Abnormal Thyroid Function Tests in Psychiatric Patients: A Red Herring?

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Thyroid abnormalities can induce mood, anxiety, psychotic, and cognitive disorders. Thus, thyroid function tests are routinely checked in psychiatric patients. However, up to one-third of psychiatric patients may demonstrate thyroid function test abnormalities that do not reflect true thyroid disease, but rather are a manifestation of secondary effects on one or more levels of the hypothalamic-pituitary-thyroid (HPT) axis. Originally termed the euthyroid sick syndrome, this phenomenon is now more commonly referred to as "non-thyroidal illness." In psychiatric patients with non-thyroidal illness, patterns of thyroid function test abnormalities may vary considerably based upon factors such as the underlying psychiatric disorder, the presence of substance abuse, or even the use of certain psychiatric medications. Thus, any abnormal thyroid function tests in psychiatric patients should be viewed with skepticism. Given the fact that thyroid function test abnormalities seen in non-thyroidal illness usually resolve spontaneously, treatment is generally unnecessary, and may even be potentially harmful.

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Thyroid hormones have a profound influence on the human brain and behavior, and the interrelationship between thyroid dysfunction and psychiatric disturbances has been well documented. Thyroid disturbances, from mild to extreme, can present with a variety of neuropsychiatric symptoms, including depressed mood, mania, acute psychosis, and dementia (1–3). It is not surprising, therefore, that thyroid function screens are among the most commonly obtained laboratory tests both in psychiatric inpatients and in medical inpatients exhibiting neuropsychiatric symptoms (4–6). Indeed, thyroid function panels are the most frequently obtained endocrine tests in the workup of mood disorders (5).

Not all thyroid function test abnormalities in our patients, however, signify true thyroid disease. Nonthyroidal illness is characterized by the presence of altered thyroid function parameters that are not considered indicative of actual thyroid disease but rather occur as a response to underlying systemic or acute psychiatric illness. This syndrome may be seen in a variety of systemic illnesses and stress states (Table 1), including severe infection, trauma, myocardial infarction, major surgery, malignancy, inflammatory disorders, and starvation (2, 7, 8), as well as in acute psychiatric illness (Table 2) (9, 10). Furthermore, nonthyroidal illness has been described in patients taking certain medications, including some that are commonly prescribed by psychiatrists (Table 3) (2, 5).

Epidemiology and Pathophysiology of Nonthyroidal Illness in Psychiatric Illness

Nonthyroidal illness is common in patients hospitalized for psychiatric disorders, with prevalence estimates ranging from 7% to 33% (10–13). Psychiatric illness and its treatment have a multitude of effects on thyroid function test results (14). Analogous to the case of patients suffering from systemic medical illness, the degree of abnormality seen in hormone levels of psychiatric patients with nonthyroidal illness tends to be correlated with the severity of their underlying psychopathology (15). Similarly, laboratory findings often normalize spontaneously with resolution of the underlying acute illness (usually within a period of 1–4 weeks in the psychiatric population) (2, 10, 16, 17). However, the patterns of laboratory findings in nonthyroidal illness typically seen in psychiatric patients differ from those seen in patients with systemic medical illness (9, 10).

The most common constellation of findings seen in patients with nonthyroidal illness and systemic medical illness includes low levels of T_3, normal to low levels of total T_4, and a high level of reverse T_3 (rT_3); these abnormal results may be seen in up to 75% of hospitalized medical patients (18). Serum TSH levels may also be influenced, even becoming frankly suppressed in more severe forms of the syndrome or elevated in the recovery phase (16, 19).

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"Ms. B" is a 28-year-old graduate student with a diagnosis of bipolar I disorder. During previous hospitalizations for severe manic episodes, she had exhibited irritability, grandiosity, and paranoia. Ms. B had recently been nonadherent to her outpatient medication regimen of valproic acid (1000 mg b.i.d.) and risperidone (3 mg h.s.).

Her mother brought her to the emergency department reporting several weeks of worsening depressive symptoms, irritability, somatic preoccupation, and delusions of persecution. On thyroid function testing, the patient's free T_4 level was elevated at 2.10 ng/dl and her thyroid-stimulating hormone (TSH) level was 3.90 μIU/mL, in the normal reference range. There were no findings on physical examination that suggested hyperthyroidism. Ms. B had no history of treatment with lithium. She was admitted to the inpatient psychiatric unit.

The treatment team obtained an endocrinology consultation and was advised that the clinical findings and laboratory test results suggested that the patient was likely euthyroid. Over the course of the next week, Ms. B was restarted on valproic acid and risperidone, and she returned to her baseline level of psychiatric functioning. On discharge, Ms. B was instructed to follow up with her internist in 1 month. At that meeting, her thyroid function test results were in the normal reference range.

The pathophysiology of changes in these hormone levels is complex and may be mediated in part by the impact of proinflammatory cytokines such as interleukin-6 (IL-6) (20), IL-1 (21), and tumor necrosis factor-α (22), among other inflammatory mediators, on the hypothalamic-pituitary-thyroid (HPT) axis (15, 16).

Altered thyroid function parameters seen in patients with acute psychiatric illness, however, are somewhat less consistent and vary among psychiatric diagnoses (Table 2) (9, 10). In contrast to the usual state of low T_4 levels seen in patients with nonthyroidal illness secondary to a medical condition, patients with acute psychiatric disorders may exhibit hyperthyroxinemia (9, 12, 23). One study (10) of a large population of psychiatric inpatients with various diagnoses (including mood, psychotic, and substance abuse disorders) found significant variability in the patterns of nonthyroidal illness, including hyperthyroxinemia, hypothyroxinemia, mildly elevated TSH levels, and suppressed TSH. A pattern of "euthyroid hyperthyroxinemia" was significantly more common in patients with mood disorders, while elevated TSH levels were highest in patients with substance use disorders. In patients with depression, T_4 levels may increase as a result of decreased peripheral conversion of T_4 to T_3; this has been speculated to represent a compensatory adaptive mechanism for maintaining homeostatic brain function (24). Again, T_4 and free T_4 levels tend to normalize in these patients with remission of the depressive episode (25).

The reason for such variety in altered thyroid hormone function parameters—particularly the prevalence of hyperthyroxinemia and high TSH levels in nonthyroidal illness specifically associated with psychiatric illness—remains unclear (10). One proposed pathophysiologic mechanism is an alteration of TSH secretion induced by abnormalities in key neurotransmitters, such as norepinephrine, serotonin, and dopamine (9). As in nonthyroidal illness associated with systemic medical illness, changes in pulsatile and nocturnal TSH secretion may result in aberrations of TSH levels (26). Potential pathophysiologic factors contributing to hyperthyroxinemia in these patients include redistribution of T_4 out of the tissues (particularly the liver), temporary pituitary thyrotroph resistance to T_4, or impairment of T_4 clearance (27). There is some evidence suggesting that centrally mediated hypersecretion of TSH is present in these patients (28).

Recreational drug abuse in psychiatric patients can also influence thyroid function tests in a variety of ways (16). Stimulants such as amphetamine may augment TSH secretion (17) and are associated with elevated concentrations of total T_4 (29). Opioids can similarly cause increases in serum T_4 and T_3 levels (30). In the case of hypothyroxinemic nonthyroidal illness seen in acute psychiatric patients, inhibition of TSH secretion and impairment of normal feedback responses may be due to production of cytokines and other humoral or local factors (31, 32).

Finally, certain medications prescribed by psychiatrists may cause changes in thyroid function tests that may not necessarily indicate actual thyroidal illness. It should be noted, however, that lithium and carbamazepine can cause true alterations of thyroid function. Lithium is well known to induce true hypothyroidism (2, 14, 16, 33). Carbamazepine induces metabolism of thyroid hormones by the liver. Therefore, patients who are on exogenous thyroid hormone replacement may become hypothyroid when treated with carbamazepine and may therefore require higher hormone replacement doses.

Thus, as in medical inpatients with nonthyroidal illness, thyroid function test measurements in patients hospitalized with acute psychiatric disorders may be misleading when attempting to assess actual thyroid status (34).

Screening

Unless there is clinical evidence of thyroid disease, routine screening with thyroid function testing is generally unhelpful. In the psychiatric population, only a minority of abnormal thyroid laboratory tests are clinically significant (6), and few of these findings will lead to actual changes in clinical management (35).

When evaluating patients at risk for nonthyroidal illness, it is useful to assess for any clinical findings on history or physical examination that might suggest actual thyroid disease, such as unexplained bradycardia or tachycardia; hypothermia; goiter or nonpalpable thyroid gland; non-

TABLE 1. Common Patterns of Thyroid Function Test Abnormalities in Nonthyroidal Illness Associated With Specific Medical Illnesses or Physiologic States

Illness or State	TSH	Total T_4	Free T_4	Total T_3	Free T_3	T_4-Binding Globulin
Starvation or fasting	↓	Usually normal; may be ↓ with time	Normal or slightly ↑	↓	↓	
Pregnancy	↓ during first trimester	↑ or normal	Usually normal (may be ↑ in first trimester or ↓ in third trimester)	↑ or normal	Usually normal	↑ or normal
Infection or sepsis	↓	↓	Usually normal	↓	↓	
HIV/AIDS	Usually normal, unless severe infection with low CD4 count; may be slightly ↑	Usually normal, unless severe infection with low CD4 count	Usually normal unless severe infection with low CD4 count	Usually normal, unless severe infection with low CD4 count; may be ↑		May be slightly ↑ (inversely related to % of CD4 cells)
Acute coronary syndromes	↓	↓		↓	May be ↓ if cardiac arrest occurs	
Nephrotic syndrome	May be ↓ in patients treated with steroids (see Table 3)	↓ or normal	Usually normal	↓ or normal	Usually normal	↓
End-stage renal disease	Usually normal	Usually normal or slightly ↓; may be ↑ in dialysis patients receiving heparin	Usually normal or slightly ↓; may be ↑ in dialysis patients receiving heparin	↓	↓	↓ in dialysis patients
Cirrhosis	May be ↑	↓	↓	↓	↑	↓
Acute hepatitis	Usually normal	↑	May be ↓	↑	Usually normal	↑
Chronic autoimmune hepatitis and primary biliary cirrhosis		↑	↓ or normal	↑	↓	↑ with chronic hepatitis, ↓ in primary biliary cirrhosis

TABLE 2. Common Patterns of Thyroid Function Test Abnormalities in Nonthyroidal Illness Associated With Specific Psychiatric Diagnoses

Diagnosis	TSH	Total T_4	Free T_4	Total T_3	Free T_3	T_4-Binding Globulin
Acute psychosis	May be normal	↑				
Rapid-cycling bipolar disorder	Slightly ↑	Slightly ↓				
Mania		↑	↑			
Mixed affective states	↑					
Depression	May be slightly ↑ or ↓	May be slightly ↑ or ↓	↑	May be slightly ↑ or ↓		
Posttraumatic stress disorder		Slightly ↑	Usually normal	Slightly ↑	Usually normal	Slightly ↑
Seasonal affective disorder			Slightly ↓			
Substance use disorders						
Amphetamines	↑	↑				
Opioids		↑		↑		↑
Alcohol		↓	↓	↓		
Nicotine	Normal or ↓			May be slightly ↑		May be slightly ↑
Eating disorders with restriction of caloric intake	↓	Usually normal; may be ↓ with time	Normal or slightly ↑	↓	↓	

pitting edema (myxedema); obtundation; weight loss; muscle weakness; and atrial arrhythmias (2, 16). Similarly, any patient with a history of previous thyroid disease, a history of neck surgery or irradiation, a history of autoimmune disorder, a family history of thyroid disease, or a history of lithium use should be considered at greater risk of having actual primary thyroid disease (2, 12). Women in general are more likely than men to suffer from true thyroid dysfunction (2, 5), and elderly patients are at greater risk than younger patients (2). Certain groups of medical

TABLE 3. Common Patterns of Thyroid Function Test Abnormalities in Nonthyroidal Illness Associated With Specific Medications

Medication	TSH	Total T_4	Free T_4	Total T_3	Free T_3	T_4-Binding Globulin
Glucocorticoids	↓ or normal	↓ or normal	Normal to slightly ↓	↓	↓	↓
Dopamine	↓	↓	↓	↓	↓	
Furosemide		↓	↑			
Heparin			↑			
Amiodarone	↑ or ↓	↑ or ↓	↑ or ↓	↑ or ↓		
Salicylates			↑			
Phenytoin	Generally normal		Usually ↓	Normal or ↓	Normal or ↓	
Carbamazepine	Generally normal	↓		↓		
β-adrenergic agonists				↓		
Oral contraceptives	Generally normal	↑	Usually normal	↑	Usually normal	↑

patients, such as cancer patients receiving immunotherapy with IL-2 (36) and patients with hepatitis C receiving recombinant interferon-α (37), are at elevated risk of developing true thyroid dysfunction. At the same time, some patients who are truly hypothyroid, particularly in the geriatric population, exhibit minimal or no symptoms (2). Furthermore, there is significant overlap between many of the symptoms of thyroidal illness and those of other underlying medical and psychiatric conditions (5, 7). Nevertheless, it is helpful to bear in mind that most patients with nonthyroidal illness do not exhibit the typical constellation of symptoms seen in thyroid deficiency or excess (7). The absence of such clinical features lowers the pretest probability of thyroid disease and therefore makes thyroid screening less useful (38).

Recommendations for Screening in Medical Inpatients With Psychiatric Symptoms

Based on the evidence outlined above, thyroid function tests should generally be deferred in hospitalized medical patients who do not have clinical features suggestive of pituitary or thyroid disease, at least until recovery from the underlying acute illness. However, there should be a lower threshold for screening in the geriatric population, since these patients may have true thyroid disease without typical signs or symptoms. We recommend that decisions regarding thyroid screening be made on a case-by-case basis, using sound clinical logic. For example, a previously healthy middle-aged patient who becomes acutely delirious in the setting of bacterial sepsis would be a poor candidate for thyroid screening. In this case, there is a clear explanation for neuropsychiatric symptoms without invoking the diagnosis of thyroid disease. Furthermore, the underlying infection might cause spurious changes in thyroid function test results, thus possibly leading the clinician astray. On the other hand, an elderly patient demonstrating neurovegetative signs and symptoms of depression in the absence of an altered sensorium might be a more appropriate candidate for screening.

If there is strong clinical suspicion for true thyroidal illness, TSH should be measured with a sensitive third-generation assay (2, 16, 23, 39, 40). Endocrinologists have recommended that in these cases, free T_4 be measured along with TSH (5, 16) and that any abnormal free T_4 values be confirmed by a dialysis method (16). Tests such as thyrotropin-releasing hormone (TRH) stimulation (40), serum T_3, or reverse T_3, on the other hand, are usually considered unhelpful in such patients (16). In cases of suspected secondary hypothyroidism, evaluation of pituitary function is recommended (16). Finally, measurements of antithyroid antibodies such as antithyroperoxidase and thyrotropin-binding inhibitory immunoglobulin may also be helpful in cases of suspected primary hypothyroidism (e.g., Hashimoto's thyroiditis) or Graves' disease (2, 16), although it should be borne in mind that lithium treatment may induce the production of these antibodies in certain cases as well (5).

Recommendations for Screening in Psychiatric Patients Without Acute Medical Illness

Because psychiatric disturbances may be a manifestation of thyroid disease, clinical assessment of physical signs and symptoms of thyroid disease should be a routine element of psychiatric evaluation. As in the medical inpatient population, the decision to order thyroid screening should be made on an individual basis, and results should be interpreted with caution. For example, a patient with chronic paranoid schizophrenia who typically presents to psychiatric emergency departments in an agitated state when off antipsychotic medication is not an ideal candidate for thyroid screening. There is a clear etiology for the agitation, making the pretest probability of thyroid disease low. Furthermore, the patient's acute psychosis could cause alterations in thyroid function test results, possibly misleading the evaluating clinician. Similarly, thyroid screening would not be warranted in a healthy-appearing young adult who presents with reactive mood changes after a psychosocial stressor. On the other hand, an elderly female outpatient with treatment-resistant depression may very well be suffering from true thyroidal illness and should be screened. Even in such a case, however, the test results must be interpreted carefully, as depressive illness

itself may exert an effect on the hypothalamic-pituitary axis, leading to alteration of thyroid function test results.

If there is suspicion for thyroid disease, measurement of TSH with a sensitive third-generation assay should be the first test obtained. Simultaneous testing of free T_4 levels is redundant and costly in psychiatric patients who are generally assumed to be medically healthy (2), and this test should be reserved for patients who have an abnormal TSH level. In these cases, the pattern of findings should be interpreted carefully, as it may help distinguish nonthyroidal illness from true thyroidal illness.

Intervention

The pattern of thyroid function abnormalities observed in test results can help distinguish nonthyroidal illness from true thyroidal illness. Thyroid or pituitary disease leads to predictable, concordant relationships between TSH and free T_4 (inverse relationships in the case of primary thyroid diseases) because of feedback mechanisms, whereas alterations of these parameters in nonthyroidal illness are typically discordant and nondiagnostic (39). In true hyperthyroidism, TSH measured by a third-generation assay is typically undetectable (2), whereas <1% of patients with nonthyroidal illness exhibit this finding (40). Hypothyroidism may also be a challenging diagnosis to make in both the medical and psychiatric inpatient populations, as up to 12% of patients with nonthyroidal illness may have elevated TSH values (40). However, <3% of these patients have TSH levels above 20 μU/ml (40). While serum TSH concentrations this high may be seen in the recovery phase of nonthyroidal illness (16), levels greater than 25–30 μU/ml strongly suggest primary hypothyroidism, particularly when coupled with suppressed T_4 and T_3 levels (2, 16). Similarly, a low level of free T_4, in the absence of treatment with drugs known to suppress TSH, also suggests hypothyroidism (16). Any patient who exhibits a pattern of thyroid function abnormalities consistent with true thyroid disease should, of course, be referred to an endocrinologist for appropriate treatment.

Intervention in Medical Inpatients With Psychiatric Symptoms

Since most patients with nonthyroidal illness exhibit recovery of HPT axis abnormalities with resolution of their underlying systemic illness (17), treatment is generally unnecessary. A further argument against treatment includes the possibility that the low T_3 syndrome is in fact adaptive or that such hormonal abnormalities are secondary to a primary process mediated by other agents, such as cytokines or glucocorticoids (16). Nonetheless, there remains significant debate about the benefits and risks of intervention in these patients. The fact that thyroid hormone concentration abnormalities are thought to be correlated with worse outcomes in patients with more severe illness has led to a number of clinical intervention trials in these patients (15, 19). It has been documented that T_3 and T_4 replacement is generally safe and well tolerated in such patients (41). Some research, particularly in the cardiopulmonary patient population, has demonstrated some improvement of hemodynamic parameters such as cardiac output and systemic vascular resistance with administration of T_3 (42). However, these findings have not been consistent across all studies (43). Furthermore, there has been no clear indication that such interventions actually have clinically significant effects on morbidity or mortality (41). In addition, exogenous administration of thyroid hormones carries the risk of further suppression of circulating levels of TSH. In the specific case of nonthyroidal illness secondary to starvation, a decline in T_3 levels is generally considered a beneficial adaptation (7), and hormone replacement has been found to be unhelpful and perhaps even harmful (44). This is also true for end-stage renal disease (45). One study (46) suggested a novel approach to the treatment of nonthyroidal illness, whereby continuous infusion of TRH along with a growth hormone secretagogue resulted in restoration of TSH pulsatility with concomitant improvement of catabolic measures. This approach may be safer than administration of thyroid hormone, as there is less likelihood of achieving supraphysiologic thyroid hormone levels (15), which may be associated with arrhythmia, coronary ischemia, and even myocardial infarction (47, 48).

Intervention in Acute Psychiatric Patients

As is the case with medical inpatients, laboratory abnormalities in acute psychiatric patients with nonthyroidal illness frequently resolve with improvement of the acute psychiatric symptoms. Thus, hormonal disruptions consistent with nonthyroidal illness should be left untreated in this population. Another argument against intervention is the possibility that such hormonal changes may in fact represent a protective homeostatic response to acute illness.

There are specific cases where fully euthyroid patients may benefit from treatment with thyroid hormone replacement (with T_3). For example, female patients in particular may experience augmentation and acceleration of response to antidepressant treatment, and rapid-cycling bipolar patients may exhibit reduced cycling frequency with thyroid hormone supplementation (5). The psychiatric practice of using thyroid hormone supplementation in treating mood disorders is distinct from the issue of treating nonthyroidal illness and thus is beyond the scope of this article.

The Question of Subclinical Hypothyroidism

In the case of an elevated TSH level with equivocal free T_4 results, subclinical hypothyroidism may be present. This is an endocrinologic entity distinct from nonthyroidal illness for which there is an extensive literature on the psychiatric population. In a psychiatric patient with an elevated TSH level and low-normal free T_4 values, it may be difficult to distinguish between nonthyroidal illness and

subclinical hypothyroidism. If such a patient exhibits other signs or symptoms of true thyroid disease, few would argue against thyroid replacement therapy. However, if there is no evidence of thyroidal illness and the patient has recently been medically hospitalized or is in the midst of an acute psychiatric episode, it may be prudent to defer hormone replacement treatment until the patient has stabilized and thyroid function tests have been repeated.

Conclusions

Nonthyroidal illness is a common finding in psychiatric patients, and abnormal thyroid function test results may represent an adaptive response to acute illness rather than true thyroid disease in this population. Thus, abnormal thyroid test results should be interpreted with caution. Given the frequent spontaneous resolution of such abnormal results with the treatment of the underlying psychiatric diagnosis, endocrinologic intervention is often unnecessary. However, current data are inadequate to definitively address the question of whether active treatment of nonthyroidal illness improves or worsens morbidity, mortality, and psychiatric symptoms (7, 15, 19). Clearly, further research is needed to answer such questions. Until then, a prudent approach would be to search actively for thyroid disease when clinically appropriate but to withhold treatment in the many psychiatric patients whose thyroid function test results are abnormal in the absence of true thyroidal illness.

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Clinical Guidance: Abnormal Thyroid Tests in Psychiatric Illnesses

Dickerman and Barnhill review abnormal thyroid function test results for psychiatric patients, who are often screened routinely. Although primary thyroid abnormalities can have significant psychiatric symptoms, most of the abnormalities detected are asymptomatic, not due to endocrine disorders, and resolve with treatment of the psychiatric illness itself. These abnormal results have little clinical significance and reflect the effects of psychiatric illness on the hypothalamic-pituitary-thyroid axis. Treating asymptomatic abnormalities with thyroid replacement can be harmful.