Hashimoto's thyroiditis

How to spot the diagnosis and how to manage it

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KEY POINTS

- Hashimoto's thyroiditis is a chronic destructive autoimmune inflammatory disorder of the thyroid gland.
- Hashimoto's thyroiditis is the leading cause of hypothyroidism in Australia.
- The decision to commence levothyroxine therapy should be based on an assessment of thyroid function tests (particularly measurement of the serum thyroid stimulating hormone level), symptoms of hypothyroidism, patient age, comorbid conditions and patient preference.
- Pregnancy requires careful management in patients with Hashimoto's thyroiditis to prevent adverse obstetric and fetal outcomes.
- Managing patients whose symptoms persist after they have achieved a euthyroid state with levothyroxine therapy is a clinical challenge.
- Hashimoto's thyroiditis is associated with other autoimmune disorders, including coeliac disease, type 1 diabetes and pernicious anaemia.

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Hashimoto's thyroiditis is a chronic destructive autoimmune disorder and the leading cause of hypothyroidism in Australia. Its high prevalence justifies a low threshold for measuring thyroid stimulating hormone (TSH) level in adults, particularly women. Decisions about who to treat should be based on thyroid function test results, symptoms of hypothyroidism, patient age, comorbid conditions and patient preference.

Hashimoto's thyroiditis, also termed Hashimoto's disease or autoimmune thyroiditis, is a chronic inflammation of the thyroid gland and the most common cause of hypothyroidism in iodine-sufficient areas of the world. It is characterised by gradual thyroid failure, with or without goitre formation, caused by autoimmune-mediated destruction of the thyroid gland.

Classically, Hashimoto's thyroiditis occurs as a painless, diffuse, firm enlargement of the thyroid gland in young to middle-aged women, ultimately progressing to hypothyroidism. Many patients do not have hypothyroidism at first presentation, and others have no goitre or may have an atrophic thyroid gland. The clinical expression in patients with Hashimoto's thyroiditis is thus quite heterogeneous. The presence of serum autoantibodies against thyroid tissues, antithyroglobulin (TgAb) and antithyroperoxidase (TPOAb), and particularly TPOAb alone without any other discernible abnormality, is considered to be sufficient evidence for the diagnosis of underlying Hashimoto's thyroiditis.

Aetiology and pathophysiology

Hashimoto's thyroiditis appears to be caused by an interaction between genetic susceptibility and environmental factors. The condition was first described in 1912 by Dr Hakaru Hashimoto, based on the observation of intense lymphocytic infiltration in thyroid gland specimens surgically resected from patients with goitre, termed 'struma lymphomatosa'.[1]

Thyroid autoimmunity in Hashimoto's thyroiditis is characterised by the production of antibodies against thyroid tissue and gradual destruction of the thyroid gland. Thyroid autoantibodies TgAb and TPOAb are found in the blood of most patients, but levels fluctuate unpredictably and they may even become undetectable, only to recur later. Serum antibody concentrations do not correlate with the degree of disease activity. Less often found are antibodies to the thyroid stimulating hormone (TSH) receptor, which characterise Graves' disease.

CLINICAL MANIFESTATIONS OF HYPOTHYROIDISM

Common signs and symptoms

- Weight gain, fluid retention, puffy face
- Dry skin and hair loss, especially outer eyebrows
- Cold sensitivity
- Voice changes (e.g. hoarse, husky)
- Bradycardia
- Fatigue
- Constipation
- Dyslipidaemia
- Delayed relaxation of ankle reflexes

Less common signs and symptoms

- Cognitive impairment
- Anxiety or depression
- Infertility or recurrent miscarriage
- Obstructive sleep apnoea
- Carotenaemia (yellowing of skin)
- Carpal tunnel syndrome
- Pericardial effusion
- Galactorrhoea
- Menorrhagia

There is a clear genetic susceptibility to Hashimoto's thyroiditis.[2] It occurs 10 times more often in females than in males and it clusters in families, sometimes alone and sometimes in combination with Graves' disease and other autoimmune disorders. The human leucocyte antigens HLA-DR3 and HLA-DR5 are linked to the disorder, with HLA-DR3 being more closely linked to the atrophic type and HLA-DR5 to the goitrous type. The recurrence risk ratio among siblings is more than 20-fold, and the concordance rate in monozygotic twins is 30 to 60%.[3] Relatives of patients with Hashimoto's thyroiditis have a ninefold increased risk of developing the disorder compared with the general population.[4]

Infection, stress, sex steroids, pregnancy, excessive iodine intake, selenium deficiency and radiation exposure have been described as possible precipitating factors for Hashimoto's thyroiditis. The role of smoking in the disorder, unlike Graves' disease, remains controversial. In genetically susceptible individuals, environmental factors may precipitate thyroid autoimmunity by inducing immunogenicity of thyroid antigens, especially thyroglobulin and thyroid peroxidase, enhancing antigen presentation and reducing self-tolerance.

A number of medications can induce Hashimoto's thyroiditis. For example, interferon-alfa, used in hepatitis C treatment, and several of the new monoclonal antibodies used in the treatment of melanoma (ipilimumab, nivolumab and pembrolizumab) can induce Hashimoto's thyroiditis, so monitoring of thyroid function is prudent in patients receiving these treatments. Amiodarone and lithium are known inducers or precipitants of hypothyroidism in patients with Hashimoto's thyroiditis.

Epidemiology

Around 10 to 20% of the population have evidence of thyroid autoimmunity based on the presence of thyroid autoantibodies, but prevalence may vary with age, sex and ethnicity. Hypothyroidism was found in 4.6% of the US population (0.3% clinical and 4.3% subclinical) in the National Health and Nutrition Examination Survey (NHANES III).[5]

A Western Australian study showed that the prevalence of elevated thyroid antibody levels was 12.4% among people with no history of thyroid disease and was more common in women than in men.[6] Thyroid antibodies have been reported in 18 to 24% of pregnant women in Sydney, indicating that Hashimoto's thyroiditis is common and mostly undetected in the population.[7,8]

Clinical features and diagnosis

The clinical presentation of Hashimoto's thyroiditis is heterogeneous. It can present with:

- goitre and a euthyroid state
- incidental detection of circulating thyroid antibodies in the absence of symptoms (increasingly detected by screening during pregnancy or investigation of infertility or miscarriage)
- subclinical hypothyroidism (an elevated TSH level but a normal free thyroxine [T4] level)
- overt hypothyroidism (elevated TSH level with a free T4 level below normal)
- hyperthyroidism (so-called hashitoxicosis)
- alternating hypothyroidism and hyperthyroidism (rare)
- postpartum thyroiditis
- Hashimoto's encephalopathy (very rare).

Clinical manifestations of hypothyroidism are listed in the Box.

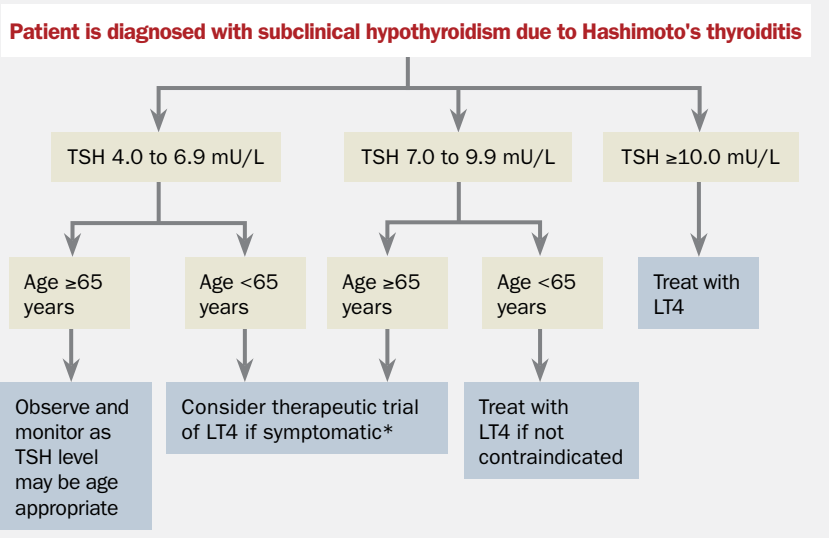
Subclinical hypothyroidism is a common presentation, defined as the presence of an elevated TSH level, with a normal free T4 level. Most patients with subclinical hypothyroidism have minimal or no specific symptoms. It can be challenging to determine the extent that a patient's symptoms are due to mild thyroid dysfunction, because of the high rate of nonspecific symptoms such as weight gain, fatigue and hair loss in the general population.

The usual course of Hashimoto's thyroiditis is a gradual loss of thyroid function

with a large array of possible symptoms and signs, many of which are nonspecific. Overt hypothyroidism occurs at a rate of about 5% per year in patients with subclinical hypothyroidism. Patients with subclinical hypothyroidism without symptoms can usually be monitored with annual laboratory and clinical assessment (Flowchart). Overt hypothyroidism, once it occurs, is permanent in nearly all cases, except in some children and postpartum women, in whom it is often but not always transient.

Infrequently, Hashimoto's thyroiditis may evolve into hyperthyroidism. The hyperthyroidism is typically transient and thought to be due to release of preformed thyroid hormone from the inflamed gland. Patients with Hashimoto's thyroiditis also have an increased risk of developing Graves' disease. Measurement of thyroid receptor antibody levels and/or a thyroid radionuclide uptake scan can usually assist in making a diagnosis.

ALGORITHM FOR THYROID HORMONE REPLACEMENT IN ADULTS WITH SUBCLINICAL HYPOTHYROIDISM DUE TO HASHIMOTO'S THYROIDITIS



Abbreviations: LT4 = levothyroxine; TSH = thyroid stimulating hormone.
* Patients who commence LT4 therapy for symptoms attributed to subclinical hypothyroidism should be reviewed after three or four months to assess response to treatment once the serum TSH returns to the reference range. If symptoms have not improved then LT4 therapy should generally be discontinued and the patient reviewed for other disorders.

Investigation

Diagnostic testing for Hashimoto's thyroiditis requires measurement of serum TSH, free T4 and thyroid autoantibodies, specifically TPOAb, which is the hallmark for diagnosis. Thyroid ultrasound examination is not routinely required in the management of Hashimoto's thyroiditis; however, a hypoechoic or heterogeneous thyroid echo pattern may be seen on ultrasound examination before circulating autoantibodies are detectable and provides early evidence for thyroid autoimmunity. Ultrasound examination may have a role in patients with clinically palpable nodules or a goitre and in those presenting with hypothyroidism with no detectable thyroid antibodies.

Hashimoto's thyroiditis is occasionally first diagnosed by thyroid fine needle aspiration cytology (FNAC) that shows lymphocytic thyroiditis in individuals undergoing diagnostic evaluation of a thyroid nodule. However, FNAC is not recommended for the purpose of diagnosing Hashimoto's thyroiditis.

Thyroid uptake scans using the isotope technetium (Tc-99m) are not generally needed in patients with Hashimoto's thyroiditis but may be useful in patients presenting with hyperthyroidism.

Can therapy prevent progression to hypothyroidism?

Patients often ask what steps they can take to preserve thyroid function and to avoid the need for thyroid hormone replacement therapy. Some choose to consult natural therapy practitioners who may provide a range of nonevidence-based supplements. There is little or no evidence to support the efficacy of any of the available natural therapies, and some may even cause harm by precipitating hypothyroidism.

Recent therapeutic interest has centred on selenium supplementation. There is proven benefit of selenium supplementation in patients with mild to moderate Graves' orbitopathy, perhaps mediated through reductions in levels of thyroid receptor antibodies.[9] Some small studies have suggested that selenium may help reduce the levels of thyroid autoantibodies, but the clinical benefit is uncertain.[10]

Excessive iodine intake may increase the incidence of autoimmune thyroiditis in populations and precipitate hypothyroidism in individuals, so supplements beyond normal physiological replacement are contraindicated. The exception is during pregnancy, when increased iodine requirements have led to a recommendation for iodine supplementation to help achieve the recommended daily intake of 250 µg/day.

Autoimmune disorders associated with Hashimoto's thyroiditis

Hashimoto's thyroiditis is associated with the development of other autoimmune disorders, such as type 1 diabetes; polyglandular autoimmune disorders involving the thyroid, adrenal gland and ovaries; lymphocytic hypophysitis; coeliac disease; atrophic gastritis and pernicious anaemia; myasthenia gravis; lupus; and Sjögren's syndrome. Clinicians should always consider the possibility of other latent or overt

autoimmune disorders coexisting with Hashimoto's thyroiditis, particularly in patients who are well treated but have unexplained symptoms.

Treatment of Hashimoto's thyroiditis

When is levothyroxine needed?

The decision to commence levothyroxine treatment should be based on thyroid function test results after consideration of clinical symptoms and signs, patient age, comorbid conditions, goitre size and patient preference.

Patients with overt hypothyroidism (serum TSH level 10 mU/L or over and serum free T4 level below the reference range) confirmed on repeat testing should be given replacement therapy with levothyroxine.

The decision to commence levothyroxine in patients with subclinical hypothyroidism is more complex and remains contentious except in pregnant women. Over the years, many different guidelines have been recommended without definitive supporting evidence. The algorithm we use in clinical practice assumes an upper limit of normal for the serum TSH level in nonpregnant adults of 4.0 mU/L and that the patient is thyroid antibody positive on at least one occasion.

Most guidelines recommend levothyroxine treatment if the TSH level is 10 mU/L or over, but a lower TSH threshold may be appropriate in younger individuals and in people who report symptoms of hypothyroidism. Patients who are not treated should have annual monitoring of thyroid function.

Age-specific local reference ranges for serum TSH should be considered when establishing a diagnosis of subclinical hypothyroidism, particularly in older people. A recent placebo-controlled, randomised, double-blind study failed to find any benefit from treatment of subclinical hypothyroidism (mean baseline TSH 6.4 mU/L) in 737 elderly patients.[11] Most elderly patients with subclinical hypothyroidism should be carefully followed up with a wait-and-see strategy, generally avoiding hormonal treatment, particularly if they have cardiovascular disease.[12]

Goals of therapy

In most patients who are established on levothyroxine therapy, hypothyroidism is permanent, requiring lifelong treatment. The goals of therapy are amelioration of hypothyroid symptoms, restoration of a euthyroid state (judged clinically and by thyroid function tests) and avoidance of overtreatment. Restoration of the euthyroid state can be readily accomplished in almost all patients by oral administration of synthetic levothyroxine. It is not necessary to supplement with tri-iodothyronine (T3).

Because the plasma half-life of T4 is long (seven days), once-daily doses result in stable serum T4 and T3 concentrations after a steady state is reached. Mildly elevated levels of free T4 may be seen if blood is taken in the first few hours after a dose. In general, it is best to base dosing decisions predominantly on TSH levels.

What dose is needed?

The average full replacement dose of levothyroxine in adults who lack a functional thyroid gland is approximately 1.6 μg/kg body weight/day (112 μg/day in a 70 kg adult), but the range of required doses is wide. Levothyroxine requirements correlate better with lean body mass than with total body weight. The dose of levothyroxine is usually less in patients with Hashimoto's thyroiditis compared with those who lack a thyroid, because of a degree of residual thyroid function, so it is prudent to start with a low dose of levothyroxine of 50 μg/day.

Levothyroxine is best taken as a single daily dose first thing in the morning. It should be taken with water and on an empty stomach, at least 30 minutes and preferably 60 minutes before the patient has any food or takes other medications that may impair absorption. Bedtime dosing may be a reasonable alternative for those unable to take their medication first thing in the morning. Care should also be taken not to coadminister levothyroxine with supplements that can reduce absorption (commonly iron, calcium and zinc).

In patients treated with levothyroxine, symptoms usually improve within a few weeks, but complete recovery can take several months. Steady-state TSH concentrations are not achieved for at least six weeks, so it is generally best not to repeat TSH testing sooner than this after initiating levothyroxine therapy or changing the dose.

In patients receiving levothyroxine therapy it is generally appropriate to target a TSH level in the normal reference range. If a patient has ongoing possible hypothyroid symptoms and the serum TSH level is confirmed by repeat measurement to be at the upper limit or above the reference range then it is reasonable to increase the dose and aim for a serum TSH level in the lower half of the normal range. Some studies have suggested that psychological wellbeing is better in patients with lower serum TSH concentrations.[13]

Thyroid surgery

Thyroid surgery may be indicated in patients with a large goitre causing symptomatic compression in the neck or a suspected or proven coexisting thyroid malignancy.

Persistent symptoms after achieving euthyroid state

Because many symptoms of hypothyroidism are nonspecific, patients often think that their levothyroxine dose is inadequate if tiredness persists or they cannot lose weight. Inadequacy of the current levothyroxine dose should be verified by measuring the serum TSH level before the dose is increased. In addition, clinicians should assess for other possible causes of symptoms, particularly associated endocrine disorders, as detailed above, and common causes of tiredness such as sleep apnoea.

There is ongoing controversy about the potential role for combination T4 and T3 therapy. In a systematic review of nine randomised trials, only one trial reported beneficial effects of combination T4 and T3 therapy on mood, quality of life and psychometric performance when

compared with levothyroxine therapy alone.[14] Studies have found that a patient preference for combination therapy is often associated with patients having a lower TSH level on this therapy (i.e. hormone over-replacement).[15]

Until clear advantages of combination therapy are demonstrated, levothyroxine alone should remain the treatment of choice for hypothyroidism. Combination T4 and T3 therapy may have a limited role in a few patients unable to convert T4 to T3 adequately in peripheral tissues. In this situation, combination therapy should generally be initiated under specialist supervision with care to avoid overtreatment. The European Thyroid Association has published guidelines with the intent of enhancing the safety of combination therapy.[16]

Desiccated thyroid extract was extensively used in the past to treat patients with Hashimoto's thyroiditis but is not recommended by any of the current expert therapeutic guidelines. It typically has a T4 to T3 ratio of 4:1 and therefore provides much more T3 than the physiological ratio of around 13:1 to 16:1. The result is that thyroid extract often produces supraphysiological T3 levels, with associated potential cardiac and bone risks.

Hashimoto's thyroiditis in pregnancy

Hashimoto's thyroiditis raises potentially serious issues for women attempting to conceive, and also during pregnancy and postpartum. Subclinical or overt hypothyroidism adversely affects fertility and, if suspected in women planning a pregnancy, should be confirmed and treated with levothyroxine.

During pregnancy, the maternal thyroid gland must increase thyroid hormone production by up to 50% over pre-pregnancy requirements to ensure normal fetal development and a good pregnancy outcome. Although the fetal thyroid commences development late in the first trimester, it contributes relatively little thyroid hormone until late in the third trimester. Thus fetal growth and development depend

almost entirely on thyroid hormone transferred from the mother. This challenge to the maternal thyroid commences within the first few weeks of pregnancy because of stimulation of the thyroid by human chorionic gonadotrophin, coupled with an oestrogen-induced increase in serum thyroxine binding globulin concentration, and increased placental de-iodination of maternal T4. Failure of the thyroid to meet the challenge predisposes to hypothyroidism and adverse obstetric events such as miscarriage, gestational hypertension, pre-eclampsia, premature birth and low birth weight.

There is a strong body of evidence that subclinical hypothyroidism can cause similar adverse obstetric events to overt hypothyroidism, but some authorities dispute this. Severe neurocognitive impairment is a well-recognised complication of overt maternal and fetal hypothyroidism, with lesser degrees of damage possible from subclinical hypothyroidism. These adverse effects are a consequence of decreased T4 transfer across the placenta to the fetus.

Although thyroid autoantibodies readily cross the placenta there is no evidence that they directly damage the fetal thyroid. Nevertheless, high titres of thyroid autoantibodies in the mother have been implicated in the increased miscarriage rates seen in women with Hashimoto's thyroiditis, independent of decreased maternal thyroid function, but the mechanism remains obscure.

Assessment and treatment in pregnancy

When assessing maternal thyroid function during pregnancy, it is important to use pregnancy-specific reference ranges for TSH and free T4 levels. As free T4 measurements are less reliable in pregnancy than in the non-pregnant state, measurement of serum TSH is the crucial test of thyroid function during pregnancy.

Although there is continuing controversy over the upper limit of normal for serum TSH in the first trimester, it is generally agreed that a serum TSH level between 4 and 10 mU/L is diagnostic of subclinical hypothyroidism during pregnancy, with a level of 10.0 mU/L and above representing overt hypothyroidism. Levothyroxine replacement is recommended for all of these patients.[17]

However, some expert guidelines define the cut-off point for subclinical hypothyroidism as a TSH level over 2.5 mU/L, so it remains a matter of opinion whether patients with TSH levels between 2.5 and 4.0 mU/L should be treated with levothyroxine.[18] Until we have better evidence from clinical trials, the authors recommend treating these women, particularly if they have detectable TPOAb, unless they decline treatment after an adequate explanation of current knowledge and expert recommendations.

Postpartum monitoring

Postpartum thyroid dysfunction occurs in approximately 10% of women within the first year after giving birth. Between 25% and 50% of women with pre-existing Hashimoto's thyroiditis during pregnancy are at risk of developing symptomatic postpartum thyroiditis, even if they remained euthyroid during the pregnancy. Consequently, all women who are positive for thyroid antibodies should be monitored clinically and with thyroid function tests if symptoms occur.

When to refer to an endocrinologist

Most patients with Hashimoto's thyroiditis and associated primary hypothyroidism can be managed by their GP. Referral to an endocrinologist should be considered for:

- children and infants
- women who are pregnant or planning conception
- patients in whom the diagnosis is uncertain
- patients with pluriglandular syndrome (associated type 1 diabetes, Addison's disease and premature ovarian failure)
- patients in whom it is difficult to achieve and maintain a euthyroid state, including those who may oscillate between hypothyroidism and hyperthyroidism
- elderly patients with coexisting cardiac disease
- patients with a goitre or nodules that raise suspicion of thyroid cancer.

Conclusion

Hashimoto's thyroiditis is characterised by chronic autoimmune thyroid destruction and is the leading cause of hypothyroidism in iodine-sufficient regions. Decisions about who to treat should be based on an assessment of thyroid function test results, symptoms of hypothyroidism, patient age, comorbid conditions and patient preference. Pregnant women with Hashimoto's thyroiditis require careful management to avoid adverse obstetric and fetal outcomes. Clinicians should always consider the possibility of other autoimmune disorders coexisting with Hashimoto's thyroiditis, particularly in well-treated patients with unexplained symptoms. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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