therefore can cause transient or prolonged decreases in thyroid production.

Some oral cholecystographic agents and the antiarrhythmic medication amiodarone are excreted slowly and can be associated with more prolonged decreases in thyroid hormone production. Iodide and medications containing iodide may precipitate a longer enduring hypothyroidism in patients with chronic autoimmune thyroiditis and in those with hyperthyroidism who have received radioactive iodine therapy or have undergone partial thyroidectomy.

The cholesterol-lowering bile acid sequestrants colestipol and cholestyramine can also inhibit thyroid reabsorption from the intestine, potentially leading to hypothy-

Box 2

EUTHYROID SICK SYNDROME

In consultative work, psychiatrists often confront abnormal thyroid tests in critically ill patients. Euthyroid sick syndrome can be a challenge to distinguish from ill patients with true thyroid or pituitary dysfunction. This syndrome is common in hospitalized patients and has been documented in more than 50% of patients in some settings.[14]

Abnormal thyroid tests are observed in a variety of medical conditions including heart failure, myocardial infarction, renal failure, liver disease, infections, stress, trauma, starvation, and autoimmune disorders. There is considerable debate about the meaning of these test abnormalities, and to date no conclusive intervention to correct abnormalities has proven to be consistently effective in ill patients.

The complex results of testing contribute to the confusion. An isolated low T3 is the most common lab abnormality found in nonthyroidal illness, related to a decrease in T4 enzymatic conversion to T3. Many disease states decrease this enzyme's (5′-deiodinase) activity. Unlike T3, TSH and T4 levels stay within normal limits in mild to moderately ill patients.

In patients who are moderately ill or who have been ill for a longer time, T4 levels fall with T3. In more severe and critically ill patients, the TSH level can decrease as well.

T4 can be elevated in sick patients without thyroid dysfunction. With this pattern, the TSH and T3 levels are normal or high. The clinical meaning of these abnormalities is unclear. Some studies suggest that the degree of thyroid hormone suppression correlates with disease severity and prognosis. Both decreased T3 and T4 levels have been shown to correlate with mortality in some disease states.[15] Debate remains as to whether these findings represent a maladaptive process or a protective response to illness.

Ill patients with hyperthyroidism generally have an elevated serum free T4 and T3 with an undetectable TSH. Ill patients with true hypothyroidism will have a TSH greater than 20 to 30 mU/ml with suppressed T4 and T3 levels. Diagnosis is more difficult when TSH levels are mildly abnormal or when the clinician is trying to distinguish secondary hypothyroidism from the low T3, T4, and TSH pattern found in many critically ill patients. Secondary testing or clinical findings such as an enlarged gland, the presence of thyroid antibodies, or abnormalities in other pituitary hormones may point to an underlying thyroid or pituitary problem in ill patients.

Table 3

WHICH MEDICATIONS CAN CAUSE THYROID DYSFUNCTION?

Drugs that increase thyroid hormone secretion
- Iodide-containing medication
- Amiodarone
- Providone-iodine antiseptics
- X-ray contrast media containing iodine

Drugs that decrease TBG,* causing a relative increase in unbound thyroid
- Androgens
- Anabolic steroids

Drugs that decrease thyroid hormone secretion
- Lithium carbonate
- Iodide
- Amiodarone

Drugs that increase hepatic metabolism of T4 and T3
- Phenobarbital
- Rifampin
- Phenytoin
- Carbamazepine

Drugs that decrease T4 absorption
- Colestipol
- Cholestyramine
- Aluminum hydroxide
- Ferrous sulfate
- Sucralfate

Drugs that increase TBG,* causing a relative decrease in unbound thyroid
- Estrogens
- Tamoxifen
- Heroin and methadone

*Thyroxine-binding globulin Table adapted from: Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med* 1995;333(25):1688-94.

roidism. Patients dependent on exogenous T4 or who have an underlying decreased thyroid function may develop hypothyroidism.

Drugs that alter thyroid hormone metabolism can also be problematic. Although thyroid hormone is metabolized mostly by deiodination, it also undergoes glucuronidation and sulfation. Phenobarbital, rifampin, phenytoin, and carbamazepine all increase T4 and T3 metabolism by inducing these hepatic enzymes. In patients with no thyroid disease, phenytoin and carbamazepine can decrease circulating free T4 levels by 20% to 40%.[12] Patients receiving T4 replacement may need their dosage increased or risk hypothyroidism if placed on one of these medications (*Table 3*).

Several medications alter total T4 and T3 levels by increasing or decreasing thyroid-binding proteins. Examples include estrogens, androgens, anabolic steroids, methadone, and heroin. Most thyroid hormone circulates as bound, but it is the unbound form that is active in peripheral tissues. Patients thus can experience changes in the binding proteins, while the proportion of unbound ("free") hormone at the tissue level remains unaffected.

Because this unbound form remains relatively unchanged, the patient with normal thyroid function remains euthyroid despite alterations in total thyroid levels. When patients with hypothyroidism start one of these medications, their replacement hormone dosage may need to be adjusted.

Bottom Line

Symptoms of psychiatric illness and thyroid dysfunction often overlap. Newer, sensitive thyroid function measures detect abnormalities in the hypothalamic-pituitary-thyroid (HPT) axis. Psychiatrists must recognize the clinical importance of these subtle abnormalities and should be familiar with the workup and treatment of overt thyroid dysfunction.

Related resources

- American Association of Clinical Endocrinologists. www.aace.com
- Clinical practice guidelines for evaluation and treatment of hypothyroidism and hyperthyroidism. Position statement on subclinical hypothyroidism and pregnancy
- Thyroid Federation International. www.thyroid-fed.org
- Online videos regarding thyroid disease (patient-directed). Patient handouts on thyroid disease
- Jameson JL, Weetman AP. Disorders of the thyroid gland. In: *Harrison's Principles of Internal Medicine*. 15th ed. New York: McGraw-Hill; 2001:2060-84

DRUG BRAND NAMES

Amiodorone • Pacerone, Cordarone
Colestipol • Colestid
Methimazole • Tapazole
Olanzapine • Zyprexa, Zyprexa Zydis
Rifampin • Rifadin, Rimactane

DISCLOSURE

The author reports no financial relationship with any company whose products are mentioned in this article.

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