Psychiatric manifestations of Hashimoto’s thyroiditis

ABSTRACT: The mental symptoms associated with Hashimoto’s thyroiditis may precede the full-blown, classic picture of hypothyroidism. The psychiatric symptoms include various mental aberrations, depression, irritability, and confusion. Indeed, patients may be mislabeled as having psychotic depression, paranoid schizophrenia, or the manic phase of a manic depressive disorder. The workup must include a thorough evaluation of thyroid function, including tests for autoantibodies. Patients usually respond favorably to thyroid replacement hormone therapy.

Since Ehrlich1 first postulated the existence of self-directed antibodies to specific organs, a condition he called “horror autotoxicus,” medicine has made great strides toward understanding autoimmune disorders. In 1912, Hashimoto2 described chronic lymphocytic thyroiditis (struma lymphomatosa). Some four decades later, Roitt3 demonstrated autoantibodies to thyroglobulin. Schmidt4 defined a syndrome, later named after him, which involved the simultaneous development of lymphocytic infiltration in the thyroid and adrenal glands. More recently, Carpenter and associates5 reported the association of lymphocytic thyroiditis with similar infiltrations in both the adrenal glands and pancreatic islets.

Recent work by Neufeld and associates6 in describing and classifying the autoimmune disorders has called the clinician’s attention to the association of thyroiditis with various other conditions.

In addition to providing a useful classification of the autoimmune polyglandular syndromes, Neufeld’s group points out that the autoimmune disorders are divided into two fundamental groups: those with organ-specific autoimmunity, such as Hashimoto’s thyroiditis, and those that are systemic, in which the autoimmune process is not confined to any single organ (primarily collagen vascular diseases). In reviewing their work and the literature that supports it, we find it particularly interesting that 12 of the 14 diseases associated with autoimmune polyglandular syndromes are specifically associated with psychiatric aberrations (acquired primary hypogonadism, chronic lymphocytic thyroiditis, Graves’ disease, hypophysisis, insulinopenic diabetes, Sjögren’s syndrome, myasthenia gravis, Addison’s disease, pernicious anemia, hypoparathyroidism, malabsorption syndrome, and chronic active hepatitis).

Several authors have called at-
Hashimoto’s thyroiditis
tention to a dramatic increase in the incidence of Hashimoto’s thyroiditis (also called autoimmune thyroiditis and Hashimoto’s disease). These studies suggest that this increase is real rather than a factor of enhanced diagnostic acumen. Some authors now feel that autoimmune thyroiditis is “the most frequent thyroid disorder in our population.”

The purpose of this paper is to report selected findings from several cases of Hashimoto’s thyroiditis that presented psychiatrically, and to draw into sharper focus for practicing clinicians the diagnostic features of this condition. Before presenting the psychiatric findings, a brief review of the disorder itself is necessary.

Incidence and course
Rallison and associates found that chronic lymphocytic thyroiditis is a frequent cause of thyroid disease in children, with a prevalence of 1.2%. They noted that the disease could present as either hyperthyroidism or hypothyroidism. Ling and associates demonstrated that 65% of children with euthyroid goiters had chronic lymphocytic thyroiditis, while only 35% had simple goiter. Hashimoto’s thyroiditis is considered the most common cause of sporadic goiter in children.

The disease is from eight to ten times more common in women than men. Its incidence is highest between age 30 and 50, but it may occur during any period of life. Its course may be persistent or it may show periods of exacerbation and remission.

Presentation and findings
 Clinically, the disorder may present as classic myxedema, as a cyclic behavioral disorder, or as thyrotoxicosis (“Hashitoxicosis”). Goiter may or may not be present. If goiter does appear, its progression is usually insidious. In rare instances, the disease may present with rapid thyroid enlargement accompanied by pain and tenderness, and thus mimic de Quervain’s (subacute) thyroiditis. More typically, painless swelling occurs. Approximately one fifth of cases are clinically hypothyroid at the time of diagnosis.

Physical examination usually reveals a thyroid of moderate size, firm, freely movable, and bosseled. The gland rarely compresses adjacent structures, and regional lymph nodes are not usually enlarged. Typically, the patient is euthyroid when seen initially, with hypothyroidism developing subsequently over several years. However, patients can also present with a dramatic and rapid progression to a clinically hypothyroid state.

Related findings
Studies have shown that the disease is related to the subsequent occurrence of pernicious anemia (often in the absence of signs of overt anemia), idiopathic adrenal atrophy, Sjögren’s syndrome, rheumatoid arthritis, progressive hepatitis, systemic lupus erythematosus, myasthenia gravis, and diabetes mellitus. The association with insulinopenic diabetes is so strong that some authors recommend that thyroid microsomal antibodies be determined in all patients with this type of diabetes. It is suggested that those found to be positive should have periodic thyroid function tests and should be screened for the presence of adrenal antibodies.

Pathologic and laboratory findings
The pathophysiology of the disease is characteristic. The thyroid tissue is firm and pale. Histologically, there is a diffuse lymphocytic infiltration of the gland with fibrosis and obliteration of the thyroid follicles. The columnar epithelial cells are destroyed and the follicular basement membrane shows degeneration and fragmentation. Epithelial cells that persist are enlarged and show a characteristic oxyphilic change in the cytoplasm; interstitial tissue is infiltrated by lymphocytes and plasma cells; and lymphoid follicles with germinal centers are present.

A variety of abnormal laboratory test findings typify Hashimoto’s thyroiditis. Protein-bound iodine (PBI) levels may be high, indicating accelerated turnover in a depleted organic iodine pool; and a perchlorate discharge test may be positive, indicating a defect in the organic binding of thyroid iodine. Abnormally released iodoproteins are found in the serum. Production of a faulty thyroid hormone often causes hypersecretion of thyroid-stimulating hormone (TSH), which subsequently produces functional evidence of thyroid hyperactivity without producing the symptoms of thyrotoxicosis.

Tests of thyroid function are extremely variable depending on the staging and activity of the disease. Initially, thyroid functioning appears hyperactive, with an increased $^{131}$I uptake and a slightly elevated PBI. Tetraiodothyronine
(T₄) concentrations at this time are usually normal, producing a large PBI-to-T₄ iodine difference. These changes reflect the secretion of an abnormal iodoprotein.

As the disease progresses, the ¹³¹ I and the serum T₂ and PBI all fall into the hypothyroid range, while serum T₃ concentrations are elevated. At this time, serum TSH is usually elevated, but the TSH-stimulation test shows diminished thyroid reserve.

According to Ingbar and Woeber,¹⁶ diagnosis of Hashimoto's thyroiditis is confirmed by the presence of high titers of thyroid autoantibodies in the serum. These authors suggest that red cell agglutination and complement fixation tests are positive in virtually all patients with the disease. They also believe that most patients register a high red cell agglutination titer (i.e., greater than 1:25,000 by the tanned red cell agglutination test). A false-positive serologic test for syphilis is not unusual. Ingbar and Woeber further believe that thyroid antibody tests are at least as reliable as the findings of needle biopsy. Thus, the latter is no longer an important diagnostic tool.

In a report by Beall and Solomon,¹⁷ about 80% of patients with histologically-proven Hashimoto's thyroiditis had antithyroglobulin hemagglutinating antibodies in concentrations of greater than 1:10, and 25% had titers greater than 1:1,000. Furthermore, 80% showed positive immunofluorescence for antithyroglobulin antibodies. Anti-thyroglobulin hemagglutinating antibody titers greater than 1:1,000 were not reported in any normal subjects or in patients surveyed who had myxedema, granulomatous thyroiditis, non-toxic nodular goiter, or thyroid carcinoma. The only condition other than Hashimoto's thyroiditis in which these IgG antibodies regularly occurred in concentrations greater than 1:1,000 was Graves' disease.

Antimicrosomal antibodies with complement fixation titers of 1:32 or higher frequently occur in pa-

These patients experienced fluctuations or alterations in their mental state for long periods before hypothyroidism was diagnosed.

patients with Hashimoto's thyroiditis. Titers of 1:4 are sometimes found in patients with other thyroid disease, but it is rare to find high titers unless the patient has Hashimoto's disease.¹⁷ Thyrotoxic antibodies to thyroid tissue have also been found in patients with Hashimoto's thyroiditis; they constitute direct evidence that the thyroid cells are disturbed by an immunologic process.¹⁸

Psychiatric manifestations

Psychiatrically, Hashimoto's thyroiditis usually presents either as a chronic insidious change in personality manifested by lability, anxiety, and withdrawal or as a progressive depression, often so gradual that it seems most compatible with a psychogenic etiology. Alternatively, the disease may present as classic "myxedema madness."¹⁹ In this case, the patient may appear to suffer from paranoid schizophrenia, psychotic depression, or manic depressive disease (manic type). The typical picture includes generalized agitation, disorientation, persecutory delusions, hallucinations, and bouts of extreme restlessness. Patients are often in a hallucinative, irritable, delusional, paranoid state with concomitant auditory and visual hallucinations. Hypersexuality may also occur during these episodes: a marked increase in sexual drive is the most characteristic feature reported.

In the more gradually progressing cases, patients may report a variety of nondescript complaints, including poorly defined abdominal or peripheral pain, lassitude, weakness, menstrual irregularities, joint aches, weight gain, and changes in hair and skin.

The following cases are representative of the types of psychiatric presentations we have seen in patients with well-documented Hashimoto's thyroiditis.

Case 1

A 34-year-old married woman began to experience unusual mental symptoms seven months after the birth of her first child. The patient's mother had been diagnosed as having hypothyroidism in her late 30s, and on at least three previous occasions, the patient had requested an evaluation for hypothyroidism. Three years before the onset of her present condition, she began complaining of fatigue, irritability, mental slowing, and weight gain. A medical evaluation revealed no objective findings of thyroid malfunction. Thyroid function studies obtained during her pregnancy were within normal limits.

For several months prior to the onset of her severe symptoms, she complained of moderate to severe depression without specific environmental precipitants. She also had what she described as "free-floating anxiety," mental sluggishness, impaired concentration and memory, weight gain, tiredness, difficulty with word-finding, and periods of episodic confusion. She had trouble sleeping at night, but
Hashimoto's thyroiditis

was often somnolent during the day. After several sleepless nights, she became increasingly suspicious, emotionally labile, intermittently hostile and clinging, and complained of racing thoughts. She had periods of lucidity during which she felt terrible, overwhelming anxiety related to forebodings that she was about to die. These periods alternated with episodes of suspiciousness when she felt that she was being poisoned—that somebody had added either amphetamines or LSD to her food. She began making a series of delusional allegations, and then expressed the need to escape from home, because she felt that someone was poisoning her. She began hallucinating and having delusions of control. After contacting her husband, she was located and admitted, in a confused state, to the hospital.

On examination she was hallucinating and appeared exhausted and confused. She complained that she was "filled with a terrible fear." At various times she was agitated, delusional, delirious, and showed signs of gross organic confusion. She had cardiac irregularities, pretibial edema, and a slowed return phase of the deep tendon reflexes. Her skin was dry and scaly, her hair, coarse. An ECG showed cardiac enlargement with diminished voltage. An EEG demonstrated generalized slowing of the brain waves. Autosomal and microsomal antibody titers were markedly elevated, and thyroid function studies indicated severe hypothyroidism. She was treated with replacement thyroid medication and chlorpromazine.

Before the metabolic nature of the patient's condition was established, she had received a variety of psychiatric diagnoses and interpretations, which included postpartum psychiatric disorder of late onset, manic depressive psychosis (manic type), and schizophrenic reaction. Following thyroid replacement therapy and a short course of supportive psychotherapy to help her adjust to the disruption of her life and to the humiliation she felt after the events that led to her hospitalization, she did quite well. During four years of follow-up observation, there have been no recurrences. The patient's condition remains well-regulated on total thyroid replacement, and her mental function is normal.

Case 2

A 35-year-old college graduate complained of depression associated with her menstrual cycles during the previous eight years. According to the patient, her menstruation left her with no physical strength or mental ability and induced a confusional state associated with loss of balance, inability to concentrate, visual disturbances, and memory loss.

During the previous 12 years, the patient noted the development of abdominal striae atrophicae (although she was quite thin), brown "blotches" over her face, deep ridges on her nails, various allergies, hair loss, and changes in the texture of her skin and hair. She experienced two episodes of depression manifested as withdrawal, mental sluggishness, and crying spells. She also had periods of hyperactivity, and marked interpersonal irritability followed by withdrawals. Further, she had intermittent constipation alternating with diarrhea, sleep disturbance with difficulty achieving and maintaining sleep, and visual hallucinations along with intermittent visual hallucinations.

Ten years before, she had seen a physician for these symptoms, and laboratory results led to a diagnosis of hypothyroidism. She was then given desiccated thyroid therapy, which produced side-effects consisting of tachycardia, restlessness, and agitation. The hormone therapy was discontinued, and repeat tests showed a normal PBI. It was assumed that the previous diagnosis of hypothyroidism was incorrect, and thyroid medication was permanently discontinued.

Five years later, she was admitted to a psychiatric hospital for depression. At that time, an EEG showed slight slowing of the brain waves. A neurologic workup was negative.

Three years before the present hospitalization, the patient attempted suicide by taking an overdose of drugs because, she explained, she did not want to live as "half a person." At this time, she noted a change in her menstrual periods. She reported a clearcut association between the onset of her menstrual periods and the worsening of her depression. During menstruation she complained of increased visual distortion and cognitive slowing. She also had increasingly frequent periods of motor retardation lasting up to ten days. She complained of unusual dreams and began to feel that "bad things" were happening to her. Intermittently, she experienced states described by various observers as hypomanic, when she became euphoric and totally unable to sleep for two to three days, and her thoughts raced. During these times she had an insatiable hunger for starches and sweets. These periods would alternate with periods of profound mental and psychomotor retardation compounded by confusion. She was finally admitted to the hospital for treatment of depression.

On admission, she had dry skin, brittle hair that was coarse and thinning, and a very slow return phase of the deep tendon reflexes. Findings of a laboratory workup were consistent with hypothyroidism; the patient had high titers of autosomal and microsomal antibodies consistent with a diagnosis of Hashimoto's thyroiditis. The EEG showed generalized paroxysms of very slow activity with no definite focal findings. Her 17-ketosteroid and 17-hydroxycorticosteroid assays were within normal limits. A computerized tomography scan (CT), brain stem-evoked potentials, visual-evoked potentials, and sleep EEG were normal except for the slowing noted above.

After several weeks of thyroid re-
placement, the patient noted stabilization of her menstrual cycle, general improvement in emotional tone, increased energy, and decreased confusion. During the next several months, she reported a return to what she considered her normal level of functioning.

Case 3
A 35-year-old male physician noticed the gradual development of periods of confusion and mild to moderate depression, which alternated with periods of anxiety, tremulousness, and increased energy. During his “hyper” periods, he experienced insomnia and episodes of apprehension and dread. He attributed these symptoms to hard work at the university where he was employed and to a variety of job changes and current academic political situations. Nevertheless, he sought a medical workup and was found to have hypothyroidism due to Hashimoto’s thyroiditis.

After he was stabilized on thyroid replacement therapy, he was able to note several interesting factors: “My illness was diagnosed in 1975 after I had taken a position on the faculty at a major university. At the time, I was clinically hypothyroid, depressed, and had difficulty in concentration and memory. I was studying for a specialty board examination and became convinced there was no way I could pass it because I could not seem to master the review material.” Several articles that he had been working on now seemed like gibberish. “Even though I had just written an article on organic brain syndrome and could well identify the subject matter, I was unaware that my difficulty was related to an organic dysfunction.”

He realized that during the five years before the diagnosis, he had experienced periods of depression lasting for several months at a time. These episodes were punctuated by periods of hyperactivity and severe anxiety, which also lasted for months. “One obvious change of hypothyroidism was my slowed mentation,” he reported. “I had always been an in-veterate reader but lost interest in reading.” A thyroid nodule was found during a physical examination two years before the diagnosis of Hashimoto’s thyroiditis, but thyroid function tests at that time were normal. Other signs preceding the diagnosis were significant weight changes, coarsening of hair, and generally decreased energy.

It took three years for the patient to become stabilized on replacement thyroid therapy. During this time he often felt “miserable” and believed he was hypothyroid. In his words, “I, like most Hashimoto’s patients, was extremely sensitive to replacement thyroid therapy and required only half the usual adult dose for the first two years.” Currently, he is taking a low replacement dose, tolerates it well, and is clinically euthyroid. His mental and emotional functions have returned to normal.

Case 4
A 33-year-old secretary became progressively tired and lethargic seven months after giving birth to her second child. She experienced intermittent cramps in her lower extremities and occasional nonspecific abdominal pains. She complained of constipation, cold intolerance, an increased need to sleep during the daytime, and evening insomnia. Her menstrual periods became scanty and irregular. She was evaluated by a local physician; thyroid function studies yielded normal results.

During the 12 to 15 months following her return to work, she noticed a progressive inability to type and spell, diminished concentration, impaired task performance, lowered frustration tolerance, and progressive mental apathy. Upon return home from work, she would “just crawl into bed.” She interacted poorly with her husband and children and reported frequent inexplicable crying episodes at home and at work. Her employer finally suggested that she seek another medical evaluation.

This time she was found to be classically hypothyroid. Thyroid function studies confirmed the diagnosis, and antibody titers were strongly positive. A diagnosis of Hashimoto’s thyroiditis was made.

Discussion
The description of these four patients highlights the difficulties that the clinician may experience in diagnosing hypothyroidism and typifies the mental reactions that commonly accompany the condition. These patients experienced fluctuations or alterations in their mental state for long periods before hypothyroidism was diagnosed. The patients in cases 1, 2, and 4 were evaluated for thyroid dysfunction several months to years before the diagnosis was confirmed. Several years prior to diagnosis, two patients (cases 1 and 2) insisted that their mental symptoms were related to a metabolic abnormality; they were carefully evaluated without confirmatory findings.

The fact that the mental changes produced by Hashimoto’s thyroiditis are insidious (cases 3 and 4) may lead the patient to attribute the altered mental state to environmental pressures. Similarly, acute presentation of the disease (case 1) may lead to a primary psychiatric diagnosis unless hypothyroidism is included in the process of differential diagnosis.

The patients in cases 1 and 2 also reported episodes of nausea and vertigo during the two years preceding the diagnosis of Hashimoto’s thyroiditis. At the time, these episodes were attributed to food poisoning or to viral labyrinthitis. The patient in case 2 also
Hashimoto's thyroiditis

complained of diminished auditory acuity before the onset of her psychiatric symptoms. Auditory acuity improved subjectively following treatment.

The four cases also illustrate that individual laboratory tests of thyroid function, such as PBI, are insufficient to make the diagnosis. Test results may be misleading, since thyroid function often fluctuates during the course of the illness. A full thyroid battery with specific evaluation for autosomal and microsomal antibody titers is in order, and the tests should be repeated in any case in which clinical suspicions persist.

The time course for recovery of these patients is also interesting, since several patients reported that it took months before they felt normal again. The persistence of various symptoms, such as slight cognitive impairment, low tolerance for frustration, and continued irritability must be recognized if the patient is to be counseled appropriately. The clinician cannot simply assume that after five days of thyroid treatment, any persistent symptoms are the result of a psychogenic process and are no longer related to the central nervous system impairment caused by thyroid deficiency. Replacement therapy must be chosen carefully, gradually built up to an appropriate level, and monitored regularly.

Because the incidence of Hashimoto's thyroiditis is increasing at a significant rate, clinicians should be aware that they are likely to see patients with this disorder who present psychiatrically.

REFERENCES