Chapter 9
Autoimmune Hypothyroidism with Persistent Elevation of TSH

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Objectives

To understand the investigation and treatment of patients with autoimmune hypothyroidism, and to recognize causes of persistent thyroid-stimulating hormone (TSH) elevation despite adequate thyroxine treatment.

Case Presentation

A 39-year-old man presented to his primary care physician in January 2005 with a 4-month history of generalized aches and pains and tiredness. There also appeared to be increased stress in his work and personal life, and a trial of amitriptyline 25 mg/day was commenced. Although his symptoms improved, they did not resolve completely. Blood tests including thyroid function tests were performed and revealed marked hypothyroidism: TSH >150 mU/L, and free thyroxine (FT_4) 3.0 pmol/L. He was referred to an endocrinologist and was seen in April 2005. A detailed history revealed a normally fit and active person who had been unable to perform his normal activities in the preceding few months. There was no history of neck swelling or pain. His skin had become very dry but with no pigmentation, he had become constipated, and he had dizziness on standing. There was no family history of thyroid disease but he had a sister and an aunt with type 1 diabetes.

His weight was 70 kg. He had mildly hypothyroid facies but no increase in pigmentation. There was no goiter and no signs of thyroid eye disease. His pulse was 68 in sinus rhythm and his blood pressure was 100/70 with no postural drop. Systematic examination was normal.

Routine blood tests revealed a normal full blood count, thyroid function, renal and liver function, cortisol and glucose. Thyroid peroxidase antibodies were positive. The TSH was >150 mU/L (normal 0.35–4.5), FT_4 was 5.4 pmol/L (normal

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T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,

10.3–21.9), and free triiodothyronine (FT_3) was 2.6 pmol/L (normal 3.5–6.5). He was commenced on thyroxine (levothyroxine) 100 μg per day and was advised to take it 30 minutes before breakfast to aid absorption of the medication.

When next seen in early June 2005, his condition was improved although he did not feel "100 percent." The serum TSH was checked, with a planned review in 3 months. The TSH had improved but was still elevated at 10.8 mU/L. He was contacted by letter and advised to increase the thyroxine to 125 μg per day.

The patient was next reviewed 2 months later. He felt better on thyroxine 125 μg per day, but had only collected his prescription 3 weeks beforehand so it was too early to recheck the TSH. He was encouraged to have a repeat TSH test in 4 weeks, but he did not come in for this investigation until 4 months later. The TSH had improved slightly but was still elevated at 8.43 mU/L with an FT_4 of 15.3 pmol/L. His thyroxine dose was increased to 150 μg/day and he was advised of the importance of compliance and attending for blood tests at appropriate times.

He was next seen in January 2006 when he was still feeling tired, particularly over the last 2 months. The TSH remained high at 9.3 mU/L (FT_4 16.2 pmol/L), even on 150 μg of thyroxine per day. When asked about compliance, he insisted that he took the prescribed dose of thyroxine every day, and had only missed three or four doses 3 months ago when he was away on a business trip. No new medications had been introduced that could interfere with thyroxine requirements. The importance of adherence with treatment was once again emphasized, and he was advised to put a 1-week supply of thyroxine in a separate bottle and to take his medication from this bottle. If any tablets were left at the end of the week he should take them all at that time.

He was reviewed again 2 months later. His TSH was once again elevated at 10.0 mU/L on 150 μg of thyroxine. Again he insisted that he was compliant with treatment. Based on a body weight of 70 kg, 150 μg was considered to be more than adequate to normalize his TSH. In view of his previous record of not collecting prescriptions or attending for blood tests on time, and having previously missed tablets, poor compliance was suspected as the cause of his persistently raised TSH. To test this hypothesis, he was asked to come to the hospital for observed administration of thyroxine (1000 μg as single dose once weekly) and measurement of thyroid function, as follows:

Baseline week 1 (immediately before the administration of thyroxine):
TSH 9.0 mU/L, FT_4 16.6 pmol/L
Week 2:
TSH 10.2 mU/L, FT_4 13.9 pmol/L
Week 3:
TSH 9.5 mU/L, FT_4 TSH 14.2 pmol/L
Week 4:
TSH 10.5 mU/L, FT_4 11.8 pmol/L
Week 5:
TSH 9.8 mU/L, FT_4 12.0 pmol/L

Weekly observed administration of 1000 μg of thyroxine did not restore his TSH to normal, suggesting that lack of compliance was unlikely to be the cause of his persistently elevated TSH. As he already suffered from one autoimmune disease and had a strong family history of type 1 diabetes, an autoantibody screen for celiac disease was performed:

Endomysial antibody immunoglobulin A (IgA):	Positive
IgA gliadin antibody:	Equivocal
IgG gliadin antibody:	Equivocal
IgA-t-transglutaminase antibody	>300 U/mL (normal 0–15)

The autoantibody screen for celiac disease was positive, and he was referred for endoscopy and duodenal biopsy. The endoscopy showed erythematous and exudative gastritis, and duodenitis and edema in the first part of the duodenum. In the second part of the duodenum, the folds of small bowel appeared scalloped and atrophic possibly due to celiac disease. Histopathology was reported as follows: "Duodenal mucosa with villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes. The appearances are consistent with a gluten-sensitive enteropathy."

The patient was commenced on a gluten-free diet and was assessed by a gastroenterologist. Three months later his TSH was low, at 0.20 mU/L on 150 μg of thyroxine and the dose of thyroxine was reduced to 125 μg per day. His latest TSH was normal at 2.1 mU/L.

How the Diagnosis Was Made

Hypothyroidism

Epidemiology

Autoimmune hypothyroidism or Hashimoto's thyroiditis is the commonest cause of acquired hypothyroidism in iodine-replete areas [1]. Individuals who suffer from or who have a family history of autoimmune thyroid disease and other autoimmune conditions such as type 1 diabetes and celiac disease are at increased risk of developing autoimmune hypothyroidism [2].

Investigation

Thyroid-stimulating hormone is the most sensitive marker of thyroid failure and is elevated in primary hypothyroidism [3]. A raised TSH may precede a low serum FT_4 concentration by several months or years as occurs in subclinical hypothyroidism. As thyroid failure progresses, the serum FT_4 concentration falls below the normal range with the development of overt clinical hypothyroidism. Serum TSH, therefore, can be used as a primary diagnostic test provided pituitary or hypothalamic disease is not suspected, and if found to be elevated, serum FT_4 should then be measured to

confirm the presence of hypothyroidism. The FT_3 concentration may not fall below normal for some time after the development of overt hypothyroidism, and is not used for the diagnosis of primary hypothyroidism. Antithyroperoxidase antibodies are present in 95% of patients, and 60% also have thyroglobulin antibodies; their detection in a biochemically hypothyroid patient confirms the diagnosis of autoimmune hypothyroidism.

Treatment

The treatment of autoimmune hypothyroidism is lifelong. Thyroxine is the drug of choice because it is converted to triiodothyronine in the tissues, a process that is autoregulated. The main factors that influence thyroxine requirement are age and lean body mass. The mean dose of thyroxine needed to restore euthyroidism in adults with total thyroid failure is 1.6 μg per kg of body weight. In those less than 60 years of age with no history of ischemic heart disease, a full thyroxine replacement dose of 100 μg per day should be commenced. In older patients and those with heart disease, there is a risk of inducing angina or myocardial infarction, and thus smaller starting doses of 25 to 50 μg are used. The TSH should be rechecked every 6 to 8 weeks, and the thyroxine dose adjusted by increments or decrements of 25 to 50 μg until the TSH has normalized. Once euthyroidism is achieved, patients should be monitored annually with a TSH measurement to ensure that thyroxine replacement is adequate.

Case Discussion

The initial presentation of vague symptoms that could be attributable to a number of conditions highlights the difficulty that may occur in diagnosing hypothyroidism. Hence anxiety and depression were suspected before hypothyroidism was diagnosed. This reflects the need for a detailed clinical assessment and appropriate investigations before making a diagnosis.

When blood tests were first requested in the hospital visit, the serum FT_3 was measured in addition to TSH and FT_4. This was unnecessary and did not provide useful additional information. Once the diagnosis of autoimmune hypothyroidism was confirmed, treatment with the correct starting dose of thyroxine for a 70-kg man was given. The patient was reviewed with a repeat TSH 2 months later when his thyroxine was increased by an increment of 25 μg per day. The timing of this test and the increase in thyroxine dose for a modestly elevated TSH (10.8 mU/L) were both appropriate. After this consultation, the patient did not collect his prescription when requested and, therefore, when next seen in the clinic, it was too early to recheck his TSH. Furthermore, he did not come in for a repeat TSH at the correct time, delaying further titration and optimization of his thyroxine. The lack of adherence with respect to collecting a new prescription or attending for blood tests when requested and the persistent elevation of TSH created suspicion that he may also be poorly compliant with his thyroxine treatment.

In some centers, weekly observed administration of oral thyroxine is used as a means of determining whether a persistently raised TSH is the result of poor compliance and as a treatment for poorly compliant patients [4]. In this case, thyroxine 1000 μg was given weekly, which is almost equivalent to the daily dose of 150 μg that this patient was prescribed. The TSH result at the end of the test showed that poor compliance was not the cause. Although poor adherence accounts for most cases of persistent TSH elevation, a number of medical conditions, drugs, and foodstuffs containing dietary fiber may increase or decrease thyroxine requirements through altered metabolism or absorption (Table 9.1) [3, 5]. It is therefore important to record a thorough medical and drug history at the initial consultation and to update the findings when presented with a patient with a persistently elevated TSH. In this case, celiac disease was screened for and found after poor compliance had been ruled out. Treatment with a gluten-free diet improves thyroxine absorption and may even reduce the thyroxine dose needed for euthyroidism, as was seen in this case. In other conditions where there is interference with absorption due to disease, drugs, or foodstuffs, the thyroxine dose may require increase or drugs taken at a different time from thyroxine. Likewise, where metabolism is altered, an increase in the thyroxine dose may be required.

Table 9.1 Causes of altered thyroxine requirements

Poor compliance
Reduced thyroxine absorption
Coexisting diseases
Diseases causing malabsorption, e.g., celiac disease, tropical sprue
Previous small intestine surgery
Conditions associated with reduced gastric acid production
H. pylori infection
Drugs
Oral iron
Aluminium hydroxide gel
Sucralfate
Calcium carbonate
Cholestyramine
Foodstuffs
Dietary soya
Fiber
Increased thyroxine clearance
Coexisting conditions
Pregnancy
Nephrotic syndrome
Other systemic illnesses
Drugs
Carbamazepine
Phenytoin
Phenobarbitone
Rifampicin
Increased binding proteins
Hormone replacement therapy

Lessons Learned

This case illustrates some of the difficulties in diagnosing and managing patients with hypothyroidism. Thyroxine doses should be started that are appropriate for a patient's weight, age, and coexisting medical conditions. Therapy should be monitored with TSH measurements at suitable time intervals, and the dose altered as necessary. Patient compliance is important to this process. Although poor adherence is the most common cause of persistent TSH elevation and should be investigated, the influence of other conditions and drugs should not be ignored.

References

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Questions

1. True or false: Autoimmune hypothyroidism

   - is less common in iodine replete areas.
   - is always associated with thyroglobulin autoantibodies.
   - is often transient.
   - occurs more commonly if there is family history of celiac disease.
   - is best treated with a combination of liothyronine and thyroxine.

2. In patients with primary hypothyroidism:

   - FT_3 as well as TSH and FT_4 should be used to confirm the diagnosis.
   - TSH and T_4 should be checked when monitoring thyroid hormone replacement.
   - Three weeks is the most appropriate time interval for repeat TFTs after the initiation of thyroxine.
   - Long-term monitoring of thyroid function should be performed annually in patients taking thyroxine.
   - The optimal dose of thyroxine is reached when the FT_4 is at the upper limit of the normal range.

3. In hypothyroid patients with persistent elevation of TSH:

   - The commonest cause is malabsorption.
   - Celiac disease should be considered as a possible cause.
   - Weekly supervised administration of thyroxine can be used to investigate the possibility of poor compliance.
   - Sodium valproate is a cause.
   - Oral iron therapy may be responsible.