Section A-Research paper

An Overview about Hashimoto's Thyroiditis; Pathogenesis and Evaluation

Ali Ashraf Ali Mohamed[1], Eman Abdallah El-Shorbagy[1], Mohamed Gaber Hamed[1], Nahla Ibrahim Zidan[2]

1 Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
2 Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt

Email: elwa870@gmail.com

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Abstract

Background: Hashimoto thyroiditis is an autoimmune disease that destroys thyroid cells by cell and antibody-mediated immune processes. It is the most common cause of hypothyroidism in developed countries. In contrast, worldwide, the most common cause of hypothyroidism is an inadequate dietary intake of iodine. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. The pathology of the disease involves the formation of antithyroid antibodies that attack the thyroid tissue, causing progressive fibrosis. The diagnosis is often challenging and may take time until later in the disease process. The most common laboratory findings demonstrate elevated thyroid-stimulating hormone (TSH) and low levels of free thyroxine (fT4), coupled with increased antithyroid peroxidase (TPO) antibodies. However, earlier on in the course of the disease, patients may exhibit signs, symptoms, and laboratory findings of hyperthyroidism or normal values. This is because the destruction of the thyroid gland cells may be intermittent.

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Introduction:

Thyroiditis is a general term often applied to a collection of gene-linked autoimmune disorders involving production of antibodies that attack thyroid proteins, especially the peroxidase enzyme and sometimes Tgb. Thyroid cells also may be attacked by lymphocytes that are attracted by the actions of antibodies with thyroid antigens. As with all thyroid disorders, thyroiditis is more prevalent in women than in men. It is sometimes the cause of hypothyroidism that follows pregnancy due to a rebound in immune activity following suppression during pregnancy. **(1)**

Types of Thyroiditis

Thyroid glands can get inflamed due to various reasons. While an infection can cause enlarged thyroid glands, it is also possible to have thyroiditis due to autoimmune conditions, medications, and other factors. However, endocrinologists broadly demarcate thyroiditis into these categories **(2)**:

- Chronic thyroiditis caused due to autoimmune conditions (Hashimoto's thyroiditis, Graves' Disease)
- Postpartum thyroiditis that affects pregnant women after delivery (usually in the first postpartum year)
- Acute thyroiditis is caused due to infections.
- Subacute thyroiditis caused due to viral infections.
- Drug-induced thyroiditis is the reaction of certain medications.

- Radiation-induced thyroiditis.
- Riedel's thyroiditis.

Hashimoto's Thyroiditis

Hashimoto thyroiditis is an autoimmune disease that destroys thyroid cells by cell and antibody-mediated immune processes. It is the most common cause of hypothyroidism in developed countries. In contrast, worldwide, the most common cause of hypothyroidism is an inadequate dietary intake of iodine. This disease is also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis. The pathology of the disease involves the formation of antithyroid antibodies that attack the thyroid tissue, causing progressive fibrosis. The diagnosis is often challenging and may take time until later in the disease process. The most common laboratory findings demonstrate elevated thyroid-stimulating hormone (TSH) and low levels of free thyroxine (fT4), coupled with increased antithyroid peroxidase (TPO) antibodies. However, earlier on in the course of the disease, patients may exhibit signs, symptoms, and laboratory findings of hyperthyroidism or normal values. This is because the destruction of the thyroid gland cells may be intermittent. **(3)**

Women are more often affected. The female-to-male ratio is at least 10:1. Although some sources cite diagnosis happening more so in the fifth decade of life, most women are diagnosed between the ages of 30 to 50 years. Conventional treatment is comprised of levothyroxine at the recommended dose of 1.6 to 1.8 mcg/kg/day. The T4 converts to T3, which is the active form of thyroid hormone in the human body. Excessive supplementation can lead to deleterious and morbid effects, such as arrhythmias (the most common being atrial fibrillation) and osteoporosis. In this chapter, we review the pathogenesis, diagnosis, and management of Hashimoto thyroiditis. **(4)**

Etiology

The etiology of Hashimoto disease is very poorly understood. Most patients develop antibodies to a variety of thyroid antigens, the most common of which is anti-thyroid peroxidase (anti-TPO). Many also form antithyroglobulin (anti-Tg) and TSH receptor-blocking antibodies (TBII). These antibodies attack the thyroid tissue, eventually leading to inadequate production of thyroid hormone. There is a small subset of the population, no more than 10% to 15%, with clinically evident disease that are serum antibody-negative. Positive TPO antibodies presage the clinical syndrome. **(5)**

It can be part of the Polyglandular Autoimmune Syndrome type 2 with autoimmune adrenal deficiency and type-1 DM. Hashimoto thyroiditis is also related to several other autoimmune diseases, such as pernicious anemia, adrenal insufficiency, and celiac disease. It was found that Hashimoto disease is associated with a variety of different nonthyroidal autoimmune diseases (NTADs), and diagnosis in adulthood made these even more prevalent. **(6)**

Epidemiology

After age six, Hashimoto is the most common cause of hypothyroidism in the United States and in those areas of the world where iodine intake is adequate. The incidence is estimated to be 0.8 per 1000 per year in men and 3.5 per 1000 per year in women. Twin studies have shown an increased concordance of autoimmune thyroiditis in monozygotic twins as compared with dizygotic twins. Danish studies have demonstrated concordance rates of 55% in monozygotic twins, compared with only 3% in dizygotic twins. This data suggests that 79% of predisposition is due to genetic factors, allotting 21% for environmental and sex hormone influences. The prevalence of thyroid disease, in general, increases with age. **(7)**

Pathophysiology

The development of Hashimoto disease is thought to be of autoimmune origin, with lymphocyte infiltration and fibrosis as typical features. The current diagnosis is based on clinical symptoms correlating with

laboratory results of elevated TSH with normal to low thyroxine levels. It is interesting to note, however, that there is little evidence demonstrating the role of antithyroid peroxidase (anti-TPO) antibody in the pathogenesis of autoimmune thyroid disease (AITD). Anti-TPO antibodies can fix complement and, in vitro, have been shown to bind and kill thyrocytes. However, to date, there has been no correlation noted in human studies between the severity of disease and the level of anti-TPO antibody concentration in serum. We do, however, know that positive serum anti-TPO antibody concentration is correlated with the active phase of the disease. Other theories implicated immune complexes, containing thyroid directed antibodies, as culprits of thyroid destruction. **(8)**

History and Physical

The organ system manifestations of Hashimoto thyroiditis are varied due to the nature of the disease. Initially, patients may have bouts of hyperthyroid symptoms, as the initial destruction of thyroid cells may lead to the increased release of thyroid hormone into the bloodstream. Eventually, when enough destruction has been caused by the antibody response, patients exhibit symptoms of hypothyroidism. These symptoms are insidious and variable and may affect almost any organ system in the body. **(9)**

The classic skin characteristic associated with hypothyroidism is myxedema, which refers to the edema-like skin condition caused by increased glycosaminoglycan deposition. This, however, is uncommon and only occurs in severe cases. Skin can be scaly and dry, especially on the extensor surfaces, palms, and soles. Histologic examination reveals epidermal thinning. Increased dermal mucopolysaccharides cause water retention and, in turn, pale-colored skin. The rate of hair growth slows, and hair can be dry, coarse, dull, and brittle. Diffuse or partial alopecia is not uncommon. **(10)**

Decreased thyroid function can increase peripheral vascular resistance by as much as 50% to 60% and reduce cardiac output by as much as 30% to 50%. Bradycardia may result from a loss of chronotropic action of thyroid hormone directly on the sinoatrial cells. However, most patients have a few symptoms directly attributable to the cardiovascular system. **(11)**

Fatigue, exertional dyspnea, and exercise intolerance are likely associated with a combination of limited pulmonary and cardiac reserve in addition to decreased muscle strength or increased muscle fatigue. Hypothyroid rats have been shown to have decreased endurance. Biochemical changes in this population have shown decreased muscle oxidation of pyruvate and palmitate, increased utilization of glycogen stores, and diminished fatty acid mobilization. Muscle weakness and myopathy are important features. **(12)**

The presentation may also be subclinical. Early symptoms may include constipation, fatigue, dry skin, and weight gain. More advanced symptoms may include cold intolerance, decreased sweating, nerve deafness, peripheral neuropathy, decreased energy, depression, dementia, memory loss, muscle cramps, joint pain, hair loss, apnea, menorrhagia, and pressure symptoms in the neck from goiter enlargement such as voice hoarseness. **(13)**

Physical findings may include Cold and dry skin, Facial edema, particularly periorbital, as well as nonpitting edema involving the hands and feet, Brittle nails, Bradycardia, The delayed relaxation phase of tendon reflexes, Elevated blood pressure, Slow speech, Ataxia and Macroglossia. Furthermore, patients can have an accumulation of fluid in the pleural and pericardial cavities rarely. Myxoedema coma is the most severe clinical presentation and has to be managed as an endocrine emergency within patient care. **(14).**

Evaluation

Hashimoto thyroiditis is an autoimmune disorder of inadequate thyroid hormone production. The biochemical picture indicates raised thyroid-stimulating hormone (TSH) in response to low free T4. A low total T4 or free T4 level in the presence of an elevated TSH level confirms the diagnosis of primary hypothyroidism.

Integrative and functional medicine practitioners may also assess free T3 and reverse T3 levels; however, Western medicine does not use this approach. **(15).**

The presence of anti-thyroid peroxidase and anti-thyroglobulin antibodies suggests Hashimoto thyroiditis. However, 10% of patients may be antibody negative. Anemia is present in 30 to 40%. There can be decreased glomerular filtration rate (GFR), renal plasma flow, and renal free water clearance with resultant hyponatremia. Creatine kinase is frequently elevated. Prolactin levels may be elevated. Elevated total cholesterol, LDL, and triglyceride levels can occur. A thyroid ultrasound assesses thyroid size, echotexture, and whether thyroid nodules are present; however, it is usually not necessary for diagnosing the condition in the majority. **(16)**

Subacute (de Quervain's) Thyroiditis

Subacute thyroiditis is believed to be triggered by a viral infection. It occurs in two phases a hyperthyroid phase and a hypothyroid phase, followed by recovery. The hyperthyroid phase causes a patient's thyroid gland to be tender to touch and abnormally enlarged (called a goiter). **(17).**

Like Hashimoto's thyroiditis, this type of thyroiditis is more common in women, especially those in their third to fifth decade of life. Subacute thyroiditis (SAT) is an inflammatory condition of the thyroid with characteristic presentations and clinical course. Patients with the classic, painful (DeQuervain's; Granulomatous) thyroiditis, (PFSAT) typically present with painful swelling of the thyroid. Transient vocal cord paresis may occur. At times, the pain begins and may be confined to the one lobe, but usually spreads rapidly to involve the rest of the gland ("creeping thyroiditis"). Pain may radiate to the jaw or the ears. Malaise, fatigue, myalgia and arthralgia are common. A mild to moderate fever is expected, and at times a high fever of 104°F (40.0°C) may occur. **(18)**

The disease process may reach its peak within 3 to 4 days and subside and disappear within a week, but more typically, onset extends over 1 to 2 weeks and continues with fluctuating intensity for 3 to 6 weeks. The thyroid gland is typically enlarged, smooth, firm and tender to palpation, sometimes exquisitely so. Approximately one-half of the patients present during the first weeks of the illness, with symptoms of thyrotoxicosis. Subsequently patients often experience hypothyroidism before returning to normalThis painful condition lasts for a week to a few months, usually demonstrates a very high erythrocyte sedimentation rate (ESR), elevated C- reactive protein (CRP) levels and has a tendency to recur. **(19)**

Thyroid auto antibodies

Autoimmune thyroid disease (AITD) causes cellular damage and alters thyroid gland function by humoral and cell-mediated mechanisms. Cellular damage occurs when sensitized T-lymphocytes and/or autoantibodies bind to thyroid cell membranes causing cell lysis and inflammatory reactions. Alterations in thyroid gland function result from the action of stimulating or blocking autoantibodies on cell membrane receptors. Three principal thyroid autoantigens are involved in AITD. These are thyroperoxidase (TPO), thyroglobulin (Tg) and the TSH receptor. Other autoantigens, such as the Sodium Iodide Symporter (NIS) have also been described, but as yet have no diagnostic role in thyroid autoimmunity. **(20)**

TSH receptor autoantibodies (TRAb) are heterogeneous and may either mimic the action of TSH and cause hyperthyroidism as observed in Graves' disease or alternatively, antagonize the action of TSH and cause hypothyroidism. The latter occurs most notably in the neonate as a result of a mother with antibodies due to AITD. TPO antibodies (TPOAb) appear involved in the tissue destructive processes associated with the hypothyroidism observed in Hashimoto's and atrophic thyroiditis. The appearance of TPOAb usually precedes the development of thyroid dysfunction. Some studies suggest that TPOAb may be cytotoxic to the thyroid. The pathologic role of TgAb remains unclear. In iodide sufficient areas, TgAb is primarily

determined as an adjunct test to serum Tg measurement, because the presence of TgAb can interfere with the methods that quantitate Tg. In iodide deficient areas, serum TgAb measurements may be useful for detecting autoimmune thyroid disease in patients with a nodular goiter and for monitoring iodide therapy for endemic goiter. **(21)**

Laboratory tests that determine the cell-mediated aspects of the autoimmune process are not currently available. However, tests of the humoral response, i.e. thyroid autoantibodies, can be assessed in most clinical laboratories. Unfortunately, the diagnostic and prognostic use of thyroid autoantibody measurements is hampered by technical problems as discussed below. Although autoantibody tests have inherent clinical utility in a number of clinical situations, these tests should be selectively employed. **(22)**

Thyroid peroxidase antibodies (TPO Ab): raised in Hashimoto's thyroiditis (or autoimmune thyroiditis) and sometimes raised in Graves' disease. **(23)**

Thyroglobulin antibodies (Tg Ab): antibodies directed against the thyroglobulin (a protein present in the thyroid gland), from which thyroid hormones are produced. May be measured as part of the monitoring of people previously treated for thyroid cancer. Also sometimes raised in Hashimoto's thyroiditis. **(24)**

Thyroid stimulating hormone receptor antibodies (TSHR Ab, also known as TRAb). TRAb is potentially stimulatory and blocking to the thyroid gland: raised in Graves' disease. **(25)**

Thyroid Stimulating Immunoglobulin (TSI): antibody specific to Graves' disease. It is a stimulatory antibody and the one that causes an overactive thyroid gland. May be raised in Graves' disease. This is not routinely tested and used mainly as a research tool. **(26)**

TPO antibodies may be checked in patients with a high TSH, to help establish the underlying cause. If the TPO antibodies are positive, it means the cause of hypothyroidism is an autoimmune disease (e.g. Hashimoto's thyroiditis). If they are negative, it means they may not have a thyroid disorder and that the high TSH may resolve spontaneously, or there is an underlying thyroid disorder caused by another factor (e.g. following a viral infection or due to prescribed medication).

It is normally only necessary to measure TPOAb once when trying to establish the cause of the thyroid disorder. TPO antibodies are found in more than 90% of people with autoimmune hypothyroidism and also in about 10% of people without a thyroid disorder where they may be 'markers' of autoimmunity. This means they may be more likely to develop autoimmune disease in the future. **(27)**

In Graves' disease, the thyroid stimulating antibodies (TRAb) mimic the thyroid stimulating hormone (TSH) secreted by the pituitary gland. This causes the thyroid to continue to produce thyroid hormones, despite the pituitary trying to switch off the thyroid by stopping production of TSH. The presence of TRAb suggests a person has Graves' disease. Approximately 95% of patients with Graves' disease will have raised TRAb and 70% will also have raised TPOAb. The severity of Graves' disease is often reflected in the levels of TRAb present. For example, where the TRAb levels are very high, the patient is less likely to achieve long-term remission following a course of treatment with antithyroid drugs. It is sometimes possible for antibodies to be negative, but for a scan to confirm a Graves' disease diagnosis. **(28)**

Thyroglobulin (Tg) is produced by thyroid cells: both noncancerous (benign) and cancerous cells. It plays a key role in helping the body create, store and release thyroid hormones. After successful thyroid surgery and radioactive iodine ablation for thyroid cancer, thyroglobulin should not be detectable in the blood. The presence of detectable thyroglobulin, particularly a rising thyroglobulin level, may give an early warning of a recurrence of the cancer. Thyroglobulin antibodies are directed against the thyroglobulin molecule and are found in approximately 10% of the general population; they can be raised in HT.

Where they are present it can affect the accuracy of the measurement of thyroglobulin and so additional

means need to be used to monitor people who have had treatments for thyroid cancer. Thyroglobulin antibodies generally do not add anything to TPO antibody results in the assessment of people with a raised TSH. **(9)**

It is rarely useful to repeat measurements of TPO Ab, as their level does not usually influence the treatment given or the response to treatment. In contrast, measurements of TRAb can be used to guide treatment decisions in Graves' disease (autoimmune thyroid overactivity). For example, relapse of Graves' disease is more likely if antithyroid drugs (ATD) are stopped when TRAb are still raised. Thyroglobulin antibodies are also measured regularly in the follow-up of thyroid cancer, to ensure the continued accuracy of the thyroglobulin measurement. **(28)**

It is possible. In Graves' disease patients, antithyroid medication, radioactive iodine (RAI) and surgery all aim to restore the thyroid function to normal. RAI and surgery destroy or remove the thyroid to 'cure' the overactivity. However, the TRAb, which are the underlying cause of the Graves' disease, may remain in the body for many years after these treatments. Sometimes the TRAb disappears after a course of ATD; however, they may return months or years after stopping ATD, causing a relapse of Graves' disease. In patients with autoimmune hypothyroidism (Hashimoto's thyroiditis), TPO antibodies usually remain in the body. Levels may reduce over time, but hardly ever normalize completely, even after medication has restored thyroid levels to normal. Autoimmune thyroid diseases are usually accompanied by the presence of anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg), and anti-thyroid-stimulating hormone receptor (TSHR) antibodies. Antibodies against thyroid antigens such as carbonic anhydrase 2, megalin, T3 and T4, sodium iodide symporter (NIS), and pendrin have also been detected, although rarely. **(29)**

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