Identifying hyperthyroidism’s psychiatric presentations

Think thyroid in workup of anxiety, depression, or mania

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 (M.s. A)
• undetected Graves’ hyperthyroidism in a bipolar-like mood syndrome with severe anxiety and cognitive decline (M.s. B)
• occult hyperthyroidism with occult anxiety (M.r. 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.

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, including generalized anxiety disorder and social phobia (Table 1, page 86). Hyperthyroid patients are significantly more likely than controls to report feelings of isolation, impaired social functioning, anxiety, and mood disturbances and are more likely to be hospitalized with an affective disorder.

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

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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.

### CAUSES OF HYPERTHYROIDISM

Approximately 20 causes of thyrotoxicosis and hyperthyroxinemia have been characterized (see Related resources). 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.

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.

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.

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).

### Excess thyroid hormone’s link to psychiatric symptoms

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

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, 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.
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 valuable19 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

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

Psychiatric symptoms seen with hyperthyroidism

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Apathy (more often seen in older patients)</th>
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</thead>
<tbody>
<tr>
<td>Cognitive Impairment</td>
<td>Delirium</td>
</tr>
<tr>
<td>Depression</td>
<td>Emotional lability</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Hypomania or mania</td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Irritability</td>
<td>Mood swings</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>Psychosis</td>
</tr>
</tbody>
</table>

Continued from page 86
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. 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.

Nonpsychiatric symptoms seen with hyperthyroidism

Metabolic

- Heat intolerance (cold tolerance)
- Increased perspiration
- Weight loss (despite good appetite)

Endocrinologic

- Exophthalmos
- Hair loss
- Premature graying (Graves’ disease)

Ophthalmologic

- Exophthalmos
- Goiter (enlarged thyroid gland)

Cardiologic

- Frequent bowel movements
- Gastrointestinal

- Premature graying (Graves’ disease)

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Orthopedic

- Osteopenia or osteoporosis

Table 2

Nonpsychiatric symptoms seen with hyperthyroidism

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Endocrinologic</th>
<th>Ophthalmologic</th>
<th>Cardiologic</th>
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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 thyroidec-tomy). If circulating TSH 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.

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.

His neurologic status was unremarkable, and physical exam revealed no significant abnormality. He was afibrile, normotensive, and had a resting pulse of 81 bpm.

Mr. C’s doctor found no history of psychiatric disorders in Mr. C nor his family. His men- tal status was within normal limits. Physical exam revealed no significant abnormality. He was afibrile, 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.

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Hyperthyroidism

Related resources

- Pearce EN. Diagnosis and management of thyrotoxicosis. BMJ 2006;332:1369-73.

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 serotonergic activity. A pituitary adenoma is mild, even as little as 300 to 450 mg of lithium may elevate a depressed mood and remove edginess and irritability.

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.

References