Nonthyroid Influences on Thyroid Function

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INTRODUCTION

In the majority of cases, abnormal results on thyroid function testing are traced to an underlying primary thyroid disease, most commonly hypothyroidism resulting from autoimmune destruction of the thyroid gland or hyperthyroidism resulting from Graves’ disease, toxic multinodular goiter, or exogenous thyroid hormone administration. However, many other factors, both exogenous and endogenous, may affect thyroid function and should be considered in the differential diagnosis.

Worldwide, the most frequent cause of thyroid dysfunction remains iodine deficiency, resulting in endemic goiter and cretinism. Lesser degrees of iodine deficiency, common even in the developed world, may also affect the thyroid, contributing to the development of multinodular goiter and altering the spectrum of thyroid cancer toward the more aggressive follicular phenotype. At the opposite end of the spectrum, excessive iodine intake also may trigger thyroid disease. In the United States, iodine-induced thyroid disease is seen increasingly in the context of cardiac arrhythmia treated with amiodarone. In addition to containing large amounts of inorganic iodide, amiodarone may have a direct impact on the deiodination of thyroid hormones, altering triiodothyronine (T3) bioavailability and complicating the interpretation of thyroid function tests.

Circulating thyroid hormone concentrations usually are stable and controlled within a very narrow range that remains essentially unchanged from early childhood. However, conditions unrelated to the thyroid may alter thyroid hormone production and metabolism, sometimes in complex ways, even in the absence of thyroid disease. This so-called nonthyroidal illness (also known as euthyroid sick syndrome) accompanies many conditions that may occur at all stages of life. The severity of the disruption of thyroid hormones correlates with the severity of illness and in some conditions may predict mortality. Whether intervention directed at the pituitary-thyroid axis might affect outcomes in these conditions remains unknown, as it is unclear whether the alterations in thyroid hormones represent a physiologic adaptation to disease or a separate pathologic process contributing to poor outcomes.

The ability to accurately determine the thyroid status of an individual has been dramatically advanced in the last 20 years by the routine availability of sensitive and accurate tests for all of the major hormones in this system. Increasingly, thyroid function tests have been used as screening tests for patients with minimal or absent symptoms of thyroid disease. Accurate interpretation of these tests depends on an intact feedback mechanism among the thyroid, pituitary, and hypothalamus. Alterations in sensitivity to thyroid hormone, which can result from inherited abnormalities of the thyroid hormone receptor, cause a physiologic adaptation that results in increased production of thyroid hormone under the stimulation of thyroid-stimulating hormone (TSH). A new steady state arises in which circulating thyroid hormone concentrations are elevated above their normal ranges but the TSH level is normal, reflecting the true thyroid status of the patient. These patients generally are euthyroid but their increased circulating thyroid hormone concentrations may be easily interpreted as hyperthyroidism. By recognizing this syndrome of thyroid hormone resistance, inappropriate therapy can be avoided.

IODINE-INDUCED THYROID DISEASE

Although iodine deficiency is common worldwide, it is rare in most of the developed world, including the United States. Nevertheless, it remains the most common cause of mental retardation worldwide, a condition that continues to frustrate the best efforts of public health officials. Although the remedy of population-based iodine supplementation is cheap, simple, and effective, prevention remains an elusive goal.

In contrast, iodine excess is largely a problem of the developed world, often reflecting the consequences of iodine supplementation in a population previously deficient in iodine or the impact of individual choice or medical necessity. Among the most common causes of excessive iodine intake is the use of the antiarrhythmic
agent amiodarone. Amiodarone (Figure 1) is a di-iodinated benzo-furanate containing 75 mg of iodine per 200 mg tablet, at least 10% (7.5 mg) of which is liberated as free iodine during drug metabolism. This amount compares to normal average daily iodide intakes of between 220 µg and 450 µg in Western Europe and North America, and reflects a greater than 20-fold increase in iodine exposure. Chronic treatment with amiodarone causes at least a 40% increase in sustained plasma and urinary iodide, and the drug’s fat solubility ensures a long biologic half-life, with increased urinary iodide excretion detected months or even years after drug withdrawal.

Amiodarone has a broad range of side effects (Table 1), including hypo- and hyperthyroidism and the induction of various autoimmune syndromes. Nevertheless, the drug’s utility as a potent antiarrhythmic agent with efficacy in both supraventricular and ventricular tachyarrhythmias has led to its increasing use in recent years. Excessive urinary iodine excretion is universal with amiodarone, and the rate of thyroid-related side effects is high. Prior to initiating treatment with amiodarone, a patient should undergo clinical assessment for evidence of underlying thyroid disease and measurement of the TSH level and thyroid peroxidase antibody (TPOAb) status. Patients with evidence of hyperthyroidism should be considered for definitive therapy (eg, iodine 131) before starting amiodarone, if possible. Patients with a high TSH level or positive TPOAb status are at particular high risk for developing amiodarone-induced hypothyroidism and should be monitored more closely as a consequence. During treatment with amiodarone, all patients should undergo routine thyroid screening, including twice-yearly measurement of TSH (patients with positive baseline tests should be screened thrice yearly), with T3 measurement as a follow-up if the TSH concentration becomes suppressed.

CASE PRESENTATION
Initial Presentation

A cardiologist refers a 72-year-old man to an endocrinologist for evaluation of abnormal findings on routine screening of thyroid function.

History

The patient suffered a large anterolateral myocardial infarction at age 69, complicated by impaired left-ventricular function, cardiac failure, and ventricular tachycardia. Approximately 18 months ago, after failed trials of several antiarrhythmic agents, the patient was started on amiodarone (200 mg twice daily), which has controlled his symptomatic ventricular tachycardia. He has had no further episodes of sustained palpitations or his previously recurrent cardiac failure. Six months after starting treatment with amiodarone, routinely performed thyroid function tests revealed suppressed TSH concentrations, and further deterioration was noted at the time of the patient’s referral. The patient has experienced a 5-lb weight loss, disturbed sleep, tremor, heat intolerance, sweating, and a recurrence of brief, self-limiting palpitations during the last 3 months. Otherwise, he remains well. Cardiac evaluation prior to this referral confirmed impaired left-ventricular function, with an ejection fraction estimated at 32% on echocardiography. Holter monitoring revealed sinus tachycardia, with frequent ventricular ectopic beats but no sustained runs of ventricular tachycardia. A chest radiograph revealed no evidence of cardiac failure.

Physical Examination

The patient is restless and anxious, with a tremor to the outstretched hands and with brisk reflexes. The pulse is 90 bpm and regular, with frequent extrasystoles. There is no clinical evidence of cardiac failure. Other than some minimal lid lag, the eyes are normal and exhibit no specific features of Graves’ disease. The thyroid gland is diffusely enlarged at an estimated 30 g (approximately 1.5 times normal size). It is firm and irregular in outline, but with no focal nodularity or tenderness. There is no overlying bruise.

Laboratory Evaluation

Thyroid function test results are as follow:

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**Figure 1.** The chemical structures of amiodarone and tetraiodothyronine, demonstrating the close structural similarity of these two molecules. Because of these structural similarities, amiodarone is thought to function as a competitive inhibitor of thyroid hormone deiodinase enzymes, in addition to its impact as a source of iodine.
• TSH, less than 0.005 µU/mL (normal, 0.3 to 5.0 µU/mL)
• Free thyroxine (FT4), 2.7 ng/dL (normal, 0.8 to 1.8 ng/dL)
• Total T3, 190 ng/dL (normal, 80 to 180 ng/dL)
• Thyroid peroxidase antibody (TPOAb), 45 U/L (normal, less than 10 U/L)

How does amiodarone affect thyroid function?

AMIODARONE-INDUCED HYPERTHYROIDISM
Pathogenesis and Pathophysiology

Amiodarone, or any other source of large amounts of iodine, can cause an acute inhibition of thyroid hormone production and release from the thyroid gland—the Wolff-Chaikoff effect. This effect may last a few weeks to a few months and can cause a transient decrease in the concentrations of circulating T3 and T4. In addition, amiodarone inhibits hepatic deiodinase, the enzyme responsible for producing 80% of circulating T3 in humans. This competitive inhibition of deiodinase is specific for amiodarone and may reflect the drug’s close structural similarity to thyroid hormone (Figure 1). As a result of these actions, the TSH increases in the face of decreasing T3 while T4 remains relatively normal due to reduced deiodination and, therefore, clearance. These changes may be transiently symptomatic of hypothyroidism but are rarely severe.

As the acute response to iodine loading fades, the normal thyroid recovers its capacity to produce and secrete thyroid hormone under the control of TSH. However, the high iodine availability results in a higher proportion of thyroid hormone released in the form of T4, while the amiodarone-induced block on T4 to T3 conversion is maintained. This causes a decrease in the circulating T3 concentration, an increase in the circulating T4 concentration, and a normal TSH. These changes are chronic and persistent for the duration of treatment with the drug. Whether the low T3 concentration is reflected in at least some tissues remains unknown, but most patients exhibit few, if any, clinical features of hypothyroidism.

Among patients with underlying thyroid disease, amiodarone may have additional effects on thyroid function and can result in both hypothyroidism and hyperthyroidism. The reported rates of these disorders depend on the prevailing iodine intake in the population under study and, presumably, the underlying prevalence of autoimmune or nodular thyroid disease. In populations with low or marginal iodine intake, hyperthyroidism may affect up to 10% of patients receiving amiodarone, whereas hypothyroidism may affect approximately 5% of those receiving the drug. In contrast, in areas with adequate or high iodine intakes (eg, the United States), hyperthyroidism is a substantially less common response to amiodarone treatment (occurring in approximately 2% of those receiving the drug), whereas hypothyroidism is very common (affecting up to 20%).

In addition to the population prevalence of thyroid diseases, individual factors play a role in predicting thyroid response to amiodarone treatment. For example, older women with a personal or family history of Hashimoto’s disease and a positive TPOAb status are at a 13.5 times greater risk for hypothyroidism following initiation of amiodarone treatment than are women with only a positive TPOAb status. This increased risk might result from several factors, including an exacerbation of underlying autoimmune thyroid disease.
resulting directly from iodine loading. Alternatively, Hashimoto’s disease may be exacerbated by the amiodarone itself, which is known to trigger autoimmunity in predisposed individuals. Finally, a diseased thyroid gland may fail to “escape” from the inhibitory impact of iodine loading, a phenomenon that is poorly understood but has been previously well-described.

**Type 1 and Type 2 Thyrotoxicosis**

Amiodarone-induced hyperthyroidism may be triggered by one of two distinct mechanisms. Type 1 amiodarone-induced thyrotoxicosis is seen among patients with underlying thyroid pathology, either Graves’ disease or, more commonly, a multinodular goiter. Iodine loading of these autonomously functioning glands results in hyperthyroidism as a reflection of increased substrate for the production of thyroid hormone—the jod-Basedow phenomenon. Once again, the precise mechanism of this phenomenon remains obscure; it may reflect the unmasking of latent hyperthyroidism by iodine supplementation and frequently is seen during iodine supplementation in iodine-deficient populations, in whom the rates of thyrotoxicosis may increase dramatically.

Type 2 amiodarone-induced thyrotoxicosis largely affects patients with previously normal thyroid gland structure and function and is caused by a subacute destructive thyroiditis, which may be induced by the amiodarone itself but also can be seen following iodine administration alone. Type 2 thyrotoxicosis does not reflect true hyperthyroidism but rather is caused by the release of preformed thyroid hormone from damaged thyroid follicles. Because of the large quantities of thyroid hormone contained within the thyroid gland and the rapid release of hormone during gland destruction, this form of thyrotoxicosis may be severe, often with an acute onset and possible associated gland tenderness. Type 2 thyrotoxicosis tends to be self-limiting and may be followed by temporary or permanent hypothyroidism once the acute inflammatory response resolves.

- **Which thyroid function test provides the most accurate assessment of the patient’s thyroid status?**

The normal ranges for thyroid hormone concentrations may be different in otherwise healthy patients being treated with amiodarone (Table 2), due to the reduced peripheral conversion of T4 to T3 caused by competitive inhibition of hepatic deiodinase. Even euthyroid patients receiving amiodarone may exhibit high T3 concentrations and sometimes lower than normal TSH levels. Among patients who become thyrotoxic, T4 concentrations may be substantially elevated, but conversion to T3 is at least partially blocked, thus minimizing the symptomatic consequences. Because T3 is the active hormone, and because T4 to T3 conversion is impaired in the liver and probably in other tissues, the degree of thyrotoxicosis is best reflected by the T3 concentration. The most frequently used T3 assays detect total T3, which can be affected by changes in thyroid hormone binding globulin (TBG) concentration. Although free T3 concentration probably provides the most accurate available assessment of thyroid status, total T3 concentrations are more widely available, faster, and cheaper, and this measurement remains the test of choice in most clinical settings.

- **What further information is needed to guide decisions regarding this patient’s management?**

**DIFFERENTIATING BETWEEN TYPE 1 AND TYPE 2 DISEASE**

Critical information that is needed to manage patients with amiodarone-induced hyperthyroidism include the degree of the thyrotoxicosis (T3 concentration), the cause (type 1 versus type 2), and the time course of the illness. The distinction between type 1 and type 2 thyrotoxicosis is important for several reasons, most prominently the prognostic implications. The type 1 response is likely to be progressive, whereas the type 2 response, although initially more severe, is likely to be self-limiting. Therefore, the management of these two conditions should be different.

Often, patients with mild type 1 thyrotoxicosis can be safely observed, in part because of the protective effect of the amiodarone-induced T4 to T3 conversion block.
Spontaneous remissions from type 1 thyrotoxicosis have been described. Not uncommonly, it is only during withdrawal of the amiodarone, when iodine loading is still very high but the impact of the drug on deiodination is diminished, that mild type 1 thyrotoxicosis deteriorates and becomes symptomatic.

The presence of a painless, irregular goiter and positive TPOAb status in this patient point to an underlying thyroid disease and make type 1 amiodarone-induced thyrotoxicosis more likely. In addition to the tests already performed, thyroid ultrasonography would help to define a multinodular goiter, whereas measurement of the TSH receptor antibody concentration may help in diagnosing Graves’ disease. Measurement of iodine uptake also may be worthwhile in differentiating type 1 from type 2 thyrotoxicosis, as the former may occasionally show detectable uptake whereas the latter shows essentially no uptake because of the destructive thyroiditis. However, iodine uptake measurements generally are low due to the high iodine load from the amiodarone, making this technique unreliable. The distinction between type 1 and type 2 thyrotoxicosis also may be made by measuring circulating interleukin-6 (IL-6). The concentration of IL-6 is elevated markedly in type 2 thyrotoxicosis, presumably reflecting the immune response to tissue injury seen in this condition. This test is rarely performed and rarely necessary.

**DIAGNOSIS AND INITIAL MANAGEMENT OF CASE PATIENT**

The patient undergoes further testing to identify any underlying thyroid pathology. Evaluation of iodine uptake is low at 1.4% after 24 hours (normal, 8% to 24%). TSH receptor antibody concentration is 4% (negative, less than 8%; equivocal, 8% to 15%; positive, greater than 15%), making Graves’ disease less likely. Thyroid ultrasonography confirms a small multinodular goiter and, thus, a diagnosis of type 1 amiodarone-induced thyrotoxicosis is made.

The patient’s cardiologist is consulted and is certain that the patient should remain on amiodarone treatment, as no suitable alternative therapy exists for his potentially life-threatening arrhythmia. Because of the mild symptoms and relatively low total T3 concentration, a decision is made to observe the situation.

- **What treatment options are available for patients with amiodarone-induced hyperthyroidism?**

**TREATMENT OPTIONS**

The first consideration in all cases of amiodarone-induced thyroid disease is whether the amiodarone might be withdrawn. It has been stated that patients should “earn their amiodarone,” implying that treatment with this toxic drug should be used as a last resort. Increasingly, however, amiodarone is being used at an early stage because of its remarkable efficacy in the treatment of arrhythmias. Alternatives should certainly be considered when thyrotoxicosis arises as a complication. Withdrawal of amiodarone is almost always effective in type 2 thyrotoxicosis, and the use of oral corticosteroids may prove beneficial, hastening recovery after amiodarone withdrawal. In contrast, antithyroid drugs have no role in the management of this form of destructive thyroiditis. Finally, radioactive iodine is largely ineffective in amiodarone-induced thyrotoxicosis because of the very low iodine uptakes that are the result of iodine loading in type 1 disease and destructive thyroiditis in type 2 disease.

**Treatment of Type 1 Disease**

As noted, not all cases of type 1 amiodarone-induced thyrotoxicosis warrant treatment. However, symptomatic thyrotoxicosis or high T3 concentrations may exacerbate the underlying predisposition to arrhythmias that the amiodarone was prescribed to prevent, so that moderate or severe thyrotoxicosis may require aggressive therapy. Also, the condition may be gradually progressive and may warrant treatment to prevent further deterioration.

Type 1 thyrotoxicosis may be self-perpetuating, so that even withdrawal of the amiodarone may not be effective in resolving the problem. The very long half-life of amiodarone caused by its high lipid solubility, and the very high iodine load that even short-term treatment provides, make drug withdrawal a slow and uncertain resolution suitable only for mild to moderate disease. In addition, withdrawal of the drug may transiently worsen the thyrotoxicosis by removing the T4 to T3 conversion block.

Thiourea drugs, including propylthiouracil and methimazole, may be used to impair iodine organification and improve type 1 thyrotoxicosis. However, this approach is slowly and incompletely effective, particularly if the amiodarone is continued, because the very high iodine load largely overcomes the effect of the propylthiouracil. High doses may be required, with the possibility of significant toxicity (eg, hepatic and bone marrow effects). Sodium or potassium perchlorate and lithium also have been used to promote iodide flux from the thyroid gland. These drugs may accelerate recovery from the iodine loading effect. Toxicity and intolerable side effects are significant problems. Once again, the efficacy of using thiourea drugs is questionable if the amiodarone must be continued.
Ultimately, the treatment of choice for type 1 disease that does not respond to more conservative measures is surgical resection of the thyroid gland followed by thyroid hormone replacement. Although many patients who are receiving amiodarone are at high surgical risk because of their underlying heart disease, improvements in general anesthesia and monitoring techniques, as well as improvements in surgical techniques, have made thyroid surgery even in this group of patients a relatively safe procedure, with reported mortality rates of less than 5%. This definitive approach should be considered for all patients with persistent symptomatic or progressive type 1 amiodarone-induced thyrotoxicosis in whom withdrawal from the amiodarone is not an option.

TREATMENT OF CASE PATIENT AND RESOLUTION

Three months later, the patient remains minimally symptomatic but his thyroid function has deteriorated, with the following laboratory results:

- TSH, less than 0.001 µU/mL (normal, 0.3 to 5.0 µU/mL)
- FT₄, 3.2 ng/dL (normal, 0.8 to 1.8 ng/dL)
- Total T₃, 207 ng/dL (normal, 80 to 180 ng/dL)

Propylthiouracil is introduced at a dose of 150 mg three times daily, and close observation continues. Repeat thyroid function testing 6 weeks later reveals further deterioration, and the patient is increasingly symptomatic. Despite the surgical risks, the patient agrees to undergo thyroidectomy under general anesthesia. Under the direct supervision of his cardiologists, and with close monitoring in the hospital setting, β-blockade is introduced to the patient’s drug regimen preoperatively. He subsequently undergoes near-total thyroidectomy without complications and begins thyroid hormone replacement (125 µg/day) 4 days later, upon dismissal from the hospital. Eight weeks postoperatively, the patient is well with no further thyrotoxic symptoms and a wound that is well healed. Thyroid function has returned to normal at this time, and the patient remains on his previous dose of amiodarone.

NONTHYROIDAL ILLNESS

Abnormalities of thyroid hormone concentrations without evidence of intrinsic thyroid or pituitary disease are seen frequently in the context of various nonthyroidal conditions, including infections, trauma, myocardial infarction, major surgery, malignancy, inflammatory disorders, and starvation. Following recovery from the underlying condition, the thyroid function normalizes. This clinical phenomenon has been called euthyroid sick syndrome, because the abnormalities seem to represent a response to the underlying condition rather than an abnormality of the thyroid gland itself. The implicit assumption that these patients are euthyroid has led to recommendations to avoid testing the pituitary-thyroid axis during intercurrent illness or hospitalization. However, whether these patients are truly euthyroid remains unproven, and some studies have shown evidence of hypothyroidism, at least in some tissues. Because of these uncertainties, the preferred term for this condition remains nonthyroidal illness.

PATTERNS OF THYROID FUNCTION

Thyroid hormone and TSH concentrations are variably affected in nonthyroidal illness, reflecting both the type of the underlying illness and its severity. Three major patterns of thyroid function are recognized.

Low T₃

This is the most common form of nonthyroidal illness, most often resulting from acute illness. The serum T₃ concentration decreases rapidly within 30 minutes to 24 hours of the onset of the causative illness, and the degree of decrease reflects the severity of the disease process. Reverse T₃ increases as T₃ decreases, reflecting altered activity of hepatic deiodinase.

Low T₃ and Low T₄

With more severe and prolonged illness, total T₄ concentrations decrease over 24 to 48 hours. Once again, the degree of decrease in T₄ correlates with severity in several conditions. FT₄ concentrations vary greatly, perhaps reflecting an impact of nonthyroidal illness on the assays used to measure FT₄. The decrease in T₄ concentration reflects a decrease in TBG and—at least in some cases—the presence of an unidentified inhibitor of T₄ binding. As a result, transient elevations in FT₄ are seen in some cases of nonthyroidal illness.

Low TSH, Low T₃, and Low T₄

In the most severe or prolonged forms of nonthyroidal illness, and in cases of starvation and malnutrition, TSH concentrations decrease despite the low T₄ and T₃ concentrations. The TSH response to exogenous thyrotropin-releasing hormone (TRH) is blunted within 24 hours of onset of nonthyroidal illness while TSH pulsatility and the normal nocturnal TSH surge are both impaired, suggesting an effect of nonthyroidal
illness on both the pituitary gland and hypothalamus. During recovery from nonthyroidal illness, TSH may rise transiently to levels above normal.

MECHANISM OF ALTERED THYROID FUNCTION

Several possible mediators of nonthyroidal illness have been suggested. Most promising are some of the known mediators of the inflammatory response, particularly members of the interleukin family. Both interleukin-1 and tumor necrosis factor-alpha (TNF-α) mimic almost all of the features of nonthyroidal illness, including reduced thyroid hormone and TSH concentrations, a blunted TSH response to TRH injection, and impaired thyroid hormone deiodination. In addition, TNF-α concentrations show a close correlation with T₃ concentrations in several studies of nonthyroidal illness. However, the precise role of these and other potential mediators remains speculative.

CASE PRESENTATION

Initial Presentation

A psychiatrist refers a 19-year-old woman to an endocrinologist following the discovery of a suppressed TSH concentration.

History

The patient has a 5-year history of intermittent weight loss and secondary amenorrhea. On entry to high school at age 14, the patient weighed 150 lb, which she currently refers to as being “obese.” She began dieting and exercising intensely at that time, losing 30 lb in 1 year. Her weight then stabilized. Just over a year later, following the death of her grandmother, the patient began losing weight again. A year later she had lost another 20 lb, prompting her mother to bring her to the family physician for the first time. The physician obtained a history of secondary amenorrhea dating from age 15 and diagnosed anorexia and possible bulimia. After several attempts to encourage weight gain, including dietetic advice, the patient was referred to a psychiatrist for further assessment and management. The psychiatrist noted a prominent thyroid gland and ordered a test of TSH level, which was returned “suppressed.” She has very little body fat, her hair is dry and slightly brittle, and her nails are ridged. Although her breasts are small and atrophic, the patient has otherwise normal female secondary sexual characteristics. No other clinical signs of hyperthyroidism are noted, but the thyroid is clearly visible and easily palpated. No masses are felt within the gland.

Laboratory Evaluation

Hormone function testing reveals the following results:

- Luteinizing hormone (LH), 0.8 IU/L (normal, 1.2 to 5.0 IU/L [follicular phase])
- Follicle-stimulating hormone (FSH), 0.5 IU/L (normal, 1.0 to 5.0 IU/L [follicular phase])
- Estradiol, 35 pg/mL (normal, 50 to 400 pg/mL [adult premenopausal])
- Prolactin, 10 ng/mL (normal, 4 to 30 ng/mL)
- Cortisol, 15 µg/dL (normal, 7 to 25 µg/dL [morning])
- TSH, 0.01 µU/L (normal, 0.3 to 5.0 µU/L)
- FT₄, 0.8 ng/dL (normal, 0.8 to 1.8 ng/dL)
- Total T₃, 48 ng/dL (normal, 80 to 180 ng/dL)
- TPOAb, 5 U/L (normal, less than 10 U/L)

What is the differential diagnosis for this patient?

This patient’s findings on history and physical examination are strongly suggestive of anorexia nervosa. Furthermore, her low T₄, low-normal T₃, and suppressed TSH levels are all features of nonthyroidal illness and support the clinical diagnosis of anorexia nervosa with malnutrition and secondary amenorrhea.

Although weight loss and amenorrhea are consistent with thyrotoxicosis—a diagnosis suggested by the patient’s suppressed TSH level—none of the other clinical or biochemical parameters support the diagnosis of thyrotoxicosis in this patient. A suppressed TSH indicates thyrotoxicosis only when the hypothalamic-pituitary feedback mechanism is intact. Hypothalamic or pituitary disease—including tumors, infarction, and trauma—may disrupt this mechanism, and the discovery of apparently inappropriate TSH suppression requires further assessment. The presence of a prominent thyroid gland in a young woman likely reflects her weight loss and the absence of subcutaneous fat.

The patient also presents with some clinical features suggestive of tissue hypothyroidism. In particular, her...
cold intolerance, fatigue, dry skin, and hair and nail changes all are consistent with a hypothyroid state. Although the TSH concentration is suppressed, both T₄ and T₃ concentrations are low, consistent with secondary hypothyroidism, a pattern also seen in central hypothyroidism caused by pituitary destruction. The limited ability to determine thyroid status at a tissue level remains one of the major barriers to understanding the impact of nonthyroidal illness. Several tissuespecific markers of thyroid hormone action are directly correlated with T₃ concentrations in nonthyroidal illness, suggesting that at least some tissues experience true hypothyroidism. Whether this tissue hypothyroidism is protective or destructive remains unknown.

Finally, the finding of hypogonadotrophic hypogonadism (ie, low concentrations of the gonadotropins LH and FSH and a low concentration of estradiol) and a low TSH level raise the possibility of hypopituitarism, making assessment of the remaining pituitary axes (particularly the corticotroph) essential. A low-dose cosyntropin stimulation test and magnetic resonance imaging (MRI) of the pituitary gland may be necessary.

- What further evaluation is needed to permit definitive treatment of this patient?

The endocrine abnormalities associated with anorexia nervosa reflect hypothalamic dysfunction and frequently result in nonthyroidal illness and hypogonadotrophic hypogonadism. In some cases, the normal diurnal variation in cortisol secretion also is impaired, and failure of cortisol suppression in response to low-dose dexamethasone may lead to a false suspicion of Cushing’s disease. The workup for this patient should include a complete endocrine evaluation, including static and dynamic hormone testing and MRI scanning of the pituitary gland. In addition, the endocrinologist should perform a thorough evaluation of the patient’s nutritional status. This evaluation may include bone densitometry to assess the impact of prolonged hypogonadism and malnutrition on bone metabolism. Beyond the endocrine status of the patient, the impact of malnutrition requires an evaluation of hepatic synthetic function (prothrombin time and albumin), cardiac status (echocardiography, electrocardiography, and chest radiography), and—most importantly—psychiatric assessment and management.

In addition to the thyroid function studies previously noted, this patient may require further assessment of her possible goiter. Measurement of thyroid iodine uptake may provide evidence of normal or slightly suppressed gland function consistent with the clinical findings, whereas ultrasonography may be useful in defining the volume and anatomy of the gland.

**DIAGNOSIS OF CASE PATIENT**

The endocrinologist orders a pituitary MRI scan, which proves normal, and bone densitometry, which shows T scores of −2.1 and −1.8 at the hip and spine, respectively. An echocardiogram also is ordered, which is normal. Nutritional assessment confirms low total caloric intake with abnormal food choices, and a registered dietitian’s assessment is anorexia nervosa. The endocrinologist returns the patient to her psychiatrist for ongoing management with a recommendation to consider an oral contraceptive for estrogen replacement therapy, but no other specific endocrine replacement.

- Should this patient have been placed on thyroid hormone replacement?

Most patients with nonthyroidal illness who recover from their underlying illness also experience prompt recovery of the hypothalamic-pituitary-thyroid axis, with no specific therapy indicated for their thyroid function. In several animal models of nonthyroidal illness, the infusion of T₃ promotes improved cardiovascular function and survival. In a few cases, however, thyroid hormone administration may actually prove to be harmful.

Few human studies of thyroid hormone replacement in nonthyroidal illness have been performed. In a small number of patients with nonthyroidal illness caused by various underlying illnesses, intravenous T₄ resulted in a more prolonged suppression of TSH and delayed the increase in T₃ during recovery from illness, perhaps impairing the recovery of the thyroid axis. Because T₄ to T₃ conversion is impaired in nonthyroidal illness, T₃ replacement may be a more logical therapeutic intervention than T₄ replacement. This approach was undertaken in an uncontrolled open-label study, in which 10 patients undergoing cardiopulmonary bypass showed improved cardiac function following T₃ infusion. A subsequent double-blind, placebo-controlled, prospective study of 142 patients undergoing coronary artery bypass surgery confirmed improved cardiac output and lower systemic vascular resistance, but no difference was seen in outcomes. In contrast, intravenous T₃ administration in 211 patients undergoing high-risk coronary artery surgery had no impact on any hemodynamic variable and failed to alter the need for postoperative inotropic support, time in intensive care, or time to hospital dismissal. In summary, no convincing, consistent evidence exists of therapeutic benefit from the administration of thyroid hormone to patients with nonthyroidal illness. Further trials are certainly justified and necessary, but will be large and difficult to perform.
The patient is started on oral contraceptives. Two years later, she has gained 18 lb, and her thyroid function has returned to normal. She remains under psychiatric monitoring.

**CASE RESOLUTION**

The patient is started on oral contraceptives. Two years later, she has gained 18 lb, and her thyroid function has returned to normal. She remains under psychiatric monitoring.

**THYROID HORMONE RESISTANCE SYNDROME**

Thyroid hormone action is thought to be entirely dependent on the binding of T3 to its receptor, with consequent alteration in the affinity of the receptor for its DNA binding sites (Figure 2). This causes changes in gene transcription, with both positive and negative regulation of gene transcription having been reported in a variety of systems.

Abnormalities of the T3 receptor have been described in which ligand (T3) binding is impaired, causing reduced T3 sensitivity. These abnormalities result in variable degrees of resistance to thyroid hormone and reflect inherited germ line mutations of the T3 receptor gene. Homozygous nonsense mutations resulting in a nonfunctional T3 receptor are lethal in utero, and it is the heterozygous mutations that have largely been described in humans. The severity of the disease correlates with the degree of inhibition of thyroid hormone binding in laboratory assays.

Resistance to thyroid hormone (RTH) may be generalized or isolated only to the pituitary gland or peripheral tissues. Although still exceptionally rare, the most common is generalized RTH. The mechanism by which pituitary RTH and peripheral tissue RTH might arise remains unclear, as the same gene is responsible for the thyroid hormone receptor in all tissues, including the pituitary gland. Nevertheless, several distinct clinical entities have been described and remain unexplained.

**CASE PRESENTATION**

**Initial Presentation**

A 51-year-old woman is referred to an endocrinologist by her primary care physician for a second opinion regarding her difficulty controlling her thyroid hormone requirements.

**History**

The patient was diagnosed with hyperthyroidism 6 years ago based on the presence of a goiter and an elevated total T4 concentration. No TSH level was drawn at that time. The diagnosis was made after the patient complained to her primary care physician of poor sleep; she recalls few other symptoms from that time. The internist had referred her to a radiologist, who measured iodine uptake and found it to be elevated at 29% (normal, 8% to 24%). The radiologist administered radioactive iodine (dose unknown) for presumed Graves’ disease. Subsequently, the patient became hypothyroid, confirmed by a decreased T4 concentration and an elevated TSH level. The patient was prescribed levothyroxine (100 µg/day) and returned to the care of her primary physician. She continues to complain of fatigue, lethargy, cold intolerance, constipation, and dry skin, and her TSH remains persistently elevated despite gradual increases in her daily thyroid hormone dosage, which is currently at 200 µg. Her physician has suspected poor compliance, which the patient has denied. As a result, the patient requested a second opinion regarding thyroid hormone replacement.

**Physical Examination**

The patient is distressed and concerned. Her skin is dry and cool, pulse is 63 bpm, and reflexes are present but slow to relax. She appears mildly hypothyroid, with myxedematous facial features. The thyroid gland is not palpable.

**Laboratory Evaluation**

Results of thyroid function testing are as follow:

- TSH, 22.4 µU/mL (normal, 0.3 to 5.0 µU/mL)
• FT₄, 2.0 ng/dL (normal, 0.8 to 1.8 ng/dL)
• Total T₃, 212 ng/dL (normal, 80 to 180 ng/dL)
• TPOAb, 0 U/L (normal, less than 10 U/L)

**What is the differential diagnosis for this patient?**

This patient has clinical evidence of thyroid hormone under-replacement, including her cool dry skin, sluggish reflexes, and myxedematous features. Hypothyroidism also is supported by her elevated TSH level. The T₄ and T₃ concentrations appear to be inappropriate to the clinical setting and high TSH level, since they are well above normal range. This would be more suggestive of over-replacement.

The most common cause of this pattern of clinical and biochemical findings is intermittent administration of levothyroxine, which typically is the result of variable compliance. Because it takes some time for TSH to respond to changes in thyroid hormone concentrations, a patient who intermittently takes levothyroxine may exhibit persistently elevated TSH levels (the true reflection of thyroid status) but have normal or even elevated thyroid hormone concentrations in the hours following ingestion of the hormone.

Among patients who previously have not been treated with thyroid ablation, a pattern of this type should raise the question of a TSH-secreting pituitary adenoma. This rare condition is associated with increased production of thyroid hormones driven by TSH stimulation. Most of these cases are associated with TSH values within or close to the normal range, but higher concentrations occasionally are seen. However, these patients often exhibit signs and symptoms of thyroid hormone excess rather than hypothyroidism. Nevertheless, the possibility of a TSH-secreting pituitary adenoma should be considered in the differential diagnosis of any patient with a goiter, elevated thyroid hormone concentrations, and inappropriately detectable or elevated TSH.

The possibility of a laboratory error also should be considered in the setting of test results that do not appear to be compatible. Each of the thyroid hormones is measured routinely by immunologically based assays, and all are prone to error if binding between the antibody and the analyte is altered. One common example is the presence in the serum of anti-mouse antibodies, which can interfere with the binding of TSH to the mouse monoclonal antibodies used in many commercial TSH assay systems. In a two-site assay, this can result in spuriously elevated TSH measurements.

However, the most likely diagnosis in the case patient is generalized RTH. The original history of goiter with elevated thyroid hormone concentrations, except in the absence of any thyrotoxic symptoms, is consistent with this diagnosis. Both the goiter and the minimally increased iodine uptake can result from generalized RTH due to the increased functional requirement from the otherwise healthy gland. Following thyroid ablation, the development of hypothyroid signs and symptoms, despite apparently normal or elevated thyroid hormone concentrations, is strongly suggestive of generalized RTH.

**What further evaluation is required?**

Confirmation of the diagnosis can be made in most cases by sequencing the thyroid hormone receptor, an assay that is not yet routinely available except in a research setting. In the future, this test will become increasingly available to practicing clinicians. In the meantime, exclusion of other causes of elevated TSH with normal thyroid hormone concentrations is required. Many laboratories are capable of screening patient serum for anti-mouse antibodies to exclude the rare case of inaccurate TSH measurements. However, this may require that the endocrinologist discuss this possibility with the clinical biochemist. MRI of the pituitary gland should be performed to exclude a TSH-secreting pituitary adenoma. Most are detectable on MRI, although tiny microadenomas have been reported.²⁷

**How should this patient be treated?**

This patient needs an increased dose of levothyroxine. She is both clinically and biochemically hypothyroid despite apparently good compliance with her thyroid hormone therapy. Ultimately, both the diagnostic confirmation and the treatment involve providing adequate thyroid hormone replacement.

**CASE RESOLUTION**

The endocrinologist orders a pituitary MRI scan, which proves normal. Repeat TSH assay after stripping the serum of anti-mouse antibodies reveals an almost identical TSH result. Sequencing of the T₃ receptor gene is undertaken in an affiliated research laboratory, confirming a mutation in exon 9 of the β-thyroid hormone receptor. Subsequent in vivo analysis confirms altered T₃ binding of this mutant receptor form. Family screening is offered to the patient, and her 12-year-old daughter also exhibits the mutation. Clinical assessment reveals the daughter to be euthyroid but with a “generous” thyroid. Advice is given to ensure that thyroid screening is based principally on TSH and that treatments directed at the thyroid are avoided except under close scrutiny of an experienced endocrinologist.
While the results of the sequencing data are pending, the patient is treated with an increased dose of levothyroxine (250 µg/day). Her symptoms rapidly improve and the TSH level decreases to 6.5 µU/mL. A further increase to 275 µg/day is well tolerated and the TSH normalizes to 3.1 µU/mL. The patient remains well 4 years later on a stable dose of thyroid hormone, with no hypo- or hyperthyroid symptoms.

REFERENCES