Chapter 10
Hashimoto's Thyroiditis and Type 1 Diabetes

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Objectives

This case history illustrates the diagnosis of chronic autoimmune goitrous (Hashimoto's) thyroiditis and the management of subclinical hypothyroidism in a young woman with type 1 diabetes. It then addresses the evidence for an association between autoimmune thyroiditis and type 1 diabetes and the current known genetic factors, as well as the importance of screening for autoimmune thyroiditis in patients with type 1 diabetes.

Case Presentation

A 26-year-old woman with type 1 diabetes worked in the City (the financial district of London) as a trader. She had recently moved to London. She had been diagnosed 2 years earlier, after having initially presented as an emergency with diabetic ketoacidosis. She had been stabilized on a "qds" insulin regime with a short-acting insulin analogue before meals and a long-acting analogue at night. She was on the oral contraceptive pill and not considering starting a family in the next few years. She was a nonsmoker. The relevant family history included an uncle with myasthenia gravis and a grandmother on thyroxine replacement for long-standing hypothyroidism. Her most recent hemoglobin A1c(HbA1c) was 7.6%. There was no significant dyslipidemia, her blood pressure was 124/76, and there was no evidence of microvascular complications of diabetes. Thyroid function tests had been included in the most recent biochemical profile and showed total thyroxine (TT_4) of 88 nmol/L (reference range, 60–140) and thyrotropin (TSH) of 3.6 mU/L (reference range, 0.2–4.0).

Six months later at her next review, all continued to be well. On this occasion the diabetes physician had included her thyroperoxidase antibody status with

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current thyroid function tests: TT_4 94 nmol/L (reference range, 60–140); TSH 4.2 mU/L (reference range, 0.4–4.4); thyroperoxidase antibody titer 220 KU/L (reference range, <20).

On examination of the neck, an asymptomatic smooth goiter was palpable and visible. She was informed that she had evidence of autoimmune thyroiditis and that regular checks of thyroid function would be performed from then on.

At her next review, 6 months later, she complained of some tenderness in the front of her neck, which caused some mild discomfort on swallowing. The view of the physician was that the goiter was smaller but firmer, with slight tenderness on palpation. Thyroid function tests had been repeated: TT_4 78 nmol/L (reference range, 60–140); TSH: 6.4 mU/L (reference range, 0.2–4.0); thyroperoxidase antibody titer 356 KU/L (reference range, <20). As she had no other symptoms, it was decided to adopt a "wait and see" policy and not treat with thyroxine at this stage but that she would need a further check of thyroid function in 6 months.

Her next outpatient appointment was delayed, so the next assessment occurred 12 months later. She had increasingly felt more tired and her blood sugars were less well controlled, with the latest HbA1c 8.5%. The goiter was no longer tender and was less visible than previously. The thyroid function tests on this occasion showed TT_4 61 nmol/L (reference range: 60–140), and TSH 15.8 mU/L (reference range: 0.2–4.0). She was commenced on lifelong thyroxine replacement therapy and on a daily dose of thyroxine 100 μg daily.

At review 2 months later, symptomatically she was much improved. Her repeat thyroid function tests showed TT_4 124 nmol/L (reference range, 60–140), and TSH 3.5 mU/L (reference range, 0.2–4.0). She attended with her husband on that occasion, explaining that she wanted to start a family shortly. The dose of thyroxine was increased slightly to 100 and 125 μg on alternate days in order to achieve a target serum TSH of between 0.5 and 2 mU/L. She was referred to the prepregnancy clinic to ensure that her target HbA1c of 6.5% was also achieved preconception. She was informed that her dose of thyroxine would need to be increased by 25 μg daily as soon as any future pregnancy test was positive.

How the Diagnosis Was Made

Hashimoto's thyroiditis (also known as chronic lymphocytic or autoimmune thyroiditis) is named after the Japanese surgeon who first described it in 1912, but the condition was not properly understood until thyroid autoantibodies were discovered in 1956. This term is sometimes now used to describe the presence of thyroid antibodies in the blood, with or without a goiter.

Hashimoto's thyroiditis is characterized clinically by gradual thyroid failure, goiter formation, or both, due to autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens; diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid-specific B and

T cells; and follicular destruction. The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors. The familial association with Graves' disease and the fact that Graves' disease may sometimes evolve into Hashimoto's thyroiditis (and vice versa) indicate that the two disorders are closely related pathophysiologically, albeit not functionally.

Hashimoto's disease is prevalent in about one in 10 women aged 30 years or over, and is an important cause of goiter, especially in women, but may also affect young girls and adolescents. It affects women 10 times more often than men. It is the most common cause of hypothyroidism in the developed world, although iodine deficiency is the commonest etiology worldwide.

The course of the disease is protracted over many years, and during this time it may wax and wane in its destructive effect on the thyroid gland. At any stage the progression of the disease may appear to be arrested and to lie dormant. The development of a small rubbery goiter, usually painless but sometimes associated with mild discomfort, may be the first manifestation of the disease. Alternatively and perhaps more commonly, the patient may only become symptomatic much later in the course of the condition when they become hypothyroid. Over the years a goiter caused by Hashimoto's thyroiditis may disappear and the thyroid gland is replaced by fibrous tissue (atrophic hypothyroidism).

This young woman with type 1 diabetes was diagnosed with Hashimoto's thyroiditis based on finding thyroperoxidase (TPO) antibodies in the blood and the presence of a classical smooth goiter. The serum TSH was in the upper half of the reference range at initial screening. Later, in the natural history, the antibody titre was seen to rise, the thyroid gland became atrophic, and the serum TSH also rose. The function of the thyroid gland has to be monitored at intervals throughout the long course of Hashimoto's thyroiditis even if the patient experiences few if any signs or symptoms beyond having a small goiter. Although treatment with thyroxine may prevent the goiter from becoming larger or reduce its size, this therapy becomes essential only when the TSH begins to rise and T_4 begins to fall, indicating failure of the thyroid gland. Thyroxine therapy to correct thyroid hormone deficiency may also reduce the level of autoantibodies with time. This patient was appropriately diagnosed, monitored, and then treated with thyroxine replacement once she was clinically and biochemically euthyroid.

Lessons Learned

Management of Subclinical Hypothyroidism

Hypothyroidism due to chronic autoimmune thyroiditis is an insidious condition with a significant morbidity, and the subtle and nonspecific symptoms and signs may be mistakenly attributed to other illnesses, particularly in those with other chronic diseases, such as type 1 diabetes, or in those who are postpartum. Biochemical tests of thyroid function reveal the diagnosis before it is clinically apparent. The term

subclinical hypothyroidism is used to describe the finding of a raised serum TSH but a normal free T_4 (FT_4). At the 20–year follow-up of the Whickham cohort, the risk of having developed hypothyroidism was examined with respect to risk factors identified in the first survey [1]. In the surviving women, the annual risk of spontaneous overt hypothyroidism was 4% in those who had both high serum TSH and antithyroid antibody concentrations, 3% if only their serum TSH concentrations was high, and 2% if only their serum thyroid antibody concentration was high; at the time of followup, the respective rates of hypothyroidism were 55%, 33%, and 27%. The probability of developing hypothyroidism was higher in those women who had serum TSH concentrations above 2.0 mU/L and high serum titers of antithyroid microsomal (TPO) antibodies during the first survey (Fig. 10.1).

There is debate regarding the potential benefits of treatment with thyroxine to normalize the TSH, and whether this alleviates symptoms and improves the lipid profile. There are observational data suggesting that subclinical hypothyroidism during pregnancy may be associated with suboptimal intellectual performance in children, but these data are based on relatively small numbers of cases. Some studies have even suggested that the maternal serum FT_4 level is more sensitive than the serum TSH in predicting the likelihood of adverse intellectual outcomes in the offspring. No intervention data on the effect of thyroxine therapy in pregnancy exist, although recent data suggest that treating evidence of mild thyroid failure may improve obstetric outcome [2]. The current consensus is that women with evidence of mild thyroid failure should be treated with thyroxine to normalize the serum TSH

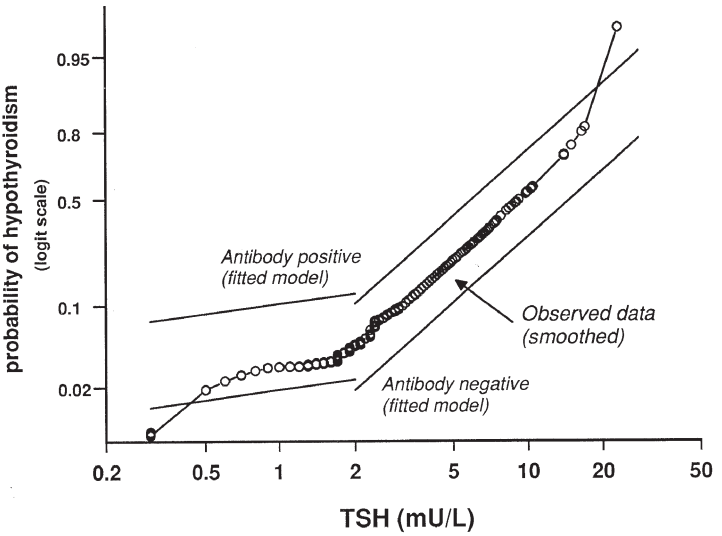

Fig. 10.1 The probability for development of hypothyroidism within 20 years with increasing values of serum TSH at first Whickham survey in 912 surviving women. (From ref. 1, with permission.)

prior to conception and that the TSH should be monitored carefully during pregnancy and targeted to within the lower end of the reference range where possible.

It was elected not to treat this patient on the basis of the initial serum TSH rise while she was asymptomatic. However, once she was symptomatic with a raised serum TSH and low T_4, she received thyroxine replacement to target a serum TSH between 0.2 and 2 mU/L in view of the possibility of pregnancy.

Evidence for an Association Between Autoimmune Thyroiditis and Type 1 Diabetes and the Current Known Genetic Factors

The occurrence of autoimmune thyroiditis in patients with type 1 diabetes and in their family members is well recognized. In large groups of families with type 1 diabetes in the United Kingdom and the United States, at least one case of autoimmune thyroid disease (AITD) was reported in relatives of 22% and 40% of patients with type 1 diabetes, respectively [3]. A higher than expected prevalence of AITD has been found in patients with other autoimmune disorders and in their families. These include other autoimmune endocrinopathies such as Addison's disease and premature ovarian failure, and nonendocrine autoimmune disorders such as pernicious anemia, celiac disease, myasthenia gravis, and rheumatoid arthritis.

Most cases of AITD along with other common autoimmune disorders are now thought to have a complex genetic basis; that is, the genetic predisposition to the disease is determined by a series of interacting susceptibility alleles of several different genes. Candidate gene studies have looked at polymorphic markers within a particular gene, which has been selected because it is thought that disruption of its function may result in the phenotype. Alternatively linkage scanning, in which widely spaced anonymous genetic markers (usually microsatellite repeat polymorphisms between genes), has been used to detect chromosomal segments with evidence for linkage in affected families. In AITD, several gene loci have been shown to determine susceptibility to the disease, with a major contribution from cytotoxic T lymphocyte antigen 4 (CTLA-4), which is an immunoregulatory molecule that is expressed on the surface of activated T lymphocytes. Other loci are involved to a lesser degree, including one or more genes in the major histocompatability complex (MHC) located on chromosome 6p2. Both CTLA-4 and MHC gene loci are associated with susceptibility to type 1 diabetes.

Screening for Autoimmune Thyroiditis in Type 1 Diabetes

There is a consensus from recent guidelines from various international organizations that screening for AITD in patients with type 1 diabetes is warranted in view of the high frequency of asymptomatic thyroid dysfunction in unselected patients, particularly women. In a randomly selected group of 1310 adult diabetic patients attending a diabetic outpatient clinic in Edinburgh, UK, who received annual screening for

thyroid disease, the overall prevalence of thyroid disease was found to be 13%, and was highest (31%) in type 1 diabetic females and lowest in type 2 diabetic males (7%) [4]. As a direct result of screening, new thyroid disease was diagnosed in 7% (89 patients) of the population screened; the commonest diagnosis was subclinical hypothyroidism (5%), followed by hypothyroidism (1%), hyperthyroidism (0.5%), and subclinical hyperthyroidism (0.5%). Women with type 1 diabetes had the highest annual risk of developing thyroid disease (12%) in a 1-year follow-up of this cohort. This study has concluded that thyroid function should be screened annually in patients with type 1 diabetes to detect asymptomatic thyroid dysfunction.

Women with type 1 diabetes are also at increased risk of postpartum thyroid dysfunction, and it has also been recommended that all such diabetic women should be tested preconception or in the first trimester for thyroid peroxidase antibodies. Forty-one women with type 1 diabetes from New York, New York, were followed prospectively during the second and third trimester of pregnancy and regularly until 1 year postpartum, with further follow-up at 31 months postpartum [5]. The incidence of postpartum thyroid dysfunction in women with type 1 diabetes was 25%, which was a threefold increase compared to a similar study by this group in a non-diabetic population.

References

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Questions

1. True or false: The diagnosis of Hashimoto's thyroiditis requires the following:

   A. Presence of a diffuse goiter
   B. Serum TSH greater than 2 mU/L
   C. Circulating thyroid peroxidase antibodies
   D. Lymphocytic infiltrate in the thyroid gland at biopsy
   E. Characteristic appearance on ultrasound

2. True or false: The following diseases are associated with Hashimoto's thyroiditis:

   A. Rheumatoid arthritis
   B. Chronic urticaria
   C. Down syndrome
   D. Fibromyalgia
   E. Sarcoidosis

3. Are these statements true or false with respect to autoimmune thyroiditis?

   A. A serum TSH greater than 2 mU/L is associated with an increased risk of developing hypothyroidism.
   B. The risk of developing hypothyroidism is greater in men who are thyroid antibody positive compared to women.
   C. The risk of hypothyroidism is not influenced by age.
   D. The majority of patients have symptoms once the serum TSH is greater than 4 mU/L.
   E. Thyroxine is indicated to reduce goiter size.