Hypothyroidism is a clinical state of thyroid hormone deficiency that may have a primary or secondary (central) cause. Primary hypothyroidism, which is more common than secondary hypothyroidism, is defined as failure of the thyroid gland to respond appropriately to thyroid-stimulating hormone (TSH) produced in the anterior pituitary gland. Primary hypothyroidism can be caused by autoimmune disease ( Hashimoto disease ), iodine deficiency, or infiltrative diseases, or it can be caused iatrogenically by surgery or irradiation of the gland. Subclinical hypothyroidism refers to mildly increased TSH levels in the setting of normal thyroxine ( T_{4} ) and triiodothyronine ( T_{3} ) levels. Secondary hypothyroidism is defined as insufficient thyroid gland stimulation by the hypothalamus or pituitary gland.

What new information does this article provide?
This article provides a simple and concise review of the varied physical and neuropsychiatric presentations of hypothyroidism and important diagnostic and treatment information.

What are the implications for psychiatric practice?
Hypothyroidism presents with a myriad of neuropsychiatric signs and symptoms. It is therefore imperative that psychiatrists are aware of the varied presentations of hypothyroidism and the appropriate assessment of laboratory tests of thyroid function and the basic treatment options.

Drugs commonly associated with thyroid dysfunction include lithium and amiodarone. Lithium has an antithyroid effect that can cause hypothyroidism at any point in treatment, which may not reverse with discontinuation of the lithium. Valproate and carbamazepine have also been found to decrease T_{4} levels in patients treated long-term.\(^1\)

The prevalence of hypothyroidism in the US general population is estimated to be 1 in 300 persons; however, rates of hypothyroidism are higher in certain populations.\(^2\) Hypothyroidism is 10 times more common in women than in men, but with increasing age, it becomes more common in persons of both sexes. Higher rates of hypothyroidism have been found in hospitalized patients in both medical and psychiatric settings than in the general public.\(^3\) Subclinical hypothyroidism is even more common and occurs in 4.3% to 8.5% of the general US population.\(^2,6\) Populations with a higher risk of hypothyroidism include postpartum women and persons with a family history, previous head or neck surgeries, endocrine conditions such as diabetes, and nonendocrine autoimmune disorders such as multiple sclerosis.

Signs and symptoms
The somatic signs and symptoms of hypothyroidism are varied and nonspecific ( Table 1 ). A majority of these signs and symptoms may be linked to a decreased rate of metabolism and the accumulation of glucosaminoglycans associated with low levels of circulating thyroid hormones. Although the signs and symptoms of hypothyroidism are nonspecific, certain symptoms, such as cold intolerance, dry skin, constipation, muscle cramps, and fatigue, may have increased specificity for the disease. The severity of the presenting complaints and physical findings usually reflects the degree of hypothyroidism. However, the presenting signs and symptoms of thyroid deficiency may vary with patient age and acuity of onset. Since the symptoms of hypothyroidism are nonspecific, many other illnesses can present with similar symptoms. The differential is broad, depending on the specific symptoms ( Table 2 ).

**CASE VIGNETTE**
Sandra is a 37-year-old woman with well-controlled type 1 diabetes mellitus who presents with depressed mood. In addition to her affective complaint, the patient endorses worsening fatigue and...
impaired concentration. A comprehensive review of symptoms reveals constipation, dry skin, cold intolerance, and weight gain. Routine vital signs indicate a mild asymptomatic bradycardia. A TSH test and a complete blood cell count are ordered. No pharmacotherapy is initiated. Laboratory evaluation shows mild normocytic anemia and an abnormally elevated TSH level. A second serum TSH test and a free T\(_4\) measurement are ordered. The serum TSH level remains elevated, and the free T\(_4\) level is abnormally low. Clinical primary hypothyroidism is diagnosed. Levothyroxine supplementation is initiated and the patient’s affective and somatic signs and symptoms slowly resolve along with the patient’s hypothyroid state.

Thyroid dysfunction is known to cause a variety of neuropsychiatric symptoms, including mood disorders, psychosis, and cognitive dysfunction. However, the mechanism by which thyroid hormone causes psychiatric disturbance is not fully understood. In the brain, the active form of thyroid hormone, T\(_3\), binds to nuclear receptors, which are widely distributed, and alters gene transcription. Thyroid receptors located in the limbic system are theorized to cause the psychiatric manifestations of hypothyroidism.\(^7\)

**Affective disorders.** Depressed mood is a well-known and accepted symptom of hypothyroidism. Clinical symptoms such as poor concentration, weight changes, memory issues, and poor energy are common overlapping symptoms of depression and hypothyroidism, so routine screening in depressed patients is prudent. In fact, approximately 40% of patients with clinical hypothyroidism have significant depressive symptoms.\(^6\)

The connection between subclinical hypothyroidism and depressed mood is more controversial. Some studies have found higher frequency and severity of depression in patients who have subclinical hypothyroidism than in euthyroid individuals.\(^9\) There is also evidence that subclinical hypothyroidism can negatively affect the treatment of depression by interfering with antidepressant response.\(^10\)

Hypothyroidism can also present with mania. While mania is an uncommon presentation for hypothyroidism, several cases have been described.\(^11,12\) In these cases, the mania has resolved with thyroid replacement. There are also case reports of aggressive titration of levothyroxine causing secondary mania.\(^13\)

There appears to be a relationship between bipolar disease and hypothyroidism. Antithyroid peroxidase antibodies have been found at higher rates in patients who have bipolar disorder than in the general public.\(^14\) Treatment of hypothyroidism in patients with rapid cycling bipolar disorder has been found to decrease the severity and frequency of manic episodes.\(^15\)

**Psychosis.** Classic myxedema madness was first described by Asher\(^16\) in 1949 in a case series of patients with severe hypothyroidism and psychosis. While myxedema madness most typically presents as delirium, psychotic symptoms secondary to hypothyroidism may present in a patient who does not have altered consciousness or cognitive impairment. In fact, an array of psychotic symptoms, including delusions, visual and auditory hallucinations, paranoia, and thought disorders, have been reported secondary to hypothyroidism.\(^17\)

Psychosis does not necessarily appear to be related to the severity of the thyroid dysfunction because psychosis has been reported in both clinical and subclinical hypothyroidism.\(^18\) While psychosis can be the presenting symptom that brings a patient to clinical attention, it typically occurs late in the disease course.

**Cognitive dysfunction.** Cognitive impairment is common in hypothyroidism and can range from mild to severe. Deficits vary from impaired concentration and slowed processing speed to general declines in intelligence, psychomotor speed, visual-spatial skills, and memory. Cognitive deficits associated with hypothyroidism tend to be more pronounced in the elderly. In fact, hypothyroidism is thought to be one of the reversible causes of dementia, and therefore a screening TSH test is indicated in all dementia workups. However, severe hypothyroidism that has progressed to dementia is not always fully reversible, even after appropriate treatment.
Diagnostic testing/workup

If thyroid dysfunction is suspected clinically, the preferred initial test is serum TSH. If the serum TSH level is abnormal, the TSH should be rechecked along with a free T₄ level. The results of these laboratory tests will allow the classification of the patient’s thyroid condition (Table 3). Primary hypothyroidism is diagnosed when the TSH level is elevated and the free T₄ level is low. Subclinical hypothyroidism is the diagnosis when the TSH level remains high on repeated testing and the free T₄ level is found to be in the normal range. A low serum free T₄ level combined with a low, or inappropriately normal, TSH level likely represents secondary hypothyroidism.

If the laboratory evaluation reveals primary hypothyroidism and the thyroid gland is normal on physical examination, additional laboratory testing or imaging is usually unnecessary. However, in the case of subclinical hypothyroidism, repeated testing of TSH and free T₄ levels in 4 to 6 months is appropriate, because TSH levels may either spontaneously normalize or progress to those indicative of clinical hypothyroidism. The risk of progression of subclinical hypothyroidism may be greatest for those patients with serum TSH levels higher than 10 mIU/L. In addition, measurement of antithyroid peroxidase antibodies may prove useful in the context of subclinical hypothyroidism, because elevated levels of antithyroid peroxidase antibodies predict an increased risk of progression to primary hypothyroidism at a later date. In patients with evidence of secondary hypothyroidism, measurement of additional pituitary hormones, MRI of the sellar region, and referral to endocrinology are appropriate.

Treatment

The initial treatment of neuropsychiatric symptoms of hypothyroidism should be directed at correcting the underlying thyroid deficiency. Thyroxine replacement is usually effective for resolving all the signs and symptoms of hypothyroidism, although the time course to resolution is very individual.

However, if the neuropsychiatric symptoms are significant, symptomatic treatment may be appropriate. For example, antipsychotics are often used in an attempt to acutely manage psychotic symptoms secondary to hypothyroidism until the underlying hypothyroid state is corrected. Patients with hypothyroidism complicated by affective or cognitive disturbance should have their hypothyroidism treated before starting psychotropic medications. If after appropriate levothyroxine treatment the patient remains symptomatic, appropriate pharmacotherapy may be initiated. Psychiatric medications should be dosed low and titrated slowly when used in patients with hypothyroidism.

Primary hypothyroidism. The goal of treatment is to resolve the signs and symptoms of hypothyroidism by returning the patient to the euthyroid state. This most frequently necessitates lifelong thyroid hormone replacement. There are many thyroid hormone preparations available for treatment of hypothyroidism. Levothyroxine is identical to the T₄ produced by the thyroid. It is the preferred medication for thyroid replacement because it has a long half-life, thereby allowing once-a-day dosing and minimal fluctuations in serum levels.

The starting dosage of levothyroxine in healthy adults younger than 60 years with primary hypothyroidism is 1.6 μg/kg of ideal body weight daily. In older patients and patients with coronary artery disease, the starting dosage of T₄ should be lower (25 to 50 μg/d)—the dose should be titrated slowly to avoid cardiac complications. The average replacement dosage ranges from 100 to 150 μg/d in women and from 125 to 200 μg/d in men. After initiation of appropriate therapy, the manifestations of hypothyroidism usually resolve over weeks to months.

-Thyroid hormone is a synthetic form of the T₃ hormone. Its use is complicated by a short half-life that requires multiple daily doses and results in peak concentrations that are often supraphysiologic, which may lead to adverse effects.
Levothyroxine and -triiodothyronine combination treatment has been tried, but a meta-analysis of combined therapy versus levothyroxine monotherapy for treatment of clinical hypothyroidism failed to find any additional benefit of combined treatment in improving quality of life and depressive symptoms.\(^\text{19}\)

Subclinical hypothyroidism. Treatment of patients with subclinical hypothyroidism is a controversial clinical issue and deserves consultation with the patient’s primary care physician or endocrinologist. Treatment should be considered for patients with a TSH level greater than 10 mIU/L (given associated adverse physiological effects and risk of progression to primary hypothyroidism) and for patients with elevated antithyroid peroxidase antibody titers (given an increased rate of conversion to primary hypothyroidism). In addition, patients with TSH levels of 5 to 10 mIU/L coupled with symptoms suggestive of hypothyroidism may benefit from levothyroxine therapy. Patients with subclinical hypothyroidism may require only 25 to 50 μg/d of levothyroxine supplementation, given the mild nature of the associated thyroxine deficiency.

**Monitoring treatment**

After initiating treatment with hormone replacement, the effectiveness of treatment should be monitored by measuring the serum TSH level in 8 to 12 weeks. This allows time for the pituitary-thyroid axis to reset and reflects the current state of circulating thyroid hormones. The biochemical goal of treatment is to keep the patient’s TSH level within the lower half of the normal range.

If, on follow-up testing, the TSH level is found to be high or low, the dosage of levothyroxine will need to be increased or decreased. The TSH level should be rechecked 2 months after any dose adjustment. Once the patient is euthyroid, the serum TSH should be checked in 6 months because metabolism of levothyroxine may be increased compared with the hypothyroid state. Thus, the initial dose of levothyroxine may be inadequate to maintain a euthyroid state.

**Summary**

Hypothyroidism is a common clinical disorder that psychiatrists frequently encounter. However, symptoms of thyroid dysfunction are often vague and nonspecific, which can lead to delayed or missed diagnosis. Thyroid dysfunction can cause an array of physical and neuropsychiatric disturbances and, thus, early diagnosis and treatment are important for reducing morbidity. Psychiatric symptoms can be the initial presentation of thyroid dysfunction. Psychiatrists must have a high degree of suspicion for potential underlying, exacerbating, or treatment-related thyroid disorders.

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**Table 1: Hypothyroidism**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Delays in visual processing</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>Constipation</td>
</tr>
<tr>
<td>Enlargement of tongue</td>
<td>Cold intolerance</td>
</tr>
<tr>
<td>Headache</td>
<td>Dry skin</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Numbness</td>
</tr>
<tr>
<td>Palpitations, tachycardia</td>
<td>Dry, itchy skin</td>
</tr>
</tbody>
</table>

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**Table 2: Differential diagnosis for hypothyroidism**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
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<td>Lyme disease</td>
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</table>

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**Table 3: Classifying hypothyroidism by laboratory**

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TSH level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Low</td>
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</tbody>
</table>

| TSH, thyrotropin-stimulating hormone, T, thyroid |
Disclosures:
Dr Estabrook is a Psychosomatic Medicine Fellow in the department of psychiatry and behavioral medicine, and Dr Heinrich is Associate Professor in the department of psychiatry and behavioral medicine and the department of family and community medicine at the Medical College of Wisconsin in Milwaukee. The authors report no conflicts of interest concerning the subject matter of this article.

References:


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