Hashimoto Thyroiditis

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Introduction

Hashimoto Thyroiditis is a chronic autoimmune disease clinically characterized by gradual thyroid failure due to the presence of specific antibodies directed to thyroid antigens. Haraku Hashimoto, a Japanese physician, first described in 1912 this condition, naming as "*struma lymphomatosa*" and referring to patients with goiter and intense lymphocytic infiltration of the thyroid gland [1]. Several studies have then stated that lymphocytic infiltration was the result of an immunological reaction to thyroid antigens and thyroid autoantibodies were identified [2]. Since then, Hashimoto thyroiditis has been considered an autoimmune disease characterized by the detection of serum thyroid autoantibodies, regardless of the presence of goiter.

Pathogenesis

Thyroid autoantibodies are detected in about 11% of the general population and in iodine sufficient areas, Hashimoto thyroiditis is considered the most common cause of hypothyroidism [3]. Hashimoto thyroiditis is more frequent in advanced age, in women, in iodine sufficient populations and in people moving from iodine sufficient to deficient areas. Its prevalence differs among races and geographical areas being more frequent in white race rather than black one and rare in Pacific Islanders.

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Nevertheless, an increased incidence over time has been reported, particularly in the last three decades [4].

The pathogenic mechanisms underlying Hashimoto thyroiditis are still largely unknown, but it seems to be the result of a combination of genetic influences, environmental triggers, and epigenetic factors.

Genetic susceptibility has firstly been proven analyzing the impact of familial predisposition on the development of the disease and it has been demonstrated a concordance rate of more than 50% in monozygotic twins [5]. Several genes have been identified, particularly those involved in the immune response regulation, such as those coded in the Human Leukocyte Antigen complex (HLA). These genes could alternatively play a role of susceptibility or resistance in the development of the disease. HLA-A*02:07, HLA-DRB4, and HLA-B* 46:01 fall in the first group [6].

The main determinant in the rising incidence of autoimmune diseases, including Hashimoto Thyroiditis, appears to be a more hygienic environment with few microbial agents. Diet has also a central role: excess of iodine may cause the onset of the thyroiditis in predisposal individuals, while insufficient selenium and vitamin D deficiency may result in a worsening of the disease. In this context, the role of smoking and alcohol is still controversial of smoking and alcohol, but some studies report a moderate consumption of alcohol as a protective factor as well as lower peroxidase antibody levels in smokers rather than nonsmokers [3]. Eventually, viral infections could represent a risk factor in predisposed subjects, probably based on molecular mimicry mechanism between viral and self-antigens, but further studies are needed to clearly demonstrate a significant association.

Environment and genetic factors are mutually dependent, and the first ones can influence genes expression inducing epigenetic modifications, such as methylation and histone modifications.

Hashimoto thyroiditis is characterized by specific histopathology modifications, such as lymphocytic infiltration, lymphatic follicular formation, and replacement of glandular tissue in a fibrotic one, in a large spectrum of phenotypes including both goiter and gland atrophy. In pathogenesis, both humoral and cellular immunity play a role. The first event is a dysfunction of B cells with overproduction of thyroid autoantibodies. Nevertheless, hypothyroidism is due to the destruction of thyroid tissue which is realized by cellular immunity through cytotoxic and apoptotic mechanisms. Recent studies pointed out other factors involved in the pathogenesis such as alteration in the function of T cell suppressors [7].

Clinical Presentation and Diagnosis

Hashimoto thyroiditis has been associated with local and systemic symptoms (Table 1), even if more frequently is clinically silent leading to a condition named subclinical hypothyroidism.

Table 1 Clinical presentation and implications of hypothyroidism

Apparatus	Clinical evidence
Cardiovascular	Pericardial effusion, hyperhomocysteinemia, ECG changes, diastolic dysfunction, arterial hypertension, increased ITM
Metabolic	Increased BMI, high triglycerides, high cholesterol levels, low metabolic expenditure, fatigue
Neurological and psychological	Reduced or impaired cognitive functions (mostly memory), neuropathy, dementia, ataxia. In extremely severe cases myxedematous coma, depression
Endocrine	Sexual dysfunction and reduced fertility, increased prolactin, multinodular goiter
Dermatological	Dry skin, alopecia areata, macroglossia, Hertoghe sign, hair loss
Others	Cold intolerance, constipation, peripheral myxedema, macrocytic anemia, arthralgia, muscle weakness, muscle cramps

The local symptoms, occurring in case of goiter, are due to compression and include dyspnea, dysphagia, and dysphonia involving respectively trachea, esophagus, and recurrent laryngeal nerve. Systemic symptoms are due to primary hypothyroidism and may involve nearly all major organs, including a wide variety of symptoms from few and not severe to myxedematous coma. The latter is the result of severe and longstanding untreated hypothyroidism which leads to altered mental status, bradycardia, hypothermia, and progressive multiple organ dysfunction. Nowadays myxedema coma is a rare condition, while the most common systemic symptoms are weight gain, constipation, lethargy, fatigue, hair loss, and infertility in case of severe hypothyroidism [3]. Systemic symptoms are nonspecific, especially in elderly patients, and up to 15% of patients with autoimmune hypothyroidism are asymptomatic [8].

The diagnosis of chronic autoimmune thyroiditis is based on the presence of antithyroid autoantibodies and peculiar ultrasonography characteristics of the thyroid gland.

The antibodies routinely used in clinical practice are antithyroglobulin (AbTg) and antithyroid peroxidase (AbTPO) [9]. The former is a fundamental protein in the formation of thyroid hormones, acting as a scaffold for the incorporation of iodine, and the latter is the enzyme that fixes iodine in the Tg during the T4 synthesis [10, 11]. These antibodies show little, if any, functional activity but act as an important marker of the thyroiditic process that occurs in Hashimoto's disease. More than 90% of the patients have AbTg and/or AbTPO positivity, usually with AbTPO having a better sensibility than the AbTg.

Thyroid ultrasound can be useful in the differential diagnosis of Hashimoto's thyroiditis: the signature characteristics tend to be a diffusely enlarged gland with low echogenicity, a dishomogeneous structure, with low blood flow at the Color Doppler imaging (Fig. 1). Often these patients also show a multinodular goiter in the gland. Usually both the ultrasonographic characteristics and the AbTPO/AbTg positivity are present at the time of diagnosis.

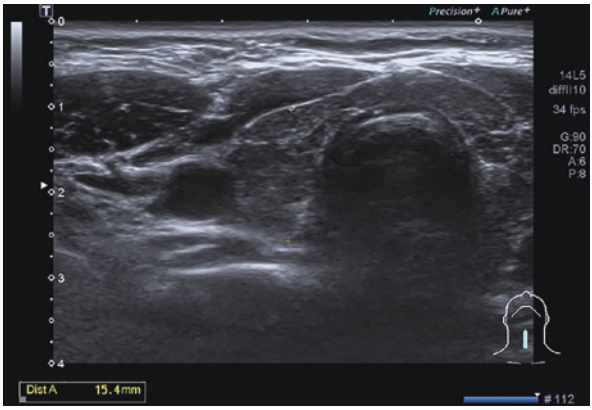

Fig. 1 Ultrasonography that shows the typical pattern of a Hashimoto thyroiditis, with hypoechoic and dishomogeneous ecostructure and the discrete presence of fibrous areas. No solid nodules were detected in this US [personal series]

There is no evidence that suggests the utility of repeating the antithyroid autoantibodies in the disease's follow-up, while the TSH levels must be periodically monitored every 9 to 12 months.

Treatment and Follow-Up

Hashimoto's disease needs no specific treatment in itself until a subclinical or overt hypothyroidism is developed by the patient. The follow-up process, once the diagnosis has been made, is based on an annual serum TSH evaluation, because approximately 5 percent per year evolve to overt hypothyroidism [12]. Thyroid ultrasonography must be repeated annually only when solid nodules are present. If TSH is less than 7 mUI/L, there is no need for specific therapy with levothyroxine. When TSH levels are between 7 and 10 mUI/L and/or hypothyroidism symptoms are developed, Hashimoto's thyroiditis can start to be treated with levothyroxine. If TSH is more than 10 mUI/l or the hypothyroidism is overt (fT4 lower than the LLR), treatment is recommended. Goals of the therapy are amelioration of symptoms and normalization of serum TSH.

The standard treatment for primary hypothyroidism is 1.2–1.6 mcg/kg/day of levothyroxine, administrated orally in a single dose in the morning, in a fasting state, at least 20 minutes before having breakfast. In patients with atherosclerotic coronary heart disease or older age (age over 60 years), the drug should be started gradually, receiving in the first weeks of treatment an increasing fraction of the full-dose therapy. Patients must be informed to avoid soy containing products and papaya during breakfast and avoid protonic pump inhibitors and mineral iron in the hours following levothyroxine to allow a better absorption of the drug. The half-life of T4 is 7 days, allowing different posology over a week to reach more accurate titration of the drug. Levothyroxine preparations can be tablets, liquid oral suspensions or gel capsules. Liquid and gel capsules formulation allow a shorter time between the administration and breakfast. Revaluation after starting levothyroxine

therapy should be performed after 6 to 8 weeks with serum TSH levels that should be between 0.5 mUI/l and the URL, usually between 4 and 5 mUI/l.

If the serum TSH is too high, levothyroxine dose must be increased by 6 to 25 mcg/day, based on the serum TSH levels, and rechecked after 6–8 weeks; the patient should also be reminded the correct way to assume the drug to allow an ideal absorption. Keep gradual dose titration until TSH is normal.

If serum TSH is too low, levothyroxine dose must be reduced by 12 to 25 mcg/day, and rechecked at 6–8 weeks, then keep gradual dose titration until TSH is normal.

When serum TSH is normal, keep an annual serum TSH check. A closer follow-up must be performed if: the patients develop symptoms of hypothyroidism or hyperthyroidism, pregnancy, initiation or discontinuation of estrogen replacement therapy, and gain or loss of more than 10% of body weight.

Recent studies have analyzed long-term consequences of hypothyroidism in terms of quality of life and association with all-causes mortality, particularly in the subclinical setting to identify conditions worthy of treatment despite the presence of symptoms.

Great attention has been given to the implications of hypothyroidism on cardiovascular system and several studies have confirmed a major risk of myocardial injuries and pericardial effusions in patients with hypothyroidism than in matched euthyroid controls. Also, subclinical hypothyroidism with TSH concentrations above 10 mUI/L has been associated with an increased risk of heart failure [13]. This is based on the evidence that low levels of thyroid hormones lead to increased vascular resistance, decreased cardiac output, and changes in markers of cardiovascular contractility.

Lastly, several studies have proposed a relationship between Hashimoto's thyroiditis and a possible malignant transformation, but this correlation is still debated and need to be further analyzed with prospective studies [14].

Sexuality and Quality of Life

Sexual dysfunction (SD), in both men and women, is a highly prevalent problem with multiple underlying etiologies. From a male perspective, SD can be classified into the categories of erectile dysfunction, ejaculation disorders (premature ejaculation (EP) and delayed ejaculation (ED)) and decreased libido.

PE is the most common male sexual disorder, occurring in 20–30% of men during their lifetime [15]. ED is a male sexual dysfunction that is highly age-dependent: it is 18% for the 50–59 age group, increasing to 37% for the 70–75 age group [16]. It is estimated that 5–15% of men suffer from decreased libido, many of whom have reported concomitant impairment in other domains of sexual functioning.

From a female perspective, SD is addressed from the domains of sexual desire, arousal/lubrication, orgasm, satisfaction, and pain with sexual activity. According to an international survey of women aged 40–80 years, 39% of women reported

dysfunction in at least one of these areas [17]. There is also an element of age-dependent change in FSD, as genitourinary syndrome of menopause is said to cause discomfort, lack of lubrication, or pain in 40% of postmenopausal women [18].

According to the study Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking, which surveyed 30,000 women in the United States, 43% of women experienced difficulties with these sexual problems. The most common symptom reported by women in the United States, at 39%, was reduced desire. Decreased arousal was reported by 26% of women and 21% had difficulty with orgasm [19].

In addition, alterations in the hypothalamic-pituitary-gonadal axis in thyroid disorders can affect fertility and stimulate recurrent pregnancy terminations.

Bear in mind that this pathology can be associated with symptoms of fatigue, weight gain, and a depressed mood, all of which contribute to reducing interest in sexual activity in both men and women.

This condition can have several major repercussions on the body and mind. Hyperthyroidism, the excessive production of thyroid hormones, often causes anxiety and irritability, tremors and weakness, sensitivity to heat, and problems gaining or maintaining one's weight. Hashimoto's syndrome can cause depression and mental confusion, soreness and inflammation, sensitivity to cold and weight changes. Severe hypothyroidism from Hashimoto thyroiditis can lead to fatigue, desensitization to the preliminaries of sexual intercourse, distraction, disturbance of arousal, inhibition of desire.

To make matters worse, the researchers admit that they did not particularly prioritize concerns regarding patients' sexual life and well-being. Recent studies suggest that, on average, at least 40 percent of people with the condition have experienced sexual consequences, whether caused directly by the change in hormone balance or as a secondary result of treatment (low-pain threshold, fatigue). Male patients report erectile dysfunction at a higher than average rate, premature ejaculation, and delayed ejaculation. People with vaginas report that they often have difficulty with lubrication and reaching orgasm.

To get pregnant, the thyroid hormones L-thyroxine (fT4 or T4) and triiodothyronine (fT3 or T3) must be in the normal range. These hormones affect, among other things, the cycle and ovulation, corpus luteum function, embryo implantation, and placental function.

Is the Desire for a Child Possible?

With Hashimoto's, these hormones get out of control. Hashimoto's disease is an autoimmune disease that attacks the body's defenses, particularly thyroid tissue, leading to chronic inflammation of the thyroid gland. In the short-term, there is the possibility of an overactive thyroid, that is, the gland secretes more hormones than usual. In general, overactive thyroid is not as bad as underactive thyroid, but it can lead to complications during pregnancy.

Infertility is not definitive. But during conception, it is important to monitor Hashimoto's disease to avoid consequences for the child. Physical or brain growth may be affected, and eventually, these changes or atrophy may affect the child's intelligence.

In these cases, the gynecologist and endocrinologist must work as a team, and the consultation of a neonatologist is not excluded.

Especially since cases of miscarriage during pregnancy are not uncommon.

Partners often suffer from the patient's fragility and show anxious-depressive symptoms, with alterations in aggression, impatience, anger.

Conclusion

Hashimoto's syndrome poses many risks to the health and quality of life of adult and adolescent patients.

The following factors are associated with an increased risk of Hashimoto's disease:

- **Sex:** Women are much more likely to get Hashimoto's disease.
- **Age:** Hashimoto's disease can occur at any age but most commonly occurs during middle age.
- **Other autoimmune diseases:** Having another autoimmune disease, such as rheumatoid arthritis, type 1 diabetes or lupus, increases the risk of developing Hashimoto's disease.
- **Genetics and family history:** You are at increased risk of getting Hashimoto's disease if other members of your family have thyroid disorders or other autoimmune diseases.
- **Pregnancy:** Typical changes in immune function during pregnancy may be a factor in Hashimoto's disease starting after pregnancy.
- **Excessive iodine intake:** Too much iodine in the diet can act as a trigger among people already at risk for Hashimoto's disease.
- **Radiation exposure:** People exposed to excessive levels of environmental radiation are more prone to Hashimoto's disease.

Moreover, although clinical research has found more adaptive therapies, *the emotional investment of the patient and caregiver is often underestimated.* From sexuality to mood disorders, from apathy to thermogenesis difficulties, every life experience seems to these patients to be an excessive burden and not always assessable in advance. The scientific diligence of clinicians often does not seem sufficient for the individual diagnosed with Hashimoto's and their partner. Often, the difficulties are emotional, from putting up with a partner's caresses, to inability to distinguish a caress from a passionate touch. *The psychosexologist can help these patients to construct a personalized approach that is not governed by the limitations of the pathology, but by alternative solutions, so that they need not give up on their life plans.*

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