An ‘incidental’ case of profound hypothyroidism - important implications on the cardiovascular system

Cameron Schauer
Trainee Intern
Auckland School of Medicine
The University of Auckland

INTRODUCTION

Mr R is a 45-year-old Fijian Indian man who presented to his General Practitioner (GP) for a routine health check. He had a background of dyslipidaemia and obesity, and was diagnosed with hypertrophic cardiomyopathy (HCM) three months ago following an episode of chest pain. During this admission, he had a normal coronary angiogram; however, the echocardiogram showed a posterior wall thickness of 1.5cm (normal 0.6-1.0 cm) with moderate concentric left ventricular hypertrophy and an ejection fraction of 65%. An outpatient exercise tolerance test showed symptomless electrocardiogram (ECG) changes, identical to those seen on this admission. At his GP, the patient’s ECG again showed T wave inversion in leads I, II, aVL, and V3 to V6, and 1 mm of ST depression in leads I, aVL, and V3 to V6. The GP did not have access to previous ECG records and admitted the patient to the hospital as he could not compare the ECG to a baseline.

At the hospital, a full systems enquiry and physical examination was completed. Mr R reported significant recent weight gain despite his diet remaining unchanged, thinning and loss of his hair, progressive hoarseness of his voice, and constipation. He had also noticed worsening fatigue, somnolence and impaired concentration. In addition, he complained of progressive swelling of his legs and was requiring more clothing to stay warm.

On physical examination, his BMI was 32 kg/m² and his skin was cool and dry. There was no goitre on palpation. His pulse was 62 and the seated blood pressure was 156/100 mmHg. Heart sounds were dual with a grade 3/6 systolic murmur at the left sternal edge which was accentuated during the Valsalva manoeuvre. There was non-pitting oedema to the mid tibial region on both legs, and his ankle reflexes relaxed slowly.

Table 1 below shows the abnormal results of his laboratory investigations. He had deranged liver function test values with increased thyroid-stimulating hormone (TSH) and creatine kinase (CK) levels. A chest x-ray showed a slightly increased cardiothoracic ratio of 0.51 but revealed no evidence of pulmonary oedema.

Table 1: Abnormal blood test results

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
<th>Normal Range</th>
<th>Investigation</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>72 U/L</td>
<td>(&lt;45)</td>
<td>Cholesterol</td>
<td>6.6 mmol/L</td>
<td>(&lt;5.0)</td>
</tr>
<tr>
<td>ALT</td>
<td>48 U/L</td>
<td>(&lt;45)</td>
<td>HDL</td>
<td>0.90 mmol/L</td>
<td>(&lt;1.0)</td>
</tr>
<tr>
<td>GGT</td>
<td>73 U/L</td>
<td>(0-60)</td>
<td>Cholesterol/HDL ratio</td>
<td>7.4</td>
<td>(&lt;14.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Triglycerides (TG)</td>
<td>3.6 mmol/L</td>
<td>(&lt;2.0)</td>
</tr>
<tr>
<td>Troponin I</td>
<td>&lt;20</td>
<td>(0-40)</td>
<td>Creatine Kinase</td>
<td>1254 U/L</td>
<td>(60-220)</td>
</tr>
<tr>
<td>TSH</td>
<td>100 mU/L</td>
<td>(2-4.0)</td>
<td>T4</td>
<td>1.8 pmol/L</td>
<td>(&lt;1.5)</td>
</tr>
</tbody>
</table>

DISCUSSION

Primary hypothyroidism is one of the most common endocrine diseases. The prevalence of hypothyroidism in the general population ranges from 3.8% to 4.6%, with suggestion of an increasing incidence. 1 Levothyroxine is now the third most commonly prescribed medication in the United Kingdom after Simvastatin and Aspirin. 2

Symptoms of hypothyroidism appear in multiple organ systems, owing to the hormonal association with nearly all major metabolic pathways. This includes protein, carbohydrate and lipid metabolism. Thyroid hormone also directly and indirectly alters other regulatory hormones such as insulin and catecholamines. 3

Studies have shown all-cause mortality to be increased in patients with untreated hypothyroidism. 4 This is particularly related to the increased risk of cardiovascular disease by increased systemic vascular resistance, decreased cardiac contractility and diastolic function, decreased cardiac output and accelerated atherosclerosis. 5

Mr R was diagnosed with HCM three months prior to this presentation. A review of literature dating back to 1980 demonstrated that 75 patients in nine separate studies with varying degrees of hypothyroidism have been described as having myocardial hypertrophy, manifested as reversible asymmetric septal hypertrophy. 6,14 The hypertrophy was corrected once they were maintained in a euthyroid state. It has been suggested that this structural change in myocardium could be a direct result of cellular deposition of myxoedematous material or just the biological effect of increased TSH levels. 14

In addition, dyslipidaemia is common in those with significant hypothyroidism. Thyroid hormones regulate the expression of enzymes involved in many different steps of lipid metabolism, including HMG-CoA reductase. Mr R’s
presentation was typical in that his total cholesterol (TC) and low density lipoprotein (LDL) were increased – this is due to decreased catabolism from decreased LDL-receptor activity. The effect of TSH is rather potent that even within the normal range, a linear increase in TC, LDL, and TGs has been observed with increasing TSH.\textsuperscript{15}

Mr R had been started on statin therapy by his GP many months before his presentation. Despite that, there had been little effect on the lipid profile but elevation of his CK level.

One study has confirmed that statins given to hypothyroid patients elevates their level of CK. Patients ‘accidently’ starting statins for dyslipidaemia with unrecognised and thus untreated hypothyroidism had significantly higher CK levels (1095 U/L) compared with T4 matched patients not taking statins (n=18; CK=395; p<0.05).\textsuperscript{17} Cases of rhabdomyolysis in patients using statin therapy with unnoticed hypothyroidism have been described.\textsuperscript{18-21} Hypothyroid patients often have elevated baseline CK levels although the pathophysiology of this remains unclear;\textsuperscript{22} Mr R certainly reported diffuse myalgia with cramping in his calves and he had an elevated CK level. Hypothyroidism is one of the most common causes of secondary dyslipidaemia, therefore appropriate evaluation of thyroid function should be undertaken before starting a lipid lowering therapy. Usually, 4-6 weeks of thyroxine replacement therapy is sufficient to see a significant improvement in the lipid profile.\textsuperscript{15}

Serum TSH level is an inexpensive and sensitive test for disorders of thyroid function. Vigorous debate exists around the issue of screening for thyroid dysfunction. The argument for screening has traditionally been based on three strands. Early recognition and treatment would prevent progression to overt hypothyroidism, reduce rates of secondary dyslipidaemia, and treat potentially unrecognised symptoms that diminish quality of life.\textsuperscript{23}

In 2000, the American Thyroid Association suggested, based on a consensus of its 780 members, that adults should be screened for thyroid dysfunction by measurement of the serum TSH concentration, beginning at age 35 years and every 5 years thereafter.\textsuperscript{24} This is corroborated by recent evidence which suggests that aggressive case finding in high risk populations may be useful so as to treat hypothyroidism at an early stage.\textsuperscript{25} In response, a randomised, double-blind crossover trial to investigate the efficacy of screening for adult hypothyroidism found that 8% (341) of the 4365 people attending wellness centres had TSH values exceeding 4.0 mU/L, with 1% of people screened having a better quality of life after treatment.\textsuperscript{26} Investigators concluded that this warranted a screening program, but granted further evidence in the form of pilot studies would be required to assess feasibility, logistics and acceptability.

Evidence for cost-effectiveness of screening is sparse. One study completed in 1996 investigated this via a cost-utility analysis based on the American Thyroid Association recommendations.\textsuperscript{23} A computer model accounted for case finding, medical consequences of mild thyroid failure, and costs of care during 40 years of simulated follow-up. The intervention used was simply adding a serum TSH assay to total serum cholesterol screening. The cost effectiveness calculated was $9223 per QALY for women and $22595 per QALY for men. Researchers concluded that screening for mild thyroid failure in adult populations over 35 years of age was cost effective, with comparable cost-effectiveness ratios for accepted practices such as breast cancer and hypertension screening.\textsuperscript{27 - 28}

The case of Mr R is of importance because it demonstrates a constellation of potentially reversible symptoms and signs of hypothyroidism. Left unrecognised and untreated, hypothyroidism has significant morbidity and mortality. In retrospect, screening in a primary care setting was indicated in this patient, particularly due to his dyslipidaemia which was refractive to treatment. This case reinforces the importance of screening for secondary causes of dyslipidaemia before prescribing lipid lowering agents.
REFERENCES


15. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. The open cardiovascular medicine journal. 2011;5:76-84.


