

CURRENT CONCEPTS IN ENDOCRINOLOGY FOR CLINICIANS AND MEDICAL STUDENTS HASHIMOTO'S THYROIDITIS: CLINICAL AND SUBCLINICAL THYROID DYSFUNCTION

CONCEITOS ATUAIS NA ENDOCRINOLOGIA PARA OS CLÍNICOS E ESTUDANTES DE
MEDICINA TIREOIDITE DE HASHIMOTO: DISFUNÇÃO TIREOIDIANA CLÍNICA E
SUBCLÍNICA

Paulo Travassos Neto*,

*Medicine School, Endocrinology Unit, Internal Medicine Department, Fluminense Federal University, UFF, Niterói, Rio de Janeiro, Brazil.

E-mail address for correspondence: ptravassos3@gmail.com

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ABSTRACT

Hashimoto's thyroiditis (HT) is an autoimmune and inflammatory disease in which antibodies are directed against the thyroid gland leading to chronic inflammation and hypothyroidism. The autoimmunity against thyroid antigens can be associated to genetic background and environmental factors. Thyroid peroxidase (TPO) and thyroglobulin (TG) are the major autoantigens for characterizing the disease. And the pathogenic mechanism is related to the activation of autoreactive CD4⁺ T cells, CD8⁺ cytotoxic T cells and antithyroid antibody producing-B cells. The treatment for hypothyroidism is based on thyroid hormone replacement, the levothyroxine. This review briefly discusses the clinical and pathogenic profile of HT and the importance of a correct diagnostics.

Key words: Hashimoto's thyroiditis, hypothyroidism, diagnostic, treatment

RESUMO

A tireoidite de Hashimoto (TH) é uma doença auto-imune e inflamatória na qual os anticorpos são direcionados contra a glândula tireoide, levando à inflamação crônica e ao hipotireoidismo. A autoimunidade contra antígenos tireoidianos pode estar associada a fatores genéticos e ambientais. A peroxidase tireoideana (TPO) e a tireoglobulina (TG) são os principais autoantígenos, responsáveis muitas vezes pelo diagnóstico da doença, que é complementado com outras análises laboratoriais e clínicas. A resposta imunológica evidenciada na TH envolve ativação de células T CD4⁺ auto-reativas, células T citotóxicas CD8⁺ e células B produtoras de anticorpos antitireoidianos. O tratamento mais comum do hipotireoidismo consiste na reposição do hormônio levotiroxina. Esta revisão discute brevemente o perfil clínico e patogênico da TH e a importância de um diagnóstico correto.

Palavras-chave: Tireoidite de Hashimoto, hipotireoidismo, diagnóstico e tratamento.

INTRODUCTION

Autoimmune thyroid diseases (AITD) constitute 30% of all the autoimmune conditions and are classified as organ specific diseases. Hashimoto's thyroiditis (HT), described in 1912 by Hakaru Hashimoto, is considered a multifactorial disease group in which antibodies are directed against the thyroid gland. The antithyroid antibodies attack thyroid stroma, causing progressive fibrosis and leading to chronic inflammation and hypothyroidism. The most common antibodies are anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) and, in some cases it is possible to detect thyroid stimulating hormone (TSH) receptor blocking antibodies (anti-TSHR) (Pyzik A, 2015; Antonelli A, 2015; Chistiakov DA, 2005). The etiology of HT is still poorly understood, but the autoimmunity against thyroid antigens has been related to the genetic and environmental factors and the disorder is prevalent in individuals aged > 60 years, with a female/male ratio ranging from 5:1 to 10:1 (Yoo WS, 2016).

PATHOLOGY AND DIAGNOSIS

The hypothyroidism is traditionally defined as deficient thyroidal production of thyroid hormone by factors affecting the thyroid gland itself; the fall in serum concentrations of thyroid hormone causes an increased secretion of TSH resulting in elevated serum TSH concentrations and, can also be caused by insufficient stimulation of the thyroid gland by TSH, due to factors directly interfering with pituitary TSH release or indirectly by diminishing hypothalamic thyrotropin-releasing hormone (TRH) release (Lee HJ, 2015; Yoo WS, 2016; Mincer, DL, 2017).

Histologically and clinically, HT is characterized by fibrosis, lymphoplasmacytic infiltration, degeneration of follicular cells and rapid progression of hypothyroidism. The pathologic examination commonly shows a symmetric enlargement of the thyroid and, it can appear to be diffuse. Interlobular fibrosis may or may not be present. In some cases, the gland may become nodular or asymmetric (Pyzik A, 2015). Initially, patients may have bouts of hyperthyroid symptoms, as the initial destruction of thyroid cells may lead to release thyroid hormones into the bloodstream. These symptoms are varied and may affect almost any organ system in the body (Pearce EN, 2003 Cooper DS, 2012; Effraimidis G, 2014).

The diagnosis of HT is based on the increase of anti-TPO and anti-TG serum levels and the typical clinical signs are associated to the change in the ultrasonographic aspects of the thyroid gland (Ben-

Skowronek I, 2013; Effraimidis G, 2014). Thyroid-stimulation hormone (TSH) is raised due to Hashimoto thyroiditis and in primary hypothyroidism that is based in low total T4 and low free T4 in the presence of an elevated TSH level (Mincer, DL, 2017; Cooper DS, 2012). Although definite diagnostic criteria are not yet available, >20 IgG4-positive plasma cells per high-power field and >30% IgG4-positive/IgG-positive plasma cells have been proposed as additional diagnostic criteria for HT (Jokisch F, 2016). A thyroid ultrasound assesses thyroid size, echotexture, and whether thyroid nodules are present. If HT is suspected and nodules are palpable or found on ultrasound, fine-needle aspiration on thyroid nodules can be performed to exclude malignancy or the presence of a thyroid lymphoma (Brand OJ, 2009; Mikos H, 2014).

A study with 290 HT patients without LT4 treatment showed that elevated TGAb levels are associated with symptom burden, suggesting a role of thyroid autoimmunity in clinical manifestations of HT and recommending a screening for TGAb for better clinical follow-up of the patient (Baric, 2018).

Although we have several up-to-date management guidelines for "subclinical" hypothyroidism, the decision for a correct treatment is still vague aspect (Ben-Skowronek I, 2013; Pyzik A, 2015). Considering the progressive changes in the levels of serum TSH and free thyroxine (T4), has been suggested a better way to classify and to differentiate "clinical" and "subclinical" forms of hypothyroidism (Pearce SH, 2013; Wiersinga WM, 2015). Subclinical thyroid dysfunction comprises subclinical hypothyroidism, defined as elevated TSH by normal free T4 (FT4), and subclinical hyperthyroidism with decreased or undetectable TSH and normal FT4. Up to 10% of the elderly have subclinical hypothyroidism, which is usually asymptomatic (Wiersinga WM, 2015). The cardiovascular system is one of the main target organs of thyroid hormones and elevated or decreased TSH levels can adversely affect the cardiovascular system (Floriani C, 2018; Jing Sun, 2017). The influence of thyroid hormones (THs) on the cardiovascular system involves the regulation of key processes related to maintenance of cardiac function. Some studies demonstrated that subclinical hypothyroidism increased cardiovascular risk factors including altered lipid profile, insulin resistance, oxidative stress, increased vascular stiffness, and endothelial dysfunction (Jing Sun et al, 2017). Thus, the treatment with THs in patients with hypothyroidism improves cardiovascular risk

factors (H. Vargas-Uricoechea, 2014; J. Wu, 2016).

PATHOGENIC MECHANISMS

The HT is one of the most prevalent human autoimmune diseases, responsible for high morbidity in women. The antithyroid inflammatory reaction in HT is enhanced by several mechanisms, counting on the participation of autoreactive CD4⁺ T cells, CD8⁺ cytotoxic T cells and anti-thyroid antibodies producing-B cells. An influx of the lymphoid cells, dendritic cells and macrophages into thyroid occurs as a consequence of inflammatory events (Antonelli A, 2015; Ben-Skowronek, 2013). The disease is a result of a Th1 immune response which triggers cell mediated immunity and thyroid follicular cell death by apoptosis. Activated antigen-specific T-helper CD4⁺ cells participate in the activation of intra-thyroid cytotoxic CD8⁺ T effector cells, B cells, which differentiate and produce autoantibodies (Zeppa P, 2006; Ates I, 2014; Mincer DL, 2017). Previous studies had already a prominent role of Th17 (CD4⁺IL-17⁺) and Treg lymphocytes (CD4⁺CD25⁺highFoxP3⁺) respectively in the induction and modulation of autoimmune reactions (Korn T, 2009; Zake T, 2018). With a very similar immunopathogenic profile, other different autoimmune diseases have been associated, such as vitiligo, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, among others. Although the etiopathogenesis is still unknown, the importance of epigenetic modifications associated with environmental factors has been discussed (Antonelli & Benvenga, 2018).

Besides that proinflammatory cytokines, which are synthesized by Th1 lymphocytes, often play a role in pathogenesis of autoimmune diseases. These proinflammatory cytokines increase the immunogenicity of antigenic structures in thyroid gland and similar tissues, which results in increased levels of IL-4, IL-5 and B lymphocytes (Zeppa P, 2006; Brenta G, 2013; Mikos H, 2014; Shen P, 2014; Pyzik A, 2015). Studies indicate that tumor necrosis factors alpha (TNF-alpha), superfamily cytokines such as B cell activation factor (BAFF; also known as BlyS) and a proliferation-inducing ligand (APRIL) are another important cytokines which can be involved in the establishment and/or maintenance of autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), diabetes and HT (Tan SM, 2003; Morel J, 2009; Fabris M, 2010; Vincent FB, 2014; Carvalho-Santos, 2015; Pinna, RA, 2018).

TREATMENT

Since Haskar Hashimoto first described AITD in 1912, significant progress has been made about chronic autoimmune inflammatory condition in the thyroid. The treatment for HT is based on thyroid hormone replacement and the drug of choice is titrated levothyroxine sodium administered orally. Surgery is considered for a large goiter with obstructive symptoms such as dysphagia, hoarseness, and stridor, or a malignant nodule, a lymphoma, or for large, unsightly goiters (Brenta G, 2003; Pyzik A, 2015; Mincer DL, 2017). In the context of the autoimmune response in HT some studies have shown that the treatment via selenium supplementation may be associated with the decrease in the levels of anti-TPO. Further it has also been shown a decrease in symptoms from a diet with adequate amounts of vitamin D and selenium (Mazokopakis EE, 2015; Liontiris MI, 2017, Rayman, 2018).

Recently, a therapeutic strategy was shown from intrathyroidal injection of glucocorticoid in patients with HT, presenting pain (Paja, 2018). Different therapeutic approaches have been suggested to attend the symptoms presented, often in a particular way by patients with thyroid disease.

FINAL CONSIDERATIONS

Hashimoto's thyroiditis (HT) is one of the most common human autoimmune diseases responsible for considerable morbidity in women. This mini-review emphasizes the importance of a correct diagnosis and ongoing research on the etiopathogenesis of thyroid diseases, as well as their association with other chronic diseases. In order to improve protocols for clinical and therapeutic follow-up for asymptomatic and symptomatic patients, always seeking a better quality of life, reducing the risks of comorbidities.

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