Hashimoto's thyroiditis

When to observe, to treat or to refer

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Most patients with Hashimoto's thyroiditis can be diagnosed and treated by their GPs, with specialist input in specific circumstances. The decision whether to observe patients or treat them with thyroxine replacement therapy depends on thyroid function results and factors such as age, symptoms and vascular risk.

Autoimmunity is the most common cause of thyroid disease in Australia, and Hashimoto's thyroiditis (HT) is the most common form of autoimmune thyroid disease. Most patients with HT can be diagnosed, investigated and treated by their GPs. Some patients may benefit from an initial consultation with an endocrinologist, but long-term specialist follow up is rarely necessary. Problems in diagnosis or arising during follow up may require endocrinologist assessment, but most patients have an uncomplicated course.

What is Hashimoto's thyroiditis?

HT is a chronic inflammation of the thyroid gland. It was first described over a century ago by Dr Hakaru Hashimoto as 'struma lymphomatosa'.[1] Originally identified in the context of goitre, the entity of HT has been broadened and now includes:

- classic goitrous HT with a firm bosselated thyroid gland with or without hypothyroidism
- nongoitrous autoimmune thyroid disease with a tendency to hypothyroidism
- atrophic thyroiditis, also termed the fibrous variant.

The condition is usually painless and presents in young to middle-aged women. Synonyms for HT include chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis and lymphomatoid goitre.

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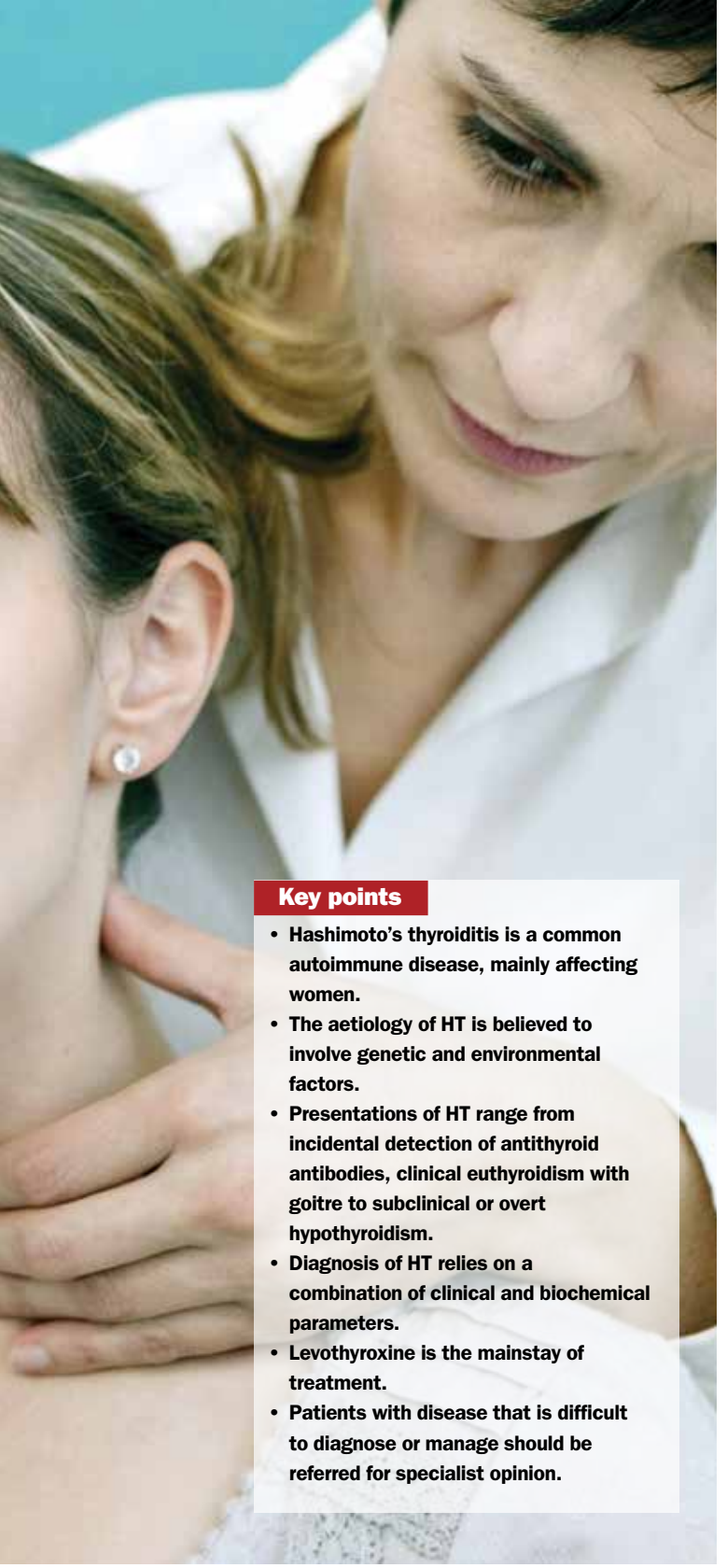


Key points

- **Hashimoto's thyroiditis is a common autoimmune disease, mainly affecting women.**
- **The aetiology of HT is believed to involve genetic and environmental factors.**
- **Presentations of HT range from incidental detection of antithyroid antibodies, clinical euthyroidism with goitre to subclinical or overt hypothyroidism.**
- **Diagnosis of HT relies on a combination of clinical and biochemical parameters.**
- **Levothyroxine is the mainstay of treatment.**
- **Patients with disease that is difficult to diagnose or manage should be referred for specialist opinion.**

Aetiology and pathophysiology

HT was defined as an autoimmune disease of the thyroid in the 1950s, when antithyroglobulin antibodies (aTg) were identified in the serum of patients with HT.[2] At the same time, an experimental model of autoimmune thyroiditis was established by autoimmunisation of rabbits with thyroglobulin.[3] In addition, a circulating factor stimulating the thyroid was identified in patients with Graves' disease, which was subsequently shown to be an antibody directed against the receptor for thyroid-stimulating hormone (TSH).[4]

Nevertheless, the pathogenesis of HT is still not completely understood. Many factors impinge on its development, including:

- genetic factors linked to the expression of autoimmunity, such as HLA type (HLA-DR3 is linked to atrophic HT and DR-5 to goitrous HT)
- environmental factors, such as iodine intake, infections, smoking, pregnancy and certain drugs.

Loss of immune tolerance to thyroid cells leads to the production of antibodies against thyroid tissue and destruction of the thyroid gland. Thyroid peroxidase, an enzyme that catalyses the oxidation of iodine and thyroglobulin, plays an important role as an autoantigen. The presence of antithyroid peroxidase antibodies (aTPO; originally termed antimicrosomal antibodies) is a more sensitive marker of thyroid autoimmunity than the presence of aTg. Measurement of aTg level survives only as an historical vestige, with its only clinical application being to validate thyroglobulin assay in the follow up of thyroid cancer.

B lymphocytes that have been stimulated by antigen-presenting cells produce the antibodies aTg and aTPO, leading to apoptosis of thyroid cells and destruction of the thyroid gland.[5] Simultaneously, cytotoxic T cells, especially T helper type 1 (Th1) cells, are also activated and secrete regulatory cytokines such as interleukin-12, interferon-γ and tumour necrosis factor-α, which also initiate apoptosis of thyroid cells.[6] Pathologically, the thyroid shows destruction of epithelial (thyroid follicular) cells, lymphocytic infiltration that may form immune follicles and germinal centres, and fibrosis. TSH-receptor antibodies may be produced, at least for a time, and can be either stimulatory as in Graves' disease or blocking in up to 10% of patients with HT.

Epidemiology

The mean incidence of hypothyroidism in women, mostly due to HT, is 4.1 per 1000 annually, according to an epidemiological study from the UK.[7] The incidence of HT in an Australian community (Busselton survey carried out in Western Australia from 1981 to 1994) is estimated to be 273 per 100,000 annually.[8] In aTPO-positive women, the prevalence of hypothyroidism (defined by a TSH level greater than 4 mIU/L) was 87%. Women are eight times more commonly affected than men, and HT is more common in Asian and European people than in African-American people.[9]

Clinical features of HT

HT has a variety of clinical presentations including:

- clinical euthyroidism with goitre
- incidental detection of antithyroid antibodies (aTPO or aTg)
- subclinical hypothyroidism (raised TSH level but normal free thyroxine [fT4] and free tri-iodothyronine [fT3] levels)
- overt hypothyroidism (raised TSH level and a low fT4 level).

Some patients present with an initial hyperthyroid phase (see below, Hashitoxicosis). HT can be associated with other immune-mediated fibroinflammatory diseases with high IgG4 levels

1. Clinical manifestations of hypothyroidism

Reduced metabolic rate

- Lethargy
- Constipation
- Weight gain
- Cold intolerance
- Slow mentation
- Bradycardia
- Delayed relaxation of tendon reflexes

Accumulation of matrix protein (glycosaminoglycans)

- Puffy face
- Loss of eyebrows
- Periorbital oedema
- Hoarseness of voice
- Oedema
- Dry skin
- Macroglossia

Other manifestations

- Pericardial effusion
- Menorrhagia
- Myopathy
- Galactorrhoea

(IgG4-related disease), including type 1 autoimmune pancreatitis, retroperitoneal fibrosis, mediastinal fibrosis and inflammatory pseudotumour.[10]

Manifestations of thyroid hormone deficiency are diverse, reflecting the wide range of cells and tissues influenced by thyroid hormone. The clinical features are often not specific, usually appear gradually and become severe with HT progression, as functional thyroid tissue become atrophic and is replaced by fibrosis.[11] Some common clinical manifestations of HT are shown in Box 1.

Clinical variations of HT

Subclinical hypothyroidism

Subclinical hypothyroidism is a very common presentation of HT. Patients have minimal or no symptoms, with a mild elevation of TSH level (usually less than 10 mIU/L) and, by definition, normal levels of fT4 and fT3.

Patients with overt hypothyroidism (low fT4 as well as raised TSH levels) generally have clinical features, although few patients have all the classic symptoms and signs. These are usually seen only when the biochemical abnormalities are marked, with a very low fT4 level (e.g. less than 5 pmol/L) and a TSH level well above 10 mIU/L. Some patients with HT have only a goitre and no symptoms of hypothyroidism or biochemical abnormalities of thyroid function.

Twenty-year follow up of patients in a UK study showed that the annual rate of progression from subclinical hypothyroidism to overt hypothyroidism was 4.3% in women who had both raised serum TSH levels and antithyroid antibodies, 3% if only serum TSH was raised, and 2% if only antithyroid antibodies were present.[7] A TSH level greater than 2 mIU/L increased the long-term risk of evolution to hypothyroidism but was not in itself diagnostic of hypothyroidism.[7] Therefore, annual surveillance of patients with subclinical hypothyroidism is appropriate to detect biochemical progression and the development of symptoms of hypothyroidism.

HT in pregnancy

HT in pregnancy is an important entity with the risk of serious clinical sequelae if untreated. Subclinical hypothyroidism can reduce fertility and thus optimisation of TSH levels before conception is appropriate. Subclinical hypothyroidism in pregnancy can increase the risk of miscarriage and premature birth; this risk is reduced by thyroxine treatment.[12] Thus current treatment guidelines recommend a TSH level less than 2.5 mIU/L in the first trimester of pregnancy and less than 3 mIU/L later in pregnancy in women with known thyroid autoimmunity. There is evidence for IQ impairment in offspring with raised maternal TSH levels through pregnancy, but whether thyroxine treatment in pregnancy prevents this has not been established.[13] The presence of aTPO increases the rate of miscarriages.[14] However, use of thyroxine in aTPO-positive women with a normal TSH level is not established practice despite one trial suggesting benefit.[12]

2. Medications that can induce Hashimoto's thyroiditis

- Alemtuzumab
- Amiodarone
- Interferon-alfa
- Ipilimumab
- Nivolumab
- Pembrolizumab
- Recombinant interleukin-2

Drug-induced HT

A number of drugs can induce HT (Box 2). Interferon-alfa used in treatment of chronic hepatitis C can induce HT (and Graves' disease), perhaps because it induces a Th1 immune response. This results in increased levels of interferon-γ, which then induces anomalous MHC class II gene expression in thyrocytes and triggers an autoimmune response against the thyroid.[15]

The new drugs ipilimumab, pembrolizumab and nivolumab used in treatment of patients with malignant melanoma can all induce HT. Ipilimumab is an antibody against a cytotoxic T-lymphocyte protein (CTL-4), which functions as an immune checkpoint to downregulate the immune response. Pembrolizumab and nivolumab are antibodies against another immune checkpoint protein, programmed cell death receptor PD-1. Both classes of drug impair inhibitory immune mechanisms and thus promote immune responses, including autoimmunity.[16] Recombinant interleukin-2 therapy in patients with melanoma can also induce HT but is now little used since the above more effective therapies became available.

Alemtuzumab, a new agent for the treatment of patients with relapsing-remitting multiple sclerosis, can induce autoimmune thyroid disease.[17] This is more likely to be Graves' hyperthyroidism, but HT can also occur.

Amiodarone-induced hypothyroidism is more likely in patients with pre-existing antithyroid antibodies. It is probably a manifestation of the adverse effect of excessive iodine on autoimmune thyroid disease via a prolonged Wolff-Chaikoff effect (see below,

Role of iodine) and enhanced immunogenicity of highly iodinated thyroglobulin.[18]

Juvenile HT

A juvenile variant of HT occurs, with a mean age of presentation of 11 years. Although most children with HT have a goitre at presentation, they are usually otherwise asymptomatic. Disease progression varies, with some experiencing remission and others developing hypothyroidism.[19] Growth retardation associated with delayed bone age can occur. Circulating antithyroid antibodies and thyroid fibrosis are less likely to be present than in the adult form of HT.

Hashitoxicosis

Hashitoxicosis is a confusing term originally defined as the clinical appearance of Graves' hyperthyroidism with the histological appearance of HT, but it is not a single entity.[20]

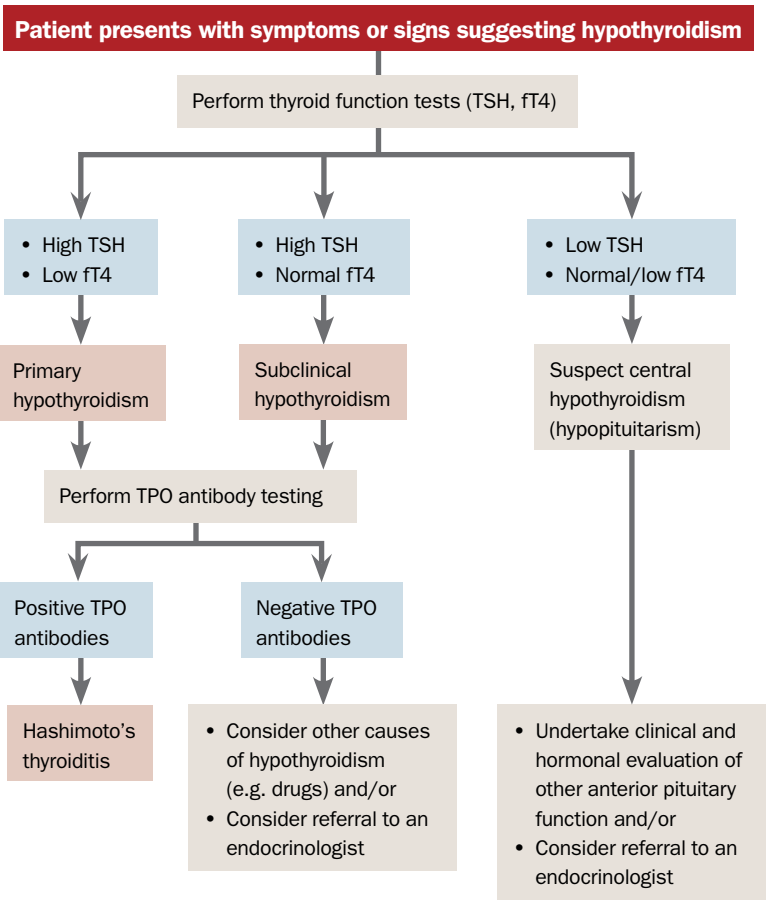
Hyperthyroidism can be associated with increased thyroidal iodine uptake and the presence of TSH-receptor antibodies – essentially Graves' disease – with an eventual high rate of evolution to hypothyroidism over three to 24 months. Hyperthyroidism in HT can also resemble the phase of subacute thyroiditis, with low iodine or pertechnetate uptake.[21]

Autoimmune thyroid disease is clearly associated with a spectrum of dysfunction, varying not only across the population and across individual families but also in some individuals over time. The presence of stimulatory TSH-receptor antibodies and sufficient responsive thyroid tissue can lead to hyperthyroidism, whereas in the absence of stimulatory antibodies, destructive antibody-mediated and cell-mediated immune processes predominate, potentially leading to hypothyroidism. These patterns can be related to changes in the relative preponderance of Th1 and T helper type 2 (Th2) immune processes over time.[22]

Silent and postpartum autoimmune thyroiditis

Silent autoimmune thyroiditis can progress similarly to subacute thyroiditis in a triphasic pattern, with initial hyperthyroidism followed by hypothyroidism and finally recovery of the thyroid gland to a normal state. It occurs sporadically but particularly during the postpartum period. In the latter case, hyperthyroidism develops within six months after delivery, usually lasts about a month and then transforms to a hypothyroid phase, which lasts up to six months, with recovery usual by a year after delivery.[23]

1. Suggested algorithm for evaluation of a patient with suspected hypothyroidism



Abbreviations: fT4 = free thyroxine; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

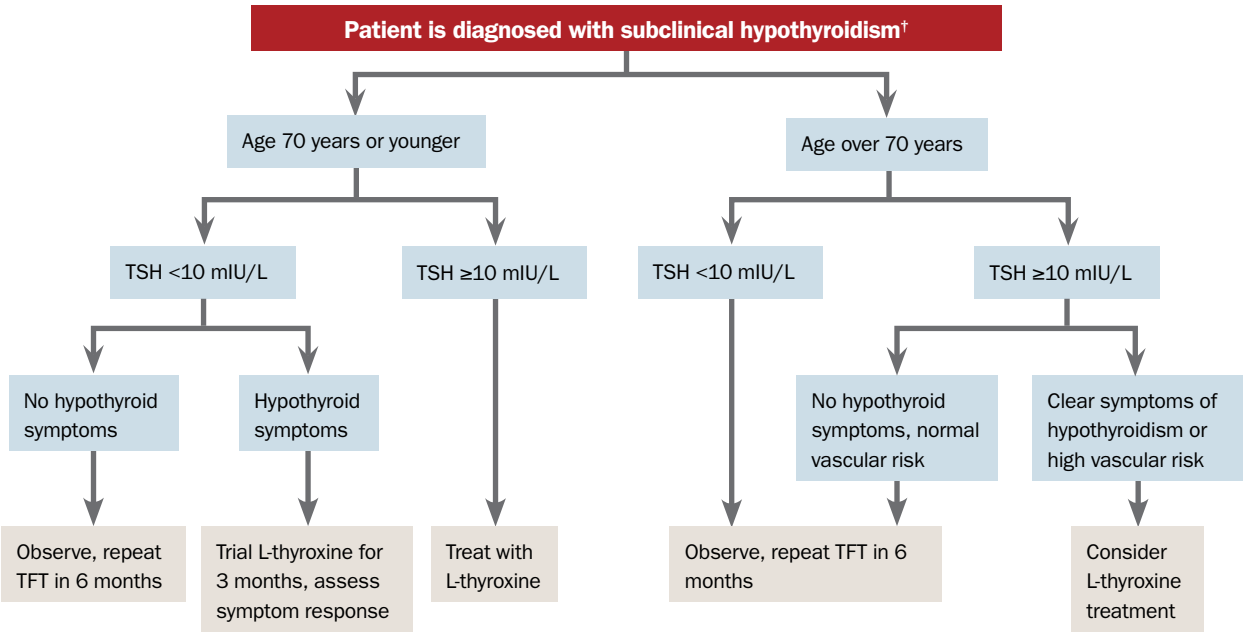
Diagnostic criteria

Diagnosis of HT is based on clinical features and results of biochemical investigations. Thyroid function tests (TFTs) should be ordered in any patient suspected to have HT. Although measurement of TSH level is a case-finding tool for primary hypothyroidism, we suggest never ordering this test alone but to always request TFTs. This allows the laboratory to reflexively measure fT4 level if the TSH level is abnormal. An increased TSH level with either a normal fT4 level (subclinical hypothyroidism) or reduced fT4 level (overt hypothyroidism) is diagnostic of primary hypothyroidism (Flowchart 1).

The best serological marker for diagnosis of HT is considered to be aTPO, as these antibodies are present in 95% of patients with HT.[24] Measurement of aTPO level is more sensitive for the diagnosis of autoimmune thyroid disease than measurement of aTg level.

Nuclear thyroid scans should not be ordered routinely. In patients with HT, uptake of technetium-99m pertechnate can be high, normal or low and is often patchy. The results of this test rarely contribute to management except when undiagnosed hyperthyroidism is present.

2. Suggested algorithm for management a patient with subclinical hypothyroidism*



* Adapted from Pearce, et al. Eur Thyroid J 2013; 2: 215-228.[34] † Defined as elevated serum TSH level and normal free thyroxine level.
Abbreviations: TFT = thyroid function test; TSH = thyroid-stimulating hormone.

Similarly, ultrasonography of the thyroid gland should not be ordered routinely but may be helpful when a thyroid nodule is found during neck examination. Surgical series suggest an association between HT and papillary thyroid carcinoma, but this was very likely caused by selection bias.[25] However, HT is associated with the rare condition of thyroid lymphoma. In patients with HT, the thyroid gland often shows a hypoechoic heterogeneous echotexture and is usually enlarged.

Fine-needle biopsy of the thyroid gland is not commonly used in patients with HT. The exception is to evaluate a thyroid nodule, when the decision to perform a biopsy should be made based on standard criteria such as irregular margin and microcalcification. In the rare cases when thyroid lymphoma is a possibility, core biopsy may be necessary.

Contributing factors and associations

Role of iodine

Iodine is an essential trace element required for thyroid function and synthesis of thyroid hormone. The recommended daily iodine intake is 150 µg, or 250 µg in pregnant women. Excess iodine has been shown to increase the incidence of HT and hypothyroidism. Epidemiological studies from China and Denmark have confirmed this association.[26,27] Iodine supplementation is believed to increase the prevalence of circulating aTPO. The underlying mechanism is yet to be elucidated but experimental models of autoimmune thyroiditis show that more highly iodinated thyroglobulin is more antigenic. Hypothyroidism may be due to a persistent inhibitory effect of iodine on thyroid hormone synthesis and secretion. This inhibitory effect, termed the Wolff–Chaikoff effect, is physiological but is pathologically persistent in HT.

Iodine supplementation should be discouraged in patients with HT as it is of no benefit and may possibly cause harm. However, the recommended daily iodine intake of 150 µg/day, or 250 µg/day during pregnancy, should not have an adverse effect on patients with HT.

Role of smoking

The association of smoking with HT is controversial. According to one study, the risk of hypothyroidism is increased among smokers with HT.[28] Conversely, patients with HT who smoke have been found to have lower aTPO levels.[29] Therefore, although smoking promotes Graves' disease severity and recurrence and Graves' ophthalmopathy, the effect on HT remains unclear.

Autoimmune associations of HT

HT has shown several associations with other autoimmune diseases. In the so-called thyrogastric cluster, HT and Graves' disease are associated with atrophic gastritis and pernicious anaemia. Therefore, patients with HT should be screened periodically, usually annually, for vitamin B_{12} deficiency and iron deficiency.

HT occurs together with Addison's disease (autoimmune primary adrenal failure) in Schmidt's disease, a type of autoimmune polyglandular syndrome. Patients with type 1 diabetes have a risk of HT of up to 30%.[30] Other autoimmune disorders, such as rheumatoid arthritis, myasthenia gravis, coeliac disease and autoimmune hepatitis, are also well-described associations of HT.[31]

Hashimoto's encephalopathy

Hashimoto's encephalopathy, first described in the 1960s, is a rare acute or subacute neurological disorder. It is characterised by progressive cognitive impairment, often apparent dementia, with confusion, hallucinations, drowsiness and recurrent episodes of focal neurological deficits, and is defined by the presence of antithyroid antibodies. Patients can be euthyroid, hypothyroid or hyperthyroid.

Neither thyroid status nor the titre of antithyroid antibodies is associated with disease severity or course. The role of thyroid antibodies in Hashimoto's encephalopathy is unclear, especially as these antibodies are common and Hashimoto's encephalopathy is rare.

Hashimoto's encephalopathy often responds dramatically to corticosteroid therapy and is thus also known as SREAT (steroid-responsive encephalopathy associated with thyroiditis).[32] The association is that of a rare autoimmune encephalopathy with a common form of thyroid autoimmunity.

Management

Management of patients with HT depends on the clinical picture. In general, the choice is between observation and thyroxine replacement therapy. Although glucocorticoid therapy can modulate the thyroiditis and improve thyroid function in the short term, the risk of such therapy is considered to outweigh the benefit. However, short-term use of prednisolone has been reported to have longer-term benefit in IgG4-disease-associated HT.[10]

To observe or to treat?

Patients with overt hypothyroidism require thyroxine replacement therapy. For those with subclinical hypothyroidism (TSH elevation but normal fT4 and fT3 levels and no symptoms), management is influenced by the increase in TSH and clinical factors, as summarised in Flowchart 2. If TSH elevation is mild then annual surveillance is appropriate. However, if the TSH level is greater than 10 mIU/L then treatment should be considered, especially as the increase in TSH in patients with subclinical hypothyroidism predicts the speed of evolution to overt hypothyroidism. Relevant symptoms in a patient with a TSH level of 5 to 10 mIU/L may also prompt consideration of thyroxine treatment.

Nevertheless, treatment is not warranted in all patients with subclinical hypothyroidism. Patients aged over 85 years with subclinical hypothyroidism may have a reduced mortality rate and do not experience symptoms such as depression or impaired cognitive function from a modestly high TSH level.[33] Thyroxine treatment of subclinical hypothyroidism can easily lead to iatrogenic subclinical hyperthyroidism with the risk of atrial fibrillation and osteoporosis.[34] Therefore, observing elderly patients with subclinical hypothyroidism may be more prudent than treating them with thyroxine replacement.[35]

Patients with thyroid antibodies but neither overt nor subclinical hypothyroidism should undergo infrequent surveillance (annually or less often).

Thyroxine replacement therapy

The goal of thyroxine replacement therapy is to achieve an appropriate clinical and biochemical response focusing on thyroid status. Levothyroxine (L-thyroxine) remains the treatment of choice.

Patients with subclinical hypothyroidism generally require an L-thyroxine dose of around 25 to 75 μg daily to achieve euthyroidism. Those with overt hypothyroidism should receive a full replacement dose, provided they do not have unstable ischaemic heart disease. The full replacement dose depends on age and body weight; approximately 1.6 μg per kg of L-thyroxine daily is considered a full replacement dose, although higher levels may be needed in some patients. Young patients can be started on a full replacement dose. Older patients (aged over 60 years) should be started on 50 μg daily, unless they have coronary heart disease when the starting dose should be reduced to 12.5 to 25 μg daily. Older patients should be instructed to report any chest pain.

The main side effects of thyroxine over-replacement are atrial fibrillation and accelerated bone loss, mainly in postmenopausal women.

Dose adjustments should be guided by serum TSH levels measured every four to six weeks (about five half-lives) until TSH levels are in the normal range. The TSH level should then be checked every six to 12 months. In patients with severe hypothyroidism, the TSH level can take up to six months to normalise, so that dose increments should be less frequent provided a normal pre-dose fT4 level has been obtained.

Guidelines for thyroxine use

L-thyroxine should be stored in a cool dry place and protected from light and moisture. It should be taken on an empty stomach with water at least 30 and preferably 60 minutes before food, usually in the morning. Other medications should be taken separately, especially calcium and iron, which should be taken in the evening.[36]

3. Common medications that may interfere with absorption of L-thyroxine

- Ferrous sulfate or gluconate
- Calcium salts (carbonate or citrate)
- Proton pump inhibitors
- Oral bisphosphonates
- Cholestyramine
- Sevelamer
- Aluminium hydroxide

Absorption of L-thyroxine is reduced by food and medications. Drugs that commonly interfere with L-thyroxine absorption are listed in Box 3. Different brands of L-thyroxine are not bioequivalent. Any brand change, even to the same nominal dose, requires TFT review and possible dose adjustment.

Problems with thyroxine therapy

Occasional patients have persistently elevated TSH levels despite high doses of L-thyroxine

4. When to refer a patient with Hashimoto's thyroiditis to an endocrinologist

- Uncertain diagnosis
- Difficult to interpret thyroid function tests
- Atypical symptoms
- If complicated by a goitre or nodules or obstructive symptoms at presentation
- Concomitant other autoimmune disease
- Inadequate biochemical and/or clinical response to treatment
- Development of a goitre or thyroid nodule during follow up (suspicion of malignancy)

(more than 200 μg daily). In these cases, possible causes include poor adherence to treatment and impaired absorption of thyroxine. Adherence to therapy, medicine storage conditions and ingestion should be reviewed, particularly with regard to any interfering medications. Small bowel disease such as coeliac disease should be considered. Specialist review may be required. Refractory poor adherence to therapy can be treated safely in many patients by supervised weekly administration of the entire weekly dose of thyroxine.[37]

Persistent symptoms despite apparent normalisation of biochemical thyroid function is another problem. Symptoms seen in patients with hypothyroidism are also common in the euthyroid population and are thus not a reliable indicator of persistent hypothyroidism.[11] In patients with persistent symptoms, it is important to assess whether the symptoms are related to concomitant disease of non-thyroidal origin (e.g. anaemia) and to treat any disease. It may be helpful to optimise the TSH level to 1 to 2 mIU/L rather than the high-normal range by careful thyroxine dose adjustment. A sympathetic and open-minded hearing of the patient's concerns rather than a dismissive attitude can go a long way to dealing with these concerns.

Alternative replacement therapy

Numerous clinical trials have failed to show that combination treatment with L-thyroxine (T4) and liothyronine (T3) has a clinically discernible benefit over L-thyroxine alone, although one widely reported trial showed a modest effect on neuropsychological function not readily apparent to the participants. Nevertheless, the possibility that a small minority of patients might benefit remains. It has been suggested that functional polymorphisms in type 2 iodothyronine deiodinase or thyroid hormone transporters may have a role in the minority of patients who are dissatisfied with T4 monotherapy. Combination treatment with L-thyroxine and liothyronine should be initiated under specialist supervision with care to avoid overtreatment.[38]

Thyroid extracts are not recommended to treat patients with hypothyroidism by any of the current guidelines.[39] Desiccated thyroid gland extract was the standard therapy for patients with HT for many decades and is clearly effective for hypothyroidism. However, it has been replaced by synthetic thyroxine in mainstream medicine because of wide variations in the hormone content and potency of thyroid extracts, the efficacy of thyroxine monotherapy in normalising serum T3, T4 and TSH levels, and the tendency of thyroid extract to produce supraphysiological T3 levels. Increasing evidence regarding the potential harm of subclinical hyperthyroidism lends further support to the use of synthetic thyroxine monotherapy. Moreover, thyroid extracts have not been submitted for efficacy and safety evaluation by regulatory agencies such as the US Food and Drug Administration, European Medicines Agency and the TGA.

Other therapy: selenium and surgery

There is much interest in the role of selenium in patients with autoimmune thyroid disease. Clinically, the only demonstrated benefit of selenium has been at a dose of 200 μg daily in patients with mild to moderate Graves' ophthalmopathy.[40] Trials are underway in Europe to examine whether selenium may have a role in patients with HT or Graves' disease but until these report we do not know if there is clinical benefit on thyroid disease.[41]

Surgical intervention for patients with HT is generally reserved for those with suspected or proven thyroid malignancy or to relieve pressure symptoms of a large goitre that has not responded to thyroxine therapy for hypothyroidism. Very rarely, HT seems to be persistently painful, and thyroidectomy may be performed for this indication.

Follow up and surveillance

After the thyroxine dose has been established, surveillance to ensure the dose remains appropriate is not usually required more than once a year. Thyroid function should be tested before a dose to avoid detecting the transient increase in serum fT4 in the several hours after thyroxine ingestion. It is appropriate to periodically check for anaemia and to measure vitamin B_{12} and perform iron studies to detect any deficiencies caused by concomitant atrophic gastritis and pernicious anaemia.

The relative risk of thyroid lymphoma is increased in patients with HT but the absolute risk is very low.[42] An enlarging goitre or nodule despite appropriate thyroxine therapy should prompt consideration of this possibility.

When to refer

Most patients with HT can be diagnosed, investigated and treated by their GP. However, some patients may pose problems that should prompt referral to an endocrinologist. A guide as to when to refer patients with HT to an endocrinologist is shown in Box 4.

The future

Recent evidence provides a proof of concept that early immunotherapy can prevent organ-specific autoimmune disease. In patients with new-onset autoimmune Addison's disease, B lymphocyte depletion following a dose of methylprednisolone plus two doses of rituximab resulted in sustained remission in one of six patients.[43] Furthermore, although thyroid cell transplantation may seem fanciful compared with simple cheap and effective thyroxine therapy, it may be on the distant horizon for patients with difficult to treat disease.[44] **ET**

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

COMPETING INTERESTS: None.

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