

Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited

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Hypothyroidism is a medical condition commonly encountered in a variety of clinical settings. The clinical presentations of thyroid hormone deficiency are diverse, complicated, and often overlooked. Hypothyroidism is a potential etiology for multiple somatic complaints and a variety of psychological disturbances. The physical complaints are primarily related to metabolic slowing secondary to lack of thyroid hormone. Psychiatric presentations include cognitive dysfunction, affective disorders, and psychosis. The realization that hypothyroidism might be the potential etiology of an assortment of symptoms is critical in the identification and treatment of the hypothyroid patient. Once hypothyroidism is identified, symptoms usually respond to appropriate thyroid hormone supplementation. This article presents a case of clinical hypothyroidism that came to clinical attention due to psychotic symptoms consisting of auditory and visual hallucinations. The case is followed by a brief discussion of the literature describing the relationship of hypothyroidism and psychiatric symptomatology. References were identified with an English language-based MEDLINE search (1966–2003) using the terms *thyroid*, *hypothyroid*, *depression*, *dementia*, *delirium*, *mania*, *bipolar disorder*, *psychosis*, and *myxedema* and utilization of referenced articles.

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Hypothyroidism, the clinical syndrome resulting from a deficiency in thyroid hormone, is a common problem encountered in the clinical setting. Deficiencies in thyroid hormone can produce numerous deleterious effects on the human body. The manifestations of hypothyroidism are varied and, to a large measure, age dependent. These abnormalities may range from global developmental abnormalities to acute metabolic derange-

ment. Hypothyroidism is usually represented in the literature as a stereotypical cluster of symptoms, most typically fatigue, cold intolerance, dry skin, hair loss, menstrual irregularities, and constipation. Commonly recognized signs may include hoarse voice, bradycardia, nonpitting edema, facial puffiness, slow speech, and delayed relaxation phase of the deep tendon reflexes. In addition, psychiatric disorders often accompany hypothyroidism. Mental status examination of a hypothyroid patient may reveal a broad spectrum of dysfunction, ranging from mild attentional impairment to significant agitated delirium or psychosis.

The onset of signs and symptoms of hypothyroidism is often subtle and develops gradually. This progression is particularly true in the elderly, in whom presenting signs and symptoms can be both insidious and diverse and are often attributed to aging. Hypothyroidism is a common disorder with highly variable presentations; no predictable progression of symptoms is apparent. Accordingly, diagnosis may be difficult at times without a high degree of suspicion. It is with this diversity of presentation in mind that we discuss a case of clinical hypothyroidism that came to medical attention due to signs and symptoms of psychosis. We also briefly summarize the literature, reviewing the relationship between hypothyroidism and various psychiatric presentations. References were identified with an English language-based MEDLINE search (1966–2003) using the terms *thyroid*, *hypothyroid*, *depression*, *dementia*, *delirium*, *mania*, *bipolar disorder*, *psychosis*, and *myxedema* and utilization of referenced articles.

CASE REPORT

Ms. A, a 73-year-old woman without known significant past medical history, presented with a 2-week history of auditory and visual hallucinations. The patient had apparently not sought medical attention since the birth of her last daughter 30 years prior to this presentation. She had always been noted by family members to be somewhat reclusive but still engaged in many normal activities. One year prior to presentation, she was noted to have decreasing vision in her left eye, first at night and then progressing to decreased vision during the day. Her vision loss slowly progressed over the year and eventually began to involve both eyes. The patient continued to refuse

medical care primarily related to a compelling fear of hospitals. In the 2 weeks before her presentation, she was noted by family to have developed some auditory hallucinations that she described as a voice inside her head telling her a variety of things; most notably she would hear voices of game show hosts or radio announcers. These symptoms persisted, and she started to note visual hallucinations as well. She had also resisted medical care for these issues but was finally convinced on the day of admission to seek medical attention as her visual and auditory hallucinations had worsened.

At the emergency department, Ms. A's vital signs included a temperature of 97.7°F (36.5°C), a pulse of 60 beats/min, and blood pressure of 175/89 mm Hg. Findings of her physical examination were remarkable for dry skin with dry and brittle hair. Findings of her heart and lung examinations were unremarkable, and she had a normal-size thyroid gland. Her neurologic examination was notable for normal strength in all extremities with a significant delay in the relaxation phase of her deep tendon reflexes. She was awake, alert, and conversant but with notable auditory hallucinations during the examination.

The patient was admitted to the hospital for further workup. Ensuing evaluation revealed laboratory values remarkable for a thyroid-stimulating hormone (TSH) level of 43.79 $\mu\text{U/mL}$, repeat TSH level of 53.13 $\mu\text{U/mL}$ (reference range: 0.50–5.00 $\mu\text{U/mL}$), thyroxine (T_4) level of less than 1.0 $\mu\text{g/dL}$ (reference range: 4.5–10.9 $\mu\text{g/dL}$), and total triiodothyronine (T_3) level of 24 ng/dL (reference range: 60–181 ng/dL). A noncontrast enhanced head computed tomography study showed mild small-vessel ischemic changes and no other abnormalities. A subsequent magnetic resonance imaging study of her brain revealed nonspecific periventricular white matter changes. The patient was started on low-dose thyroid replacement therapy. She was also started on a low dose of risperidone to treat the hallucinations. Her auditory and visual hallucinations slowly began to disappear, and, by 2 to 3 weeks into therapy, the patient had no further psychiatric symptoms.

Ms. A self-discontinued risperidone after 2 weeks with no reoccurrence of her psychiatric symptoms. Her loss of bilateral vision was thought to be due to dense cataracts, which were confirmed on further examination by the neuro-ophthalmology service and were removed, with subsequent return of her vision. At follow-up, Ms. A remained stable and euthyroid on thyroid replacement and an antihypertensive regimen. Ms. A was able to resume all regular activities with her family without apparent sequelae.

HISTORICAL NOTES

The study of hypothyroidism in the later half of the 19th century provides an impressive account of scientific

exploration and discovery. William Gull first described adult hypothyroidism in 1874 during an address to the Clinical Society of London.¹ A few years later, William Ord coined the term “myxedema” to describe the nonpitting edema he observed in some patients with hypothyroidism.² This event was followed by the first reported effective treatment of hypothyroidism—with sheep thyroid extract—by George Murray in 1891.³

In 1888, the Committee on Myxedema of the Clinical Society of London first linked hypothyroidism with psychosis. The Committee reported on 109 patients with myxedema and noted that “delusions and hallucinations occur in nearly half the cases, mainly where the disease is advanced” (p. 31).⁴ Asher reiterated the relationship between psychosis and hypothyroidism in 1949 and added the terminology “myxedema madness” to the literature.⁵ Since that time, numerous case reports have continued to explore and report on the diverse physical and psychiatric consequences of hypothyroidism.^{6–8}

PREVALENCE

The prevalence of hypothyroidism ranges from 0.5% to 18%, depending on the study population.⁹ The pathophysiology of hypothyroidism can include hypothalamic or pituitary disease, tissue resistance to thyroid hormone, and disorders directly affecting the thyroid gland.

Hypothyroidism is more common in older women than in younger women and 10 times more common in women than in men. In general, hypothyroidism affects 4% to 10% of women, increasing with age.¹⁰ A significant proportion of individuals have asymptomatic chronic autoimmune thyroiditis, and 8% of women (10% of women over age 55 years) and 3% of men have subclinical hypothyroidism; the disease is also more prevalent in hospitalized patients.^{11,12} In one study of an elderly inpatient population, 4.9% had primary hypothyroidism, 8.2% had secondary hypothyroidism, and 17.9% had sick euthyroid syndrome.¹³ A comprehensive medical history and physical examination can uncover signs and symptoms that may help confirm the diagnosis of hypothyroidism.

ETIOLOGY

Hypothyroidism is a clinical state resulting from a deficiency of thyroid hormone. The pathogenesis of hypothyroidism is classically divided into primary hypothyroidism, secondary hypothyroidism, and iatrogenic hypothyroidism. Primary hypothyroidism results from a failure of the thyroid gland to respond appropriately to TSH released from the pituitary gland. Primary hypothyroidism has several potential causes: (1) failure of the thyroid after Hashimoto's thyroiditis, (2) atrophy of the thyroid after autoimmune attack, (3) iatrogenic destruction of the gland by surgery or radioactive iodine, and (4) overtreatment

with antithyroid medication. Secondary hypothyroidism is quite rare and results from disease of the pituitary gland, in which the pituitary gland fails to respond appropriately to falling levels of T_4 and releases inadequate amounts of TSH.

A variety of drugs can produce hypothyroidism. Lithium, a medication used in the treatment of bipolar disorder, is one such agent.¹⁴ Lithium's effect on the thyroid can occur at any stage of treatment. It has a reversible antithyroid effect, thereby leading to hypothyroidism. If hypothyroidism does occur, lithium may be discontinued or thyroid hormone replacement initiated. Overtreatment of hyperthyroidism with an antithyroid drug can produce hypothyroidism with concurrent psychiatric disturbance.¹⁵ Amiodarone, an antiarrhythmic agent, contains iodine and may, therefore, also lead to hypothyroidism.¹⁶

HYPOTHYROID PRESENTATIONS

Psychiatric Signs and Symptoms

The hypothyroid patient may, among the earliest and most prominent signs or symptoms, report psychiatric symptoms.¹⁷ At times, the psychiatric presentation may be so striking that patients are first diagnosed with a primary psychiatric disturbance rather than hypothyroidism.¹⁸ The association between thyroid deficiency and psychiatric presentation is not infrequent and is commonly overlooked as an etiology for behavioral, affective, and cognitive changes.

Many symptoms of psychological dysfunction have been described with hypothyroidism. Those symptoms most commonly related to thyroid deficiency include forgetfulness, fatigue, mental slowness, inattention, and emotional lability. The predominant affective disorder experienced is depression. Perceptual changes may develop with alterations of taste, hearing, and vision. Delusions and hallucinations may also occur as the disease progresses. No correlation, however, appears to exist between the degree of thyroid dysfunction and psychiatric symptoms that subsequently develop.¹⁹

The prevalence of neuropsychiatric sequelae of thyroid deficiency is related to the fact that most hormones present in the human body are represented in the central nervous system. The hormones are present either through synthesis within the central nervous system or through synthesis at a point distant and admission across the blood-brain barrier. The brain appears to have a unique sensitivity to thyroid hormone and to utilize thyroid hormone differently than other organ systems.^{20,21} Hormone receptors are located within neural networks throughout the brain. High concentrations of T_3 receptors are found in the amygdala and hippocampus.²² These receptors, in turn, are able to influence neural activity. The effects of thyroid dysregulation on brain function are variable at different stages of life. The thyroid is important for both

the maturation of the central nervous system and the maintenance of homeostasis.

There are a few studies that point to the importance of T_4 in the activity of the brain. For example, it has been demonstrated that in hypothyroidism the utilization of available thyroid hormone favors the brain.²³ The neurobehavioral effect of T_4 on the brain may be related to its action on neurotransmitters. It has been shown that in rats rendered hypothyroid, for example, an increase in cerebral dopamine is observed along with an increase in tyrosine hydroxylase activity.²⁴ Hyperthyroid rats, however, display a decrease in brain tyrosine hydroxylase activity.²⁵

Psychosis

Traditionally, lethargy and lassitude were thought to be the typical psychiatric manifestations of hypothyroidism.² Studies have shown, however, that 5% to 15% of myxedematous patients have some form of psychosis.²⁶ Asher described the classic manifestations of hypothyroid-induced psychosis in 1949.⁵ Although Asher's study of 14 patients and resulting description of myxedema madness has been often cited as a typical example of psychosis secondary to hypothyroidism, subsequent case reports have revealed considerable variation in clinical psychotic presentations.^{27,28} For example, a case of Capgras syndrome, a delusion that a significant other has been replaced by an identical appearing imposter, has been reported in a patient suffering from myxedema.²⁹ As a result, no typical constellation of psychotic symptoms is likely in the myxedematous patient. Manifestations of thought disorders reported include delusions, visual hallucinations, auditory hallucinations, perseveration, loose associations, and paranoia. These psychotic symptoms can occur without the impaired level of consciousness seen in delirium or the cognitive deficits of dementia.

Psychosis typically emerges after the onset of physical symptoms, often after a period of years or months.³⁰ Disorders of thought may occur in patients with either clinical or subclinical hypothyroidism, which suggests that psychosis may be unrelated to the absolute degree of thyroid hormone deficit.³¹

Affective Disorders

Depression has been the major affective illness described in hypothyroid patients. It has long been recognized that there is a strong relationship between thyroid disorders, particularly hypothyroidism, and disturbance in mood. Most patients suffering from a depressive disorder have normal thyroid function.³² A minority, however, do have laboratory evidence of thyroid perturbation. In one study, 20% of patients with prominent depressive symptoms had detectable titers of antithyroid antibodies compared with 5% to 10% of the general population.³³ This relationship between thyroid dysfunction and depression is apparent in both clinical and subclinical forms of hypo-

thyroidism. Approximately 40% of clinically hypothyroid patients have significant signs and symptoms of depression.³⁴ The relationship between subclinical hypothyroidism and depression remains somewhat more controversial, although evidence suggesting a relationship between treatment-resistant depression and subclinical hypothyroidism appears more firmly established. In a meta-analysis performed by Howland,³⁵ approximately 50% of patients with refractory depression had evidence of subclinical hypothyroidism compared with 8% to 17% in an unselected population of depressed patients. In addition, treatment-resistant depression has been shown to respond to thyroid hormone supplementation without laboratory investigation revealing evidence of thyroid malfunction.³⁶ In patients suffering from major depression, subclinical hypothyroidism may make them less responsive to antidepressant treatment.³⁷ The risk of suicide must also be addressed in patients suffering from an affective illness regardless of etiology. Parker reported on a patient in 1935 who, while suffering from myxedema and depression, jumped to his death from a tall building.³⁸

The etiologic relation between thyroid hormone deficiency and depression remains theoretical, but a few intriguing hypotheses have been proposed. The concept that a central pathologic factor in the development of depression is a central serotonergic deficiency may be linked to hypothyroidism by the findings that brain serotonin levels correlate positively with T_3 levels in the rat, i.e., serotonin synthesis is reduced in hypothyroid states.³⁹ Another hypothesis proposes that depressive symptoms represent a state of relative cerebral hypothyroidism.⁴⁰ The active thyroid hormone in the brain is T_3 . The relative hypothyroidism localized to the brain may be secondary to inhibited activity of the type II 5-deiodinase enzyme, which is responsible for the conversion of T_4 to T_3 .⁴¹ The relationship of depression, brain catecholamine deficiency, and thyroid function may be observed by the finding that T_3 levels are found in increased concentrations in the noradrenergic nuclei and their projection sites within the rat's central nervous system.⁴²

An association between bipolar disorder and hypothyroidism has also been proposed. Clinical and subclinical hypothyroidism may adversely affect the course of bipolar disorder. In a recent study of patients in a depressive phase of bipolar I disorder, it was found that lower values of free T_4 index and higher levels of TSH, both of which were within the normal range, were significantly associated with a slower response to treatment.⁴³ Hypothyroidism may also serve as a risk factor for the development of the rapid-cycling form of bipolar disorder. Antithyroid antibody titers have been found in up to 50% of rapid-cycling bipolar patients.⁴⁴ Another study, although complicated by the patients' concurrent use of lithium, revealed overt hypothyroidism in 12 of the 24 rapid-cycling bipolar patients and none of the 19 non-rapid-cycling pa-

tients.⁴⁵ Reus⁴⁶ noted that hypothyroidism may cause a kindling-type of action, which could account for its ability to reduce seizure threshold and potentially induce rapid-cycling bipolar disorder. Treatment of refractory bipolar disorder⁴⁷ and rapid-cycling bipolar disorder⁴⁸ with thyroid hormone has also been reported effective in open trials. Management of hypothyroidism, whether clinical or subclinical, in patients with an affective illness is imperative.

Cognitive Disorders

Cognitive dysfunction also may be a result of hypothyroidism. A review of the literature performed by Dugbartey⁴⁹ revealed that the cognitive deficits most commonly associated with hypothyroidism include psychomotor slowing, deficits in memory, visuo-perceptual skills, and constructional dexterity. Cognitive decline due to thyroid deficiency may represent dementia and has traditionally been characterized as one of the reversible causes of dementia. Prompt recognition and treatment may reverse the cognitive and functional deficits. It is important to be aware, however, that the impairment may not be entirely reversible. Haggerty et al.⁵⁰ reported on 2 cases in which irreversible cognitive impairment developed secondary to "marginal" hypothyroidism that may have existed for up to 1 year prior to discovery and treatment. Furthermore, a review of the literature on dementia caused by hypothyroidism found little evidence to suggest that thyroid supplementation leads to complete resolution of the cognitive deficits.⁵¹

Physical Signs and Symptoms

Hypothyroidism can present with a variety of physical signs and symptoms, mostly related to slowing of the metabolic process secondary to lack of effects of thyroid hormone. Fatigue, cold intolerance, slow speech, weight gain, delayed deep tendon reflexes, and bradycardia are all symptoms that result from a slowing of metabolic processes. The skin can become pale and cool secondary to decreased blood flow. Dryness and roughness of the skin can result from the atrophied cellular layer as well as hyperkeratosis accompanied by a yellowish skin discoloration from carotenemia. The hair can be coarse and brittle along with decreased sweating from decreased acinar gland secretion. In severe disease, nonpitting edema (myxedema) can occur from infiltration of the skin with glycosaminoglycans with associated water retention. Enlargement of the tongue and hoarseness can also result from a buildup of matrix glycosaminoglycans in the interstitial spaces.

Hypothyroidism can also result in a number of cardiac manifestations including reduced cardiac output resulting in shortness of breath and decreased exercise compliance with no symptoms of heart failure. Hypertension can result from increased peripheral resistance. A decrease in

cholesterol metabolism can also result in hypercholesterolemia. Hypoventilation from respiratory muscle weakness can further exacerbate shortness of breath. One of the most common complaints in patients with hypothyroidism is constipation secondary to decreased gut motility. Patients may also report a moderate weight gain secondary to a decreased metabolic rate. A neurologic examination may show decreased central nervous system function. Other neurologic findings include delayed relaxation phase of deep tendon reflexes and carpal tunnel syndrome.

A number of laboratory abnormalities may also occur, including a normochromic normocytic anemia secondary to a decreased red blood cell mass. Antiparietal cell antibodies may cause gastric atrophy, resulting in a pernicious anemia. Hyponatremia may also develop from a reduction in free water clearance.

DIAGNOSTIC EVALUATION

Laboratory Testing

Initial evaluation of the patient with suspected hypothyroidism usually begins with a measurement of the TSH level. The TSH level is the most sensitive test for detecting primary hypothyroidism. The free T_4 level is also important in distinguishing primary and secondary hypothyroidism. Primary hypothyroidism is usually diagnosed when a patient has a high TSH level and a low T_4 level. A low free T_4 level in the setting of a serum TSH level that is low, normal, or only mildly elevated is indicative of central hypothyroidism. An elevated TSH level in the setting of a normal free T_4 level is more often seen in subclinical hypothyroidism. A free T_4 level can be calculated by measuring a total T_4 and T_3 resin uptake, by measuring a thyroid hormone binding index and calculating the T_4 , or by measuring the serum T_4 directly. There are a number of drugs that can interfere with TSH secretion and offset the utility of the test, including amiodarone, phenytoin, glucocorticoids, metoclopramide, and other dopamine antagonists. Also, in acutely or chronically ill hospitalized patients, there are a number of issues that may affect TSH secretion.

EEG, PET, and SPECT Studies

The electroencephalogram (EEG) has been used to study patients with psychiatric manifestations of hypothyroidism with varied findings. The most often cited EEG finding is a reduction in alpha wave activity. The decrease has been shown to resolve with treatment and return to a euthyroid state.⁵² Positron emission tomography (PET) studies have revealed a generalized decrease in cerebral blood flow and cerebral glucose metabolism in hypothyroidism of short duration.⁵³ A single photon emission computed tomography (SPECT) study on a patient with dementia secondary to hypothyroidism revealed dif-

fuse cerebral hypoperfusion that reversed after symptom resolution.⁵⁴

TREATMENT

Thyroid Replacement

Thyroid replacement is the cornerstone of hypothyroidism treatment. Patients may receive either synthetic T_4 or a combination of T_3 and T_4 . Synthetic T_4 is usually given orally, and once-daily treatment is sufficient given the relatively long half-life of T_4 (7 days). The prohormone T_4 is converted peripherally to T_3 , which has a much higher affinity for T_3 receptors than T_4 and is thus the active form of the hormone. The replacement dose of T_4 is approximately 1.6 $\mu\text{g}/\text{kg}$, but older patients and those with cardiovascular conditions should probably be started on a lower dose.⁵⁵ After starting replacement thyroid hormone therapy, the TSH level should be measured in 3 to 6 weeks and the dosage adjusted accordingly. Successful treatment with thyroid replacement usually reverses the effects of hypothyroidism, although the psychiatric and neurologic sequelae may take longer to resolve. Some patients may benefit from treatment with a combination T_3 and T_4 , particularly those with mood and neuropsychological symptoms.⁵⁶

Psychiatric Treatment

As mentioned previously, appropriate thyroid replacement usually results in gradual improvement and eventual resolution of the psychiatric manifestations of hypothyroidism. Whenever possible, treatment should first be directed at the underlying endocrinopathy, as clearing of the psychiatric disturbance usually follows. The delusions and hallucinations that often characterize myxedema madness usually remit in about 1 week after beginning appropriate thyroid replacement.⁸ If thyroid replacement is started at too high of a dose or titrated too rapidly, an acute confusional state or exacerbation of the psychosis may occur.⁵⁷ The addition of antipsychotic medications may lead to earlier remission of psychotic symptoms than thyroid replacement alone. Case reports indicate that atypical antipsychotics initiated at a low dose appear to be well tolerated.⁵⁸ Discontinuation of thyroid supplementation may lead to the return of symptoms.⁵⁹

As mentioned earlier, delay in effective hypothyroid treatment may result in symptoms that fail to remit completely. Patients with hypothyroidism and affective disturbance should be treated first with thyroid hormone replacement. If, after euthyroid state is established, the patient continues to display a mood disturbance, the appropriate antidepressant or mood stabilizer should be started. If psychiatric medications are utilized in patients with hypothyroidism, low starting doses and gradual titration are recommended by the authors. Medication side effects should also be considered and may exacerbate the

signs and symptoms of already present endocrinopathy. If treatment is initiated carefully, most physical and mental symptoms resolve over a brief period of time. It is not uncommon, however, for patients to report that months have passed before feeling that they have returned to their normal baseline mental status.²⁶

SUMMARY

There is little doubt that thyroid hormone plays a major role in the regulation of mood, cognition, and behavior. As a result, persons with thyroid dysfunction frequently experience a wide variety of neuropsychiatric sequelae. The range of physical and psychiatric presentations and their potential subtle manifestations make hypothyroidism a diagnosis that is easy to miss. Behavioral changes may occur in the absence of the classical physical signs and symptoms of the disorder. As a result, it is imperative to remember that many patients presenting with psychiatric disorders may have alterations in endocrine function. The endocrine dysfunction may be the cause of the presenting complaint, a factor complicating the management of an underlying illness, or a consequence of treatment. Since psychiatric complaints may be one of the earliest manifestations of hypothyroidism, they are often misdiagnosed as functional psychiatric disorders, rather than a psychiatric disorder due to a general medical condition. This confusion leads to delayed treatment and a high likelihood of increased morbidity. The frequency of misdiagnosis and mistreatment and the potential for poor prognosis point to the importance of a high degree of suspicion of thyroid dysfunction and the need for thyroid screening in psychiatric patients.

Drug names: amiodarone (Cordarone), lithium (Lithobid, Eskalith), metoclopramide (Reglan and others), phenytoin (Dilantin and others), risperidone (Risperdal).

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