

Hashimoto's thyroiditis and the role of selenium.

Current concepts

Abstract

Hashimoto's thyroiditis (HT) is part of the spectrum of autoimmune thyroid diseases. Clinical manifestations of HT are variable and commonly include diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism and permanent hypothyroidism. Uncommonly, HT causes acute destruction of thyroid tissue and release of stored thyroid hormones, causing transient thyrotoxicosis (hashitoxicosis). The contribution of methods and techniques of nuclear medicine to diagnosis and differential diagnosis of HT is indisputable. In HT patients with overt hypothyroidism L-thyroxine (L-T₄) should be given in the usual replacement doses, but in HT patients with a large goiter and normal or elevated serum thyroid-stimulating hormone (TSH), L-T₄ may be given in doses sufficient to suppress serum TSH. Symptomatic patients with hashitoxicosis and low 24-hour thyroid radioactive iodine (¹²³I or ¹²³I) uptake (RIU) may be treated with beta-blockers (as propranolol) and sodium ipodate or iopanoic acid (iodinated contrast agents) that block the peripheral conversion of T₄ to T₃. Recent clinical studies have documented the suppressive effect of selenium treatment on serum anti-thyroid peroxidase concentrations in patients with HT.

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Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is part of the spectrum of autoimmune thyroid diseases (AITD) [1, 2]. By strict criteria, HT is a histological diagnosis first described in 1912 by Hakaru Hashimoto, a Japanese surgeon working in Berlin, Germany [3]. Thyroid cells destruction is observed in HT but there is a debate regarding its exact mechanism [1, 4]. HT is characterised by an enlargement of the thyroid gland with infiltration with lymphocytes, oncocytes and fibrosis elements, associated with various degrees of thyroid hypofunction and circulating antibodies to thyroid antigens [5]. Current views referring to diagnosis and treatment of HT will be presented.

The contribution of nuclear medicine to diagnosis and differential diagnosis of HT is remarkable. Most of the laboratory tests for the evaluation of thyroid gland function and structure are nuclear medicine tests providing more accurate results as compared to the tests unrelated to nuclear medicine. The measurement of serum concentration of thyroid-stimulating hormone (TSH), total and free thyroxine (T₄) and + riodo thyronine (T₃), antithyroid peroxidase (anti-TPO), antimicrosomal (anti-TM) or antithyroglobulin (anti-Tg) antibodies are performed with radioimmunoassays (RIA) or immunoradiometric assays (IRMA). The measurement of thyroid uptake and scintigraphy studies are also important. Studies indicate that thyroid peroxidase (TPO) is the major component of thyroid microsomal antigen recognized by autoantibodies. Determination of autoantibodies against TPO has the same significance as the measurement of antibodies against microsomal antigen. Values of thyroid microsomal (TM) and thyroglobulin (Tg) antibodies below 50 IU/ml are usually considered as negative although every laboratory should define its own clinical range of significance.

Women express thyroid autoimmunity more frequently than men. This tendency is even more obvious at the postmenopausal period. These women with significant autoantibody levels against the TM or the TPO antigen, against Tg and to a lesser extent against TSH receptor, are prone to develop HT resulting in thyroid atrophy and hypothyroidism [1, 2].

In HT the thyroid gland is usually diffusely enlarged, firm, and finely nodular [2]. One thyroid lobe may be asymmetrically enlarged, raising concerns about neoplasm. Patients with HT who have a thyroid nodule should have an ultrasound-guided fine needle aspiration (FNA) biopsy, since the risk of concurrent papillary thyroid cancer is about 8% in these patients [2]. About 10% of cases at the time of diagnosis, particularly elderly women, have an atrophic and fibrotic thyroid gland [2].

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Clinical manifestations of HT are variable and commonly include diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism which shows a combination of elevated serum TSH concentrations and normal free T₄ and T₃ concentrations and permanent hypothyroidism. Not often, HT causes acute destruction of thyroid tissue and release in blood of stored thyroid hormones, causing transient thyrotoxicosis. This condition has been termed “Hashitoxicosis” or “painless sporadic thyroiditis”, or “painless postpartum thyroiditis” when occurs in women after delivery [1, 2]. In Hashitoxicosis serum TSH is suppressed, and total and free T₃ and T₄ are elevated. Also, serum T₄ is proportionally higher than T₃, reflecting the ratio of stored hormones in the thyroid gland, whereas in Graves’ disease (GD) and in toxic nodular goiter, T₃ is preferentially elevated [1]. Rarely, a hypofunctioning gland in HT may become hyperfunctioning with the onset of coexistent GD. In patients with GD, HT is usually present concurrently [2].

Elevated anti-TPO or anti-Tg antibody titers are the most specific laboratory findings to establish the diagnosis of autoimmune thyroid disease (AITD), typically making biopsy unnecessary. The 24-hours thyroid radioactive iodine-123 or -131 (¹²³I or ¹³¹I) uptake (RIU) is also helpful to distinguish Hashitoxicosis from GD; the RIU is low in patients with Hashitoxicosis, whereas it is elevated in those with GD [1, 2]. ¹²³I is preferred than ¹³¹I because it has a shorter half-life (13 hours for ¹²³I, 8 days for ¹³¹I) allowing quicker dissipation of background radiation [2, 6]. Since radioactive iodine is secreted in breast milk, and ¹²³I has a short half-life, it is recommended for diagnostic thyroid studies in nursing mothers [1, 2]. Breast milk must be pumped and discarded for 2 days after the intake of ¹²³I either used for thyroid uptake or for thyroid scanning [1].

Scintigraphy reveals in-homogeneous activity throughout the gland in 50% and a pattern suggestive of either hot or cold nodules or a combination of both in 30% of patients. Twenty percent of patient with HT have normal findings at the scintigraphic thyroid imaging.

If overt hypothyroidism is present, the treatment of choice for HT is the administration of L-thyroxine (L-T₄) in the usual replacement doses. We also use L-T₄ to treat patients with HT subclinical hypothyroidism and high serum thyroid antibody concentrations, because in these cases a progression to overt hypothyroidism is common and hyperlipidemia and atherosclerotic heart disease may develop [1]. L-T₄ may mildly and indirectly suppress serum concentrations of autoantibodies due to decreased stimulation of thyroid tissue by TSH and causing reduction of antigenic production [7, 8]. The goal of treatment is to restore clinically and biochemically an euthyroid state. For that, free T₄ levels must be within the reference range and TSH at the lower half of the reference range. The usual dose of L-T₄ is 1.6-1.8 µg/kg per day and is patient dependent. Elderly patients usually require a smaller dose of L-T₄, sometimes less than 1 µg/kg per day. The initial dose and the optimal time needed to establish the full replacement dose as above should be individualised relative to age, weight and cardiac status.

In HT patients with a large goiter and normal or elevated serum TSH, L-T₄ may be given in doses sufficient to suppress serum TSH in an effort to shrink the thyroid [2]. Suppressive doses of L-T₄ tend to shrink the goiter by average of 30% over 6 months [2]. If the goiter does not regress, the L-T₄ doses are lowered. Goiters that are hard and fibrotic do not respond to L-T₄ treatment.

If the thyroid gland is only minimally enlarged, the patient is euthyroid and TSH levels are normal, the patient should remain under medical supervision, since hypothyroidism may often develop years later [2]. Also, patients should be informed about the importance of compliance with replacement treatment and instructed to report any symptoms suggesting hyperthyroidism that could be due to an overdose of L-T₄.

The intake of L-T₄ should be apart by at least 4 hours from other drugs like calcium carbonate, ferrous sulfate, cholestyramine, sucralfate, iron-containing multivitamins, antacids containing aluminum hydroxide, phenytoin sodium, carbamazepine and amiodarone HCL, all of which impair the absorption/metabolism of L-T₄ [9, 10].

Selenium (Se) supplementation in patients with AITD, including HT, seems to modify the inflammatory and immune responses, probably by enhancing plasma glutathione peroxidase (GPX) and thioredoxin reductase (TR) activity and by decreasing toxic concentrations of hydrogen peroxide (H₂O₂) and lipid hydroperoxides, resulting from thyroid hormone synthesis [11,12]. When Se intake is adequate the intracellular GPX and TR systems protect the thyrocyte from these peroxides, considering that oxidative stress induces TR1 and GPX [11,13]. The current recommended dietary intake of selenium in humans to achieve the maximal activity of GPX in plasma or in erythrocytes is between 55 and 75 µg per day [14,15]. It must be considered that organic forms of Se such as Se-methionine and yeast-bound Se, have a much lower toxicity and a much higher effectiveness and safety than inorganic Se like sodium selenate. Several studies have revealed a significant reduction of anti-TPO concentrations in patients with AITD treated with 200 µg Se per day for three, six, or nine months [16-19]. Duntas et al. found an overall decrease of 46% of AITD at 3 months (P<0.0001) and of 55.5% at 6 months (P<0.05) of treatment with L-selenomethionine plus L-T₄ [17]. Others found a decrease of 26.2% at 3 months (P<0.001) and an additional 23.7% at 6 months (P<0.01) after L-Se-methionine treatment [18]. A significant decrease in the mean serum anti-TPO levels was also noted after the daily intake of 200 µg sodium selenite for 3 months [16]. This decrease amounted to 36.4% in the selenium-taking group of patients versus 12% in the control group (P = 0.013) [16]. A recent in press prospective study of ours in 80 Greek women with HT showed a significant reduction of serum anti-TPO levels during the first 6 months of L-Se-methionine treatment (P<0.0001). Anti-TPO decreased by 5.6% and by 9.9% after 3 and 6 months of L-Se-methionine treatment, respectively [20]. The extension of L-Se-methionine supplementation for 6 more months resulted in an additional 8% decrease, while cessation of treatment resulted to a 4.8% increase, in the an-

ti-TPO concentrations [20]. Further controlled and extensive studies are needed to clarify the exact mechanisms by which Se exerts effects on anti-TPO production, and investigate the long-term clinical effects of Se treatment.

In a study involving 21 patients with HT and subclinical hypothyroidism, simvastatin in a daily dose of 20 mg orally for a period of eight weeks improved thyroid function inducing an increase in serum free T₃ and free T₄ levels and a decrease in TSH levels. Decreases in anti-TPO and anti-Tg antibodies were not statistically significant, possibly by stimulating apoptosis of certain types of lymphocytes [4]. Further controlled and extensive studies are needed to investigate the effectiveness of statins treatment on the course of HT.

Patients with Hashitoxicosis may have only mild thyrotoxicosis and may not require treatment. Antithyroid drug treatment with thiourea drugs is contraindicated, because there is no excess of thyroid hormone production [1, 2]. Patients who have more symptoms should have a 24-hours thyroid RIU test and a radioiodine scan to determine whether GD may be present and may be treated with beta-blockers [1, 2]. In symptomatically thyrotoxic patients with low thyroid ¹²³I uptake test, propranolol treatment is continued and sodium ipodate or iopanoic acid may also be given in doses of 500 mg daily orally, until the patient is euthyroid [2]. Sodium ipodate and iopanoic acid are known iodinated contrast oral cholecystographic agents that inhibit peripheral 5'-monodeiodination of thyroxine, thereby blocking its conversion to active T₃ [2, 21]. Patients having low thyroid RIU do not respond to thiourea medication.

Patients with HT and a large goiter with pressure symptoms such as dysphagia, voice hoarseness, stridor and respiratory distress, may require surgical care. Also, in HT the presence of a malignant nodule or of a thyroid lymphoma diagnosed by histology after a fine-needle aspiration is an absolute indication for thyroidectomy.

The above indicate the special clinical and laboratory characteristics of HT and the importance of nuclear medicine procedures for its diagnosis and treatment. Se supplementation seems to have a therapeutic role in the disease. Treatment of HT is a rather complex procedure. Hopefully, more research will bring more therapeutic means for HT in the future.

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