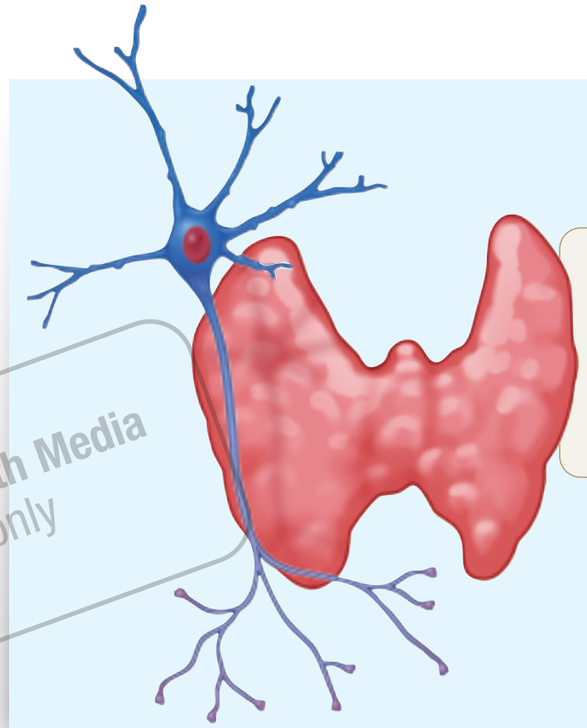
Current PSYCHIATRY

Identifying hyperthyroidism's psychiatric presentations

Think thyroid in workup of anxiety, depression, or mania

Thomas D. Geracioti, Jr, MD
Research service
Cincinnati Veterans Affairs Medical Center
Department of psychiatry
University of Cincinnati College of Medicine
Cincinnati, OH



The brain has among the highest expression of thyroid hormone receptors of any organ, and neurons are often more sensitive to thyroid abnormalities than are other tissues.

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Ms. A experienced an anxiety attack while driving home from work, with cardiac palpitations, tingling of the face, and fear of impending doom. Over the following 3 months she endured a "living hell," consisting of basal anxiety, intermittent panic attacks, and agoraphobia, with exceptional difficulty even going to the grocery store.

A high-functioning career woman in her 30s, Ms. A also developed insomnia, depressed mood, and intrusive ego-dystonic thoughts. These symptoms emerged 10 years after a subtotal thyroidectomy for hyperthyroidism (Graves' disease).

Hyperthyroidism's association with psychiatric-spectrum symptoms is well-recognized (*Box 1, page 86*).[1-4] Hyperthyroid patients are significantly more likely than controls to report feelings of isolation, impaired social functioning, anxiety, and mood disturbances[5] and are more likely to be hospitalized with an affective disorder.[6]

Other individuals with subclinical or overt biochemical hyperthyroidism self-report above-average mood and lower-than-average anxiety.[7]

Ms. A's is the first of three cases presented here to help you screen for and identify thyrotoxicosis (thyroid and nonthyroid causes of excessive thyroid hormone). Cases include:

- recurrent Graves' disease with panic disorder and residual obsessive-compulsive disorder (Ms. A)
- undetected Graves' hyperthyroidism in a bipolar-like mood syndrome with severe anxiety and cognitive decline (Ms. B)
- occult hyperthyroidism with occult anxiety (Mr. C).

These cases show that even when biochemical euthyroidism is restored, many formerly hyperthyroid patients with severe mood, anxiety, and/or cognitive symptoms continue to have significant residual symptoms that require ongoing psychiatric attention.[6]

MS. A: ANXIETY AND THYROTOXICOSIS

Ms. A was greatly troubled by her intrusive ego-dystonic thoughts, which involved:

- violence to her beloved young children (for example, what would happen if someone started shooting her children with a gun)
- bizarre sexual ideations (for example, during dinner with an elderly woman she could not stop imagining her naked)
- paranoid ideations (for example, "Is my husband poisoning me?").

She consulted a psychologist who told her that she suffered from an anxiety disorder and recommended psychotherapy, which was not helpful. She then sought endocrine consultation, and tests showed low-grade overt hyperthyroidism, with unmeasurably low thyroid stimulating hormone (TSH) concentrations and marginally elevated total and free levothyroxine (T4). Her levothyroxine replacement dosage was reduced from 100 to 50 mcg/d, then discontinued.

Without thyroid supplementation or replacement, she became biochemically euthyroid, with TSH 1.47 mIU/L and triiodothyronine (T3) and T4 in mid-normal range. Her panic anxiety resolved and her mood and sleep normalized, but the bizarre thoughts remained. The endocrinologist referred her to a psychiatrist, who diagnosed obsessive-compulsive disorder. Ms. A was effectively treated with fluvoxamine, 125 mg/d.

Discussion. Many patients with hyperthyroidism suffer from anxiety syndromes,[8-10] including generalized anxiety disorder and social phobia (*Table 1, page 89*). "Nervousness" (including "feelings of apprehension and inability to concentrate") is almost invariably present in the thyrotoxicosis of Graves' disease.[11]

Hyperthyroidism-related anxiety syndromes are typically complicated by major depression and cognitive decline, such as in memory and attention.[9] Thus, a pituitary-thyroid workup is an

Box 1

Excess thyroid hormone's link to psychiatric symptoms

The brain has among the highest expression of thyroid hormone receptors of any organ,[1,2] and neurons are often more sensitive to thyroid abnormalities—including overt or subclinical hyperthyroidism and thyrotoxicosis, thyroiditis, and hypothyroidism[3]—than are other tissues.

Hyperthyroidism is often associated with anxiety, depression, mixed mood disorders, a hypomanic-like picture, emotional lability, mood swings, irritability/edginess, or cognitive deterioration with concentration problems. It also can manifest as psychosis or delirium.

Hyperthyroidism affects approximately 2.5% of the U.S. population (~7.5 million persons), according to the National Health and Nutrition Examination Survey (NHANES III). One-half of those afflicted (1.3%) do not know they are hyperthyroid, including 0.5% with overt symptoms and 0.8% with subclinical disease.

NHANES III defined hyperthyroidism as thyroid-stimulating hormone (TSH) <0.1 mIU/L with total thyroxine (T4) levels either elevated (overt hyperthyroidism) or normal (subclinical hyperthyroidism). Women are at least 5 times more likely than men to be hyperthyroid.[4]

important step in the psychiatric evaluation of any patient with clinically significant anxiety (*Box 2, page 90*).[3]

CNS hypersensitivity to low-grade hyperthyroidism can manifest as an anxiety disorder before other Graves' disease stigmata emerge. Panic disorder, for example, has been reported to precede Graves' hyperthyroidism by 4 to 5 years in some cases,[12] although how frequently this occurs is not known. Therefore, re-evaluate the thyroid status of any patient with severe anxiety who is biochemically euthyroid. Check yearly, for example, if anxiety is incompletely resolved.

CAUSES OF HYPERTHYROIDISM

Approximately 20 causes of thyrotoxicosis and hyperthyroxinemia have been characterized (*see Related resources*).[11,13-15] The most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and toxic thyroid adenoma. Another is thyroiditis, such as from lithium or iodine excess (such as from the cardiac drug amiodarone). A TSH-secreting pituitary adenoma is a rare cause of hyperthyroidism.[16]

A drug-induced thyrotoxic state can be seen with excess administration of exogenous thyroid hormone. This condition usually occurs inadvertently but is sometimes intentional, as in factitious disorder or malingering.

Graves' disease is an autoimmune disorder that occurs when antibodies (thyroid-stimulating hormone immunoglobulins) stimulate thyroid TSH receptors, increasing thyroid hormone synthesis and secretion. Graves' disease—seen in 60% to 85% of patients with thyrotoxicosis—is the most common cause of hyperthyroidism.[15]

Patients most often are women of childbearing years to middle age. Exophthalmos and other eye changes are common, along with diffuse goiter. Encephalopathy can be seen in Graves' disease and Hashimoto's thyroiditis because the brain can become an antibody target in autoimmune disorders.

Toxic multinodular goiter consists of autonomously functioning, circumscribed thyroid nodules with an enlarged (goitrous) thyroid, that typically emerge at length from simple (nontoxic) goiter—characterized by enlarged thyroid but normal thyroid-related biochemistry. Onset is typically later in life than Graves' disease.[11,17]

Thyrotoxicosis is often relatively mild in toxic multinodular goiter, with marginal elevations in T4 and/or T3. Unlike in Graves' disease, ophthalmologic changes are unusual. Tachycardia and weakness are common (*Table 2, page 91*).

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Adenomas. Toxic thyroid adenoma is a hyperfunctioning ("toxic") benign tumor of the thyroid follicular cell. A TSH-secreting pituitary adenoma is a rare cause of hyperthyroidism.[16]

Thyroid storm is a rare, life-threatening thyrotoxicosis, usually seen in medical or surgical patients. Symptoms include fever, tachycardia, hypotension, irritability and restlessness, nausea and vomiting, delirium, and possibly coma.

Psychiatrists rarely see these cases, but propranolol (40 mg initial dose), fluids, and swift transport to an emergency room or critical care unit are indicated. Antithyroid agents and glucocorticoids are the usual treatment.

Thyrotoxic symptoms from thyroid hormone therapy. Thyroid hormone has been used in psychiatric patients as an antidepressant supplement,[18] with therapeutic benefit reported to range from highly valuable[19] to modestly helpful or no effect.[20] In some patients thyroid hormone causes thyrotoxic symptoms such as tachycardia, gross tremulousness, restlessness, anxiety, inability to sleep, and impaired concentration.

Patients newly diagnosed with hypothyroidism can be exquisitely sensitive to exogenous thyroid hormone and develop acute thyrotoxic symptoms. When this occurs, a more measured titration of thyroid dose is indicated, rather than discontinuing hormone therapy. For example, patients whose optimal maintenance levothyroxine dosage proves to be >100 mcg/d might do better by first adapting to 75 mcg/d.

Thyroid hormone replacement can increase demand on the adrenal glands of chronically hypothyroid patients. For those who develop thyrotoxic-like symptoms, a pulse of glucocorticoids—such as a single 20-mg dose of prednisone (2 to 3 times the typical daily glucocorticoid maintenance requirement)—is sometimes very helpful. Severe eye pain and periorbital edema has been reported to respond to prednisone doses of 120 mg/d.[13]

Table 1
Psychiatric symptoms seen with hyperthyroidism

Anxiety
Apathy (more often seen in older patients)
Cognitive impairment
Delirium
Depression
Emotional lability
Fatigue
Hypomania or mania
Impaired concentration
Insomnia
Irritability
Mood swings
Psychomotor agitation
Psychosis

MS. B: HYPERTHYROIDISM AND MOOD

Ms. B, age 35, an energetic clerical worker and fitness devotee, developed severe insomnia. She slept no more than 1 hour per night, with irritability, verbal explosiveness, "hot flashes," and depressed mood. "Everything pisses me off violently," she said.

She consulted a psychiatrist and was diagnosed with major depression. Over a period of years, she was serially prescribed selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and older-generation sedating agents including trazodone and amitriptyline. She tolerated none of these because of side effects, including dysphoric hyperarousal and cognitive disruption.

"They all made me stupid," she complained.

Zolpidem, 20 mg at night, helped temporarily as a hypnotic, but insomnia recurred within weeks. Diazepam was effective at high dosages but also

Box 2

Lab testing for hyperthyroidism

Serum TSH is a sensitive screen. Low (<0.1 mIU/mL) or immeasurably low (<0.05 mIU/mL) circulating TSH usually means hyperthyroidism. A TSH screen is not foolproof, however; very low TSH can be seen with low circulating thyroid hormones in central hypothyroidism or in cases of laboratory error.

The recommended routine initial screen of the pituitary-thyroid axis in psychiatric patients includes TSH, free T4, and possibly free T3.[3] Suppressed TSH with high serum free T3 and/or free T4 (accompanied by high total T4 and/or T3) is diagnostic of frank biochemical hyperthyroidism. If circulating thyroid hormone concentrations are normal, hyperthyroidism is considered compensated or subclinical. Although only free thyroid hormones are active, total T4 and total T3 are of interest to grossly estimate thyroid hormone output.

When you identify a thyrotoxic state, refer the patient for an endocrinologic evaluation. Antithyroid antibodies are often positive in Graves' disease, but anti-TSH antibodies (which can be routinely ordered) are particularly diagnostic. If thyroid dysfunction is present—especially if autoimmune-based—screening tests are indicated to rule out adrenal, gonadal, and pancreatic (glucose regulation) dysfunction.

dulled her cognition. The psychiatrist did not suspect a thyroid abnormality and did not perform a pituitary-thyroid laboratory evaluation.

Ms. B consulted a gynecologist, who prescribed estrogen for borderline low estradiol levels and with the hope that Ms. B's symptoms represented early menopause. This partially ameliorated her irritability, possibly because estradiol binding of circulating T4 reduced free thyroid hormone levels.

Ms. B tried to continue working and exercising, but within 4 years her symptoms progressed to severe depression with frequent crying spells, feelings of general malaise, excessive sweating, occasional panic attacks, fatigue, sleepiness, deteriorating vision, and cognitive impairment. She struggled to read printed words and eventually took sick leave while consulting with physicians.

Finally, a routine thyroid screen before minor surgery revealed an undetectable TSH concentration. Further testing showed elevated thyroxine consistent with thyrotoxicosis. Graves' disease was diagnosed, and euthyroidism was established with antithyroid medication.

Residual mood and anxiety symptoms persisted 1 year after euthyroidism was restored, and Ms. B sought psychiatric consultation.

Discussion. Hyperthyroidism can trigger or present as a hypomania or manic-like state, characterized by increased energy, hyperactivity, racing thoughts, hair-trigger verbal explosiveness, and decreased need for sleep.

Hypertalkativeness is common, even without pressured speech, as is irritability. Mood may be elevated, depressed, mixed, or cycling. A hyperthyroidism-related mixed syndrome of depression and hypomania can be confounding.

MR. C: OCCULT HYPERTHYROIDISM

Mr. C, age 26, was apparently healthy when he was admitted into a neuroendocrine research protocol as a volunteer. His job performance was excellent, and his interactions with others were good; he was in good general health and taking no medication.

Formal psychiatric screening found no history of psychiatric disorders in Mr. C nor his family. His mental status was within normal limits. Physical exam revealed no significant abnormality. He was afebrile, normotensive, and had a resting pulse of 81 bpm.

His neurologic status was unremarkable, and laboratory screening tests showed normal CBC, liver and renal profiles, glucose, platelets and clotting times. Tests during the study, however, showed frankly elevated T4, free thyroxine (FT4), and T3 concentrations, along with undetectable TSH. Mr. C was informed of these results and referred to an endocrinologist.

Graves' disease was diagnosed, and Mr. C received partial thyroid ablation therapy. He later reported that he had never felt better. In retrospect, he realized he had been anxious before he was treated for hyperthyroidism because he felt much more relaxed and able to concentrate after treatment.

Discussion. Subjective well-being in a patient with occult biochemical thyrotoxicosis can be misleading. Mr. C was much less anxious and able to concentrate after his return to euthyroidism.

TREATMENT

Refer your hyperthyroid patients to an endocrinologist for further work-up and, in most cases, management. Hyperthyroidism is usually easy to treat using a form of ablation (antithyroid drugs, radioactive iodine, or partial thyroidectomy).

Remain involved in the patient's care when psychiatric symptoms are prominent, however, as they are likely to persist even after thyrotoxicosis is corrected.[6] Reasonable interventions include:

- control of acute thyrotoxic symptoms such as palpitations and tremulousness with propranolol, 20 to 40 mg as needed, or a 20-mg bolus of prednisone (especially if thyroiditis is present)
- address mood cycling, depression, edginess, anxiety, lability, insomnia, and/or irritability with lithium[3]
- oversee smoking cessation in patients with Graves' disease (smoking exacerbates the autoimmune pathology).

Address and correct hyperthyroidism that is artifactual (caused by overuse or secret use by a patient) or iatrogenic (related to excessive prescribed hormone dosages).

Subclinical hyperthyroidism can be transient and resolve without treatment. Lithium can be helpful when a mood disorder coexists with sub-

Table 2

Nonpsychiatric symptoms seen with hyperthyroidism

Metabolic
Heat intolerance (cold tolerance)
Increased perspiration
Weight loss (despite good appetite)
Endocrinologic
Goiter (enlarged thyroid gland)
Ophthalmologic
Exophthalmos
Lid lag
Stare/infrequent blinking
Ophthalmoplegia
Neurologic
Tremor
Hyperreflexia
Motor restlessness
Proximal muscle weakness/myopathy
Cardiologic
Tachycardia
Palpitations
Arrhythmia
Worsening or precipitation of angina, heart failure
Sexual
Oligomenorrhea/amenorrhea
Rapid ejaculation
Dermatologic
Warm, moist skin
Fine hair
Velvety skin texture
Onycholysis
Myxedema/leg swelling
Ruddy or erythemic skin/facial flushing
Eyelash loss
Hair loss
Premature graying (Graves' disease)
Pruritus
Gastrointestinal
Frequent bowel movements
Diarrhea
Nausea
Orthopedic
Osteopenia or osteoporosis

Related resources

- For comprehensive tables of hyperthyroidism's causes, refer to Pearce EN. Diagnosis and management of thyrotoxicosis. *BMJ* 2006;332:1369-73, or Lazarus JH. Hyperthyroidism. *Lancet* 1997; 349:339-43.
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DRUG BRAND NAMES

Fluvoxamine • Luvox
Lithium • Lithobid, others
Levothyroxine • Synthroid, others
Prednisone • Various brands
Propranolol • Inderal
Zolpidem • Ambien

DISCLOSURE

Dr. Geracioti reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

clinical hyperthyroidism. Start with 300 to 600 mg every evening with dinner. If the mood disorder is mild, even as little as 300 to 450 mg of lithium may elevate a depressed mood and remove edginess and irritability.

Lithium is antithyroid, decreases thyroid hormone output, and increases serum TSH within 24 hours of initiation, but it can provoke autoimmune hyperthyroidism in some individuals.[21]

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Hyperthyroidism-related anxiety is often complicated by major depression and cognitive decline. A pituitary-thyroid workup is important in the psychiatric evaluation of any patient with clinically significant anxiety. Refer hyperthyroid patients for endocrinologic management, but remain involved in treating those with prominent psychiatric symptoms.

Bottom Line