CLINICAL VIGNETTE

Less Common Symptoms of Uncontrolled Hypothyroidism

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Case Presentation

Case 1

A 65-year-old female with chronic myelogenous leukemia in remission, impaired glucose tolerance, and Graves' disease s/p radioiodine therapy 14 years prior presents with hypothyroidism despite levothyroxine. The patient reports increased depression/tearfulness, fatigue, and sleeping difficulties over the last two months. She denies weight changes, appetite changes, diarrhea, or constipation. She has chronic hair thinning, but not significantly worse than before. She denies palpitations, lower extremity swelling, and cold or heat intolerance. She had been on levothyroxine 25 mcg/day chronically. This was reduced to 13 mcg/day two months prior, after reporting "feeling hyperthyroid," despite a normal TSH of 2.1. She does not miss doses and is not taking biotin supplements. On examination, she has thin hair, but no patches of alopecia. Her skin is cool to touch with subtle hypopigmented patches in the upper extremities, particularly on the dorsal surface of her hands. According to her recent ophthalmology evaluation, her Graves ophthalmopathy is stable.

Routine annual blood testing was remarkable for elevated fasting lipids,with LDL of 200 mg/dL, and TSH elevation to 19.2 mIU/L from 2.1 two months prior. Her LDL was previously 91 mg/dL the year prior. She denies any changes in her diet and adheres to a low saturated fat diet. She exercises 2-3 times per week with walking or bicycling.

Over the next 5 months, her levothyroxine dose was gradually increased back to her prior dose of 25 mcg/daily, while monitoring TSH levels (Table 1). The patient continued with her well balanced diet and exercise routine. Once her TSH returned to the normal reference range, her LDL was rechecked and improved without the use of statins.

Table 1.

Date	**Thyroid Stimulating Hormone (Ref range 0.3-4.7)**	**LDL cholesterol**
06/16/2017	2.3	91
10/17/2018	19.2	200
03/01/2019	3.7	148

Case 2

A 65-year-old female with long-standing hypothyroidism on levothyroxine presented to primary care with chronic, intermittent tongue changes and irritation. She stated that she has had multiple prior episodes characterized by tongue discomfort, tongue enlargement and changes in tongue coloration. She had previously attributed her tongue symptoms to her diet but was unable to identify any specific food triggers. The tongue symptoms would spontaneously improve and recur over weeks to months.

Upon examination, the patient had macroglossia, tongue fissures, and geographic tongue. Laboratory testing revealed low vitamin B12 of 299 elevated mean corpuscular volume of 100.8 fL, and elevated TSH of 14.7 mIU/L.

After levothyroxine dose was increased from 50 mcg/day to 75 mcg/day and starting vitamin B12 orally, which was later switched to monthly injections her labs normalized and her tongue symptoms resolved and have not re-occurred.

Discussion

Overview

Thyroid dysfunction is the second most common endocrine disorder affecting 4.6% of the US population over 12 years and is commonly seen by primary care physicians. Women are five to eight times more likely than men to have thyroid problems.[1] In developed countries, the most common causes of hypothyroidism are Hashimoto's thyroiditis and prior treatment for Graves' disease with thyroidectomy or radioiodine treatment.

Thyroid hormone regulates multiple metabolic functions. Even minor changes in concentrations of circulating thyroid hormones (Free T4 and Free T3) can significantly impact thyroid stimulating hormone levels. Commonly recognized signs and symptoms of hypothyroidism include:

- Fatigue
- Weight gain
- Constipation
- Dry skin
- Irregular menstrual cycles
- Decreased heart rate
- Thinning hair
- Depression
- Memory changes

Less Common Cardiovascular Effects

Less common cardiovascular effects include bradycardia and fatigue. However, overt hypothyroidism is also associated with decreased lipid clearance leading to an elevation of free fatty acids and low-density lipoprotein cholesterol concentrations. Specifically, thyroid hormones induce HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A) which is the first step in cholesterol biosynthesis. Furthermore, T3 (triiodothyronine) regulates LDL receptor's gene expression by binding to specific thyroid hormone responsive elements and has also been found to protect LDL from oxidation.[2]

A study of patients newly diagnosed with hyperlipidemia, reported prevalence of hypothyroidism approximately twice that of the general population.[3] A meta-analysis evaluating the effects of T4 therapy on total cholesterol concentration in patients with overt hypothyroidism, found patients with initial cholesterols less than 310 mg/dL had an average decrease of 46 mg/dL after initiating levothyroxine therapy.[4]

Because thyroid dysfunction (specifically TSH level >10mIU/L) can dramatically affect cholesterol levels, the current guidelines from the National Cholesterol Education Program, the American Association of Clinical Endocrinologists, and the American Thyroid Association recommend screening for hypothyroidism in patients with newly diagnosed hyperlipidemia prior to starting a lipid-lowering agent.[5]

Nutritional Deficiencies

Patients with autoimmune thyroiditis have greater risk of other autoimmune diseases, like pernicious anemia, compared to the general population. However, 40% of hypothyroid patients without antibodies to gastric parietal cells, were found to have vitamin B12 deficiency compared to only 3-4% in the general population. Causes of vitamin B12 deficiency in hypothyroid patients include pernicious anemia and inadequate absorption due to decreased bowel motility, bowel wall edema, bacterial overgrowth, and decreased intake.[6] Because some of the common signs and symptoms of hypothyroidism are similar to those of vitamin B12 deficiency, the diagnosis of vitamin B12 deficiency may be delayed. Concurrent vitamin B12 deficiency and hypothyroidism are common and symptoms often overlap, so clinicians may consider checking vitamin B12 levels in patients with ongoing symptoms, despite normalized TSH levels.

Other Nutritional Concerns

Other nutritional deficiencies can affect thyroid function. The classic example is iodine's impact on T4 production. In developing countries without iodized salt, the thyroid gland frequently enlarges into a goiter, as it attempts to produce more thyroid hormone. Some geographic areas with little dietary iodine have high rates of symptomatic hypothyroidism, with fatigue, mental slowing, depressed mood, and weight gain.

Protein is also needed for healthy thyroid function, and synthesis of TSH. Symptoms of protein deficiency are those of hypothyroidism but may also include muscle and joint pains, as well as decreased immunity.

Selenium is needed for T3 formation. T3 is the active form of thyroid hormone, which is converted to T4, the storage form. Without T3, patients may experience feeling tired and sluggish, with decreased mental acuity.

Other important nutrients that assist with thyroid formation are magnesium, vitamin A, and vitamin B2. The most common reason patients lack these nutrients is due to poor gastrointestinal absorption. This can be in the stomach due to reduced acid levels or in the intestines due to inflammation or potentially celiac disease, which damages the intestinal cells resulting in nutrient malabsorption. Although uncommon, nutrients deficiency should be considered in patients with risk factors.

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