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Hashimoto's Thyroiditis: A Comprehensive Review of Pathogenesis, Clinical Manifestations, and Management Strategies

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Abstract

Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, an autoimmune disorder targeting the thyroid gland, presents a global health concern. This review compiles current knowledge, advancements in research findings, and emerging trends related to this condition's etiopathogenesis, diagnosis, management, and complications. The intricate interplay of genetic predisposition, environmental triggers, and immunological mechanisms underscores the development of Hashimoto's thyroiditis. Novel insights into the genetic landscape and immune dysregulation pathways contribute to a deeper understanding of disease susceptibility and progression. Diagnostic advancements, including hormonal estimation, serological tests, ultrasound, and molecular imaging modalities, are pivotal in early detection and prognosis.

Furthermore, the review delineates the heterogeneous clinical manifestations and challenges in managing the diverse symptomatology, emphasizing the necessity for personalized and tailored therapeutic approaches. The spectrum of treatment modalities spans conventional hormone replacement therapy to evolving interventions targeting immune modulation and personalized medicine. Lifestyle modifications and nutritional interventions also merit attention in optimizing patient outcomes. This review aims to furnish a comprehensive resource for clinicians, researchers, and healthcare stakeholders, fostering a nuanced understanding of Hashimoto's thyroiditis. This review seeks to inspire further investigations and innovative approaches towards improving patient care and outcomes by elucidating current trends and potential future directions.

Keywords: Hashimoto's Thyroiditis; Autoimmune Thyroiditis; Autoimmune Disease; Hypothyroidism; Myxedema

Abbreviations: HT - Hashimoto's Thyroiditis; TSH - Thyroid-Stimulating Hormone; TPO - Thyroid Peroxidase; TG – Thyroglobulin; TPOAb - Anti-Thyroid Peroxidase Antibodies; TgAb - Anti-Thyroglobulin Antibodies; SN-CAT - Serum Antibody-Negative Chronic Autoimmune Thyroiditis; HLA-DR - Human Leukocyte Antigen - DR isotype; CTLA-4 - Cytotoxic T-Lymphocyte-Associated Protein 4; PTPN22 - Protein Tyrosine Phosphatase Non-Receptor Type 22; IU - International Units; CSF - Cerebrospinal Fluid; PTC - Papillary Thyroid Carcinoma; PTL - Primary Thyroid Lymphoma; MALT - Mucosa-Associated Lymphoid Tissue

Introduction

Hashimoto's thyroiditis, also called chronic lymphocytic thyroiditis, is named after Japanese physician Dr. Hakaru Hashimoto, who first described it in 1912. It is currently considered the most common autoimmune disease affecting the thyroid gland [1]. This chronic condition arises from an autoimmune assault on the thyroid, leading to infiltration by inflammatory

cells and subsequent destruction of the thyroid follicles [2]. This condition is characterized by the production of autoantibodies targeting thyroid-specific proteins such as thyroglobulin and thyroid peroxidase [2]. Although a brief hyperthyroid phase may precede Hashimoto's thyroiditis, it most commonly presents as hypothyroidism, causing a range of symptoms, including fatigue, weight gain, cold intolerance, constipation, and depression [2]. Inadequately treated or long-standing disease can result in a myxedema coma [3].

The prevalence of this condition varies across the world, affecting women at a significantly higher rate than men, with peak incidence observed during middle age [4]. Recent epidemiological studies have suggested that genetic predisposition contributes the most to this disease, followed by environmental triggers and hormonal influences [4]. Despite advancements in our understanding of etiopathogenesis and the advent of extensive diagnostic modalities, Hashimoto's thyroiditis poses a challenge due to its diverse clinical presentations, its associations and complications, and the necessity for personalized therapeutic approaches. This literature review aims to synthesize current knowledge and highlight the latest research findings, diagnostic modalities, treatment options, and emerging therapeutic strategies in managing Hashimoto's thyroiditis.

Etiology & Pathogenesis

The pathogenesis of HT involves a combination of genetic susceptibility and environmental triggers. Studies in twins suggest genetics plays an important role, with disease concordance rates of 55% in monozygotic twins versus 0% in dizygotic twins [5]. The implicated genes are still being elucidated but include immune regulatory genes such as HLA-DR, CTLA-4, and PTPN22 [6]. On top of the genetic predisposition, environmental factors such as infection, stress, pregnancy, dietary iodine excess or deficiencies, toxins, and medications can trigger abnormal immune responses against thyroid proteins [7]. This activates both cell-mediated (Th1) and humoral (Th2) immunity against TG, TPO, and the thyroid-stimulating hormone (TSH) receptor [8]. Key steps include loss of self-tolerance, activation of thyroid-specific T and B cells, and proliferation of autoreactive lymphocytes that infiltrate the thyroid gland [9]. The sustained autoimmune attack leads to apoptosis of thyroid follicular cells, impaired hormone synthesis, and eventual thyroid destruction [10].

Epidemiology & Risk Factors

Hashimoto's thyroiditis is estimated to affect up to 5% of the general population, with a female-to-male ratio ranging from 4:1 to 10:1 [11]. The disease most commonly presents between ages 30-50 but can be seen at any age [12]. Twin studies estimate the heritability of Hashimoto's to be around 75% based on concordance data [13]. Aside from genetics, hypothesized risk factors include excessive iodine intake, vitamin D deficiency, gut dysbiosis, stress, and certain toxins/medications [14]. Studies have demonstrated an association between Hashimoto's thyroiditis and other autoimmune conditions; the most commonly seen in adults are arthropathies and connective tissue diseases, while type 1 diabetes and celiac disease were seen in children/adolescents. Skin diseases were represented with similar prevalence in both groups, vitiligo being the most common [15]. An ethnic preponderance has been established, with the white race characterized by a higher incidence than black or Asian and Pacific Islanders being rarely affected [16]. Within the United States, higher rates were observed in some areas like the Midwestern United States compared to coastal areas [17]. Further research is needed to clarify non-genetic predisposing factors.

Clinical Manifestations

The clinical manifestations of Hashimoto Thyroiditis vary due to the nature of the disease. Initially, patients may experience hyperthyroid symptoms due to the destruction of the thyroid cells, leading to the release of thyroid hormone into the bloodstream. Eventually, patients exhibit symptoms of hypothyroidism when enough destruction has occurred to the thyroid gland. This presentation is rather insidious [18]. Skin findings due to hypothyroidism can include myxedema. This is uncommon and only present in severe cases. More commonly, the skin can be somewhat scaly and dry. Hair growth is impeded and can become coarse or brittle. The patients can also present with fatigue, exertional dyspnea, and exercise intolerance due to limited pulmonary and cardiac reserve. In addition, there is muscle weakness or decreased strength. Other symptoms can include cold intolerance, weight gain, constipation, decreased sweating, depression, and menorrhagia [18]. As well there can be symptoms due to a goiter, such as voice changes, dysphagia, and neck pain [19]. Findings on clinical examination can include cold/dry skin, non-pitting edema, brittle nails, increased blood pressure, bradycardia, and delayed relaxation of tendon reflexes [18].

Diagnosis and Laboratory Evaluation

Diagnosing Hashimoto's thyroiditis (HT) is a comprehensive approach that combines clinical examination, laboratory testing, and imaging studies [20]; due to HT being often asymptomatic at baseline, extensive laboratory examination is inevitable for early diagnosis and opportune intervention. Confirmation of the immunological nature of the disease is based on the detection of thyroid autoantibodies, particularly anti-thyroid peroxidase (TPOAb), which are the most important feature because they are present in about 95% of patients and anti-thyroglobulin (TgAb) that can be found in about 60-80% of cases [21,22]. A TPOAb level above 200 UI per mL strongly suggests HT [23]. Some studies define TgAb as the expression of an early immune response, whereas TPOAb may result from an immune escalation, given that they are a late immune response [22]. Ultrasounds and additional imaging modalities can enhance the scope of laboratory findings, unveiling pivotal features such as decreased echogenicity, heterogeneity

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hypervascularity, and presence of hypoechoic micronodules with an echogenic rim [22]; also, these procedures can be helpful in the diagnostic of serum antibody-negative chronic autoimmune thyroiditis (SN-CAT) whose prevalence is estimated at 5% of cases [24]. In recent years, computer-aided ultrasonography could distinguish HT from normal thyroids with an accuracy of 80%, sensitivity of 76%, specificity of 84%, and positive predictive value of 83.3% [23]. The cytological examination is performed when a thyroid nodule is present with suspicion of malignant transformation; the key feature to distinguish HT and thyroid tumors is the presence of lymphocytes in contact with thyroid cells [22].

Prevention & Treatment Strategies

Autoimmune hypothyroidism prevention is a topic that receives far too little attention worldwide from both medical professionals and policymakers [25]. It involves a wide variety of public health and medical factors, in which preventing the emergence of risk factors, postponing the onset of symptoms, and reducing the severity of the disease are the main goals of primordial and primary preventions of autoimmune thyroid disorders. A significant contribution from environmental factors is strongly supported by incomplete concordance observed in monozygotic twins or other siblings of people with autoimmune thyroid disease [25]. According to a study by Rosaria et al., consuming fewer animal products may protect against thyroid autoimmunity. Also, it may benefit redox balance and other illnesses linked to oxidative stress, which is a significant risk factor leading to the disease [26].

Furthermore, while the characteristics of a Mediterranean diet were protective, eating meat was linked in a logistic regression analysis to an increased odds ratio of developing thyroid autoimmunity [26]. Other studies have also shown that children raised in higher socioeconomic circumstances had a higher prevalence of thyroid autoimmunity; these findings are consistent with the hygiene theory, which postulates that early virus exposure may divert the immune system from Th2 responses, such as allergy and autoimmunity [27]. Additionally, Brazilian research has demonstrated that compared to controls, those who live near a petrochemical complex have higher rates of thyroid autoantibodies and Hashimoto's thyroiditis [28]. Subsequent studies also demonstrated clearly that smoking cessation is linked to the presence of thyroglobulin antibody and, to a lesser degree, thyroid peroxidase autoantibody, as the risk of being diagnosed with overt autoimmune hypothyroidism is more than six times higher in the first two years after quitting smoking [29,30]. Drinking in moderation was also associated with a lower risk of developing overt autoimmune hypothyroidism regardless of gender or type of alcohol consumed, as demonstrated in a multivariate regression model [31]. More research is required to assess vitamin D's therapeutic and preventive benefits in autoimmune thyroid disease. But a study done in Egypt proved a significant correlation as it concluded that in comparison to 20.0% of healthy controls, 76.7% of those with Hashimoto thyroiditis lacked vitamin D. Additionally, the vitamin D deficiency in the Hashimoto thyroiditis group was negatively correlated with antithyroglobulin and antithyroid peroxidase [32].

Currently, the treatment for hypothyroidism is thyroid hormone replacement. The drug of choice is levothyroxine sodium, taken orally. It is important to note that this drug should not be taken with iron or calcium supplements, aluminum hydroxide, and proton pump inhibitors, as it prevents absorption [33]. The standard dosing is 1.6-1.8 mcg/kg per day, commenced on patients less than 50 years of age, those older, or with cardiovascular diseases; it is recommended to start on a lower dose; typically, the starting dose of 25 mcg/day is reevaluated in six to eight weeks. In pregnancy, it is recommended to increase the dose by 30%, and in all patients who have short bowel syndrome, it is recommended to maintain a euthyroid state [33]. Some evidence suggests that selenium can be used as supplementation with adjunctive therapy in treating Hasimoto's thyroiditis. A 3-month meta-analysis showed that supplementation was associated with a significant decrease in TPOab titers and that patients improved mood and overall well-being [6.10]. The four studies showed random effects weighted mean difference: −271.09, 95% confidence interval: −421.98 to −120.19, $p < 10-4$ [34].

Complications

There are several complications of Hashimoto's thyroiditis, ranging from the acute presentation of myxedema coma to the insidious complications of papillary carcinoma of the thyroid and thyroid lymphoma. Myxedema coma or myxedema crisis is seen in long-standing undertreated or undiagnosed cases of Hashimoto's thyroiditis [35]. Most cases of myxedema crisis are precipitated by a particular trigger that disrupts homeostatic mechanisms in hypothyroid patients. This trigger could be an infection, gastrointestinal bleeding, cardiac failure, surgical stress, burn injuries, traumatic injuries, hypoglycemia, hypothermia, or even drugs, such as beta-blockers, lithium, amiodarone, and diuretics [36]. The pathogenesis of myxedema coma can be explained by reduced intracellular levels of T3, which lead to suppression of thermogenesis and cause hypothermia. Hypothermia leads to a decrease in heart rate and cardiac output, resulting in cardiogenic shock. Activation of the renin-angiotensin-aldosterone system will lead to fluid retention and dilutional hyponatremia. Due to CNS depression, there is reduced sensitivity to hypoxia, hypercapnia, and subsequent respiratory failure. The presence of triggers will worsen the aforementioned pathophysiological mechanisms and lead to an acutely decompensated state with altered mentation known as myxedema coma [37]. A detailed history should be taken regarding the thyroid supplementation dose, medication adherence, thyroid surgery, radioactive iodine ablation, possible triggers, and concomitant drug intake [37]. The system-wise

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manifestations of myxedema coma are as follows:

1.1. Cardiovascular manifestations

The typical cardiovascular manifestations include shock, hypotension, arrhythmias, and heart blocks. Hypotension results from decreased cardiac output and myocardial contractility brought on by hypothermia and myxedema. Sinus bradycardia flattened T-waves, low voltage complexes, bundle branch blocks, and even complete heart blocks have been seen in myxedema coma [36,37]. Prolongation of the QT interval resulting in polymorphic ventricular tachycardia, which responds to thyroid supplementation, has been reported in severe hypothyroidism [37].

1.2. Neurological manifestations

The term myxedema coma is a misnomer. Usually, patients are present with lethargy, especially in the initial phase of the disease. There is a slow progression to a comatose state. The patient may also present with depression, psychosis, confusion, poor cognition, seizures, and, rarely, status epilepticus. Lumbar puncture, if done, may show increased opening pressure and raised CSF protein levels [36,37].

1.3. Gastrointestinal manifestations

Patients with myxedema coma can show symptoms of acute abdomen such as nausea, vomiting, abdominal pain, and loss of appetite. They may also show constipation, paralytic ileus, and toxic megacolon. Ascites have been reported in a few cases. Due to the increased risk of coagulopathy in myxedema, there can be gastrointestinal bleeding. Gastric atony caused by myxedema may reduce the absorption of oral medications [36,37].

1.4. Renal manifestations

The typical finding in myxedema coma is dilutional hyponatremia due to fluid retention by the kidneys under the effect of aldosterone and vasopressin. Urine sodium may be normal or elevated. Due to fluid retention, urine osmolarity is higher than plasma osmolarity. There may also be urine retention due to bladder atony [36,37].

1.5. Hematological manifestations

Normocytic normochromic anemia in myxedema crisis patients may result from reduced oxygen requirement and erythropoietin. Macrocytic anemia can be associated with pernicious anemia or low folate absorption [37]. A decrease in factors V, VII, VIII, IX, and X and an acquired von Willebrand syndrome type 1 enhance the risk of bleeding in patients with myxedema coma. Studies have demonstrated that T4 treatment can reverse acquired von Willebrand syndrome [36]. In coagulation studies, patients may show raised bleeding and clotting times, raised aPTT, low to normal factor VIII activity, and reduced platelet adhesion [37]. While patients with myxedema coma show coagulopathy, patients with mild hyperthyroidism usually show hypercoagulability [36].

1.6. Respiratory manifestations

Impaired hypoxic and hypercapnic ventilatory response, along with the resulting weakening of the diaphragmatic muscles, cause hypoventilation in myxedema coma. It appears that respiratory depression brought on by a reduced reaction to hypercapnia is the leading cause of coma in myxedema patients. Additionally, obstructive sleep apnea caused by enlargement of the vocal cords and tongue contributes to respiratory failure. A decrease in tidal volume due to ascites or pleural effusion is another problem that may be involved [36].

Another complication of Hashimoto's thyroiditis is Hashimoto's encephalopathy or steroid-resistant encephalopathy associated with autoimmune thyroiditis (SREAT). There are 4 major criteria to diagnose SREAT, which include an altered level of consciousness accompanied by cognitive changes, psychiatric symptoms that are new or worsening, raised serum TPO-Abs levels (≥0.5 U/mL) or other antithyroid antibodies, such as antithyroglobulin (TG) or antithyroid microsomal antibodies, and ruling out infections, toxic, metabolic, or carcinomatous etiologies that could contribute to symptoms [38]. It presents as an acute or subacute-onset encephalopathy with convulsions, myoclonus, tremor, and stroke-like episodes. Most patients, however, are euthyroid, unlike Hashimoto's thyroiditis, and this condition responds to steroids [37].

Papillary thyroid carcinoma (PTC) is the most common type of cancer associated with Hashimoto's thyroiditis. Although this association is well established in current literature, there is a lack of a causal relationship between the two. Both diseases show female preponderance, have a relatively high prevalence, and are seen in iodine-replete regions [39]. Most cases of Hashimoto's show mutations of RET/PTC oncogenes, which is characteristic of PTC as well [40]. PTC, which arises in patients of Hashimoto's, has a relatively favorable prognosis. The disease is more common in younger females, has smaller nodules, and has a lower rate of lymphatic spread. Thus, Hashimoto's thyroiditis is a favorable prognostic factor in patients of PTC [39]. Hashimoto's thyroiditis is a predisposing factor for primary thyroid lymphoma (PTL), with 80% of PTL cases being positive for Hashimoto's [41]. The risk of PTL is increased by 40 to 80 times in patients of Hashimoto's thyroiditis [42]. PTL is a non-Hodgkin B-cell lymphoma that affects about 0.6% of patients of Hashimoto's thyroiditis [41]. The most prevalent histological types include diffuse large B-cell lymphoma followed by mucosa-associated lymphoid tissue (MALT) lymphoma [43].

Conclusion

Hashimoto's thyroiditis (HT) is a complex autoimmune disorder with a multifaceted etiology involving genetic susceptibility and environmental triggers. While immune regulatory genes play a crucial role, factors like infection, stress, and dietary iodine levels contribute to abnormal immune responses targeting thyroid

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proteins. The disorder predominantly affects women, peaking during middle age. Diagnosis is challenging due to diverse clinical manifestations, necessitating a comprehensive approach with clinical, laboratory, and imaging assessments. Addressing environmental risk factors through dietary changes and lifestyle modifications is vital in prevention and treatment. Complications range from severe hypothyroidism-associated myxedema coma to an elevated risk of thyroid cancer and lymphoma. Levothyroxine sodium remains the primary treatment, but ongoing research explores promising adjunctive therapies, offering hope for more personalized interventions. Understanding HT requires a holistic perspective, and ongoing research aims to uncover additional insights for improved management.

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