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

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

Cameron Schauer is a current Trainee Intern at Auckland University. He spent his 5th year in Whangarei Hospital for the regional-rural medical program, and is now in Auckland working at Middlemore Hospital. General Medicine and its subspecialties are of particular interest to him, and he is hoping to work as a first year house officer in Whangarei where there is plenty of hands-on action.

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/m^2 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.

Investigation	Result	Normal Range	Investigation	Result	Normal Range
AST	72 U/L	(<45)	Cholesterol	6.6 mmol/L	(<5.0)
ALT	48 U/L	(<45)	HDL	0.90 mmol/L	(>1.0)
GGT	73 U/L	(0-60)	Cholesterol/HDL ratio	7.4	(<4.5)
			Triglycerides (TG)	5.4mmol/L	(<2.0)
Troponin I	<20	(0-40)	Creatine Kinase	1254 U/L	(60-220)
TSH	100mU/L	(0.4-4.0)			
T4	5.8pmol/L	(9-19).			

Table 1: *Abnormal blood test results*

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 lipoprotien (LDL) were increased – this is due to decreased catabolism from decreased LDL-receptor activity. [15] 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. [16]

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; $p<0.05$).[17] Cases of rhabdomyolysis in patients using statin therapy with unnoticed hypothyroidism have been described. [18-21] Hypothyroid patients often have elevated baseline CK levels although the pathophysiology of this remains unclear. [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. [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. [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.[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.[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.[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.[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.[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

1.Leese GP, Flynn RV, Jung RT, Macdonald TM, Murphy MJ, Morris AD.
Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS).
Clinical endocrinology. 2008;68(2):311-6.

2.Chakera AJ, Pearce SH, Vaidya B.
Treatment for primary hypothyroidism: current approaches and future possibilities.
Drug design, development and therapy. 2012;6:1-11.

3.Peppa M, Betsi G, Dimitriadis G.
Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease.
Journal of lipids. 2011;2011:575840.

4.McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ.
Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study.
Thyroid : official journal of the American Thyroid Association. 2011;21(8):837-43.

5.Klein I, Danzi S.
Thyroid disease and the heart.
Circulation. 2007;116(15):1725-35.

6.Santos AD, Miller RP, Mathew PK, Wallace WA, Cave WT, Jr., Hinojosa L.
Echocardiographic characterization of the reversible cardiomyopathy of hypothyroidism.
The American journal of medicine. 1980;68(5):675-82.

7.Farooki ZQ, Hoffman WH, Perry BL, Green EW.
Myocardial dysfunction in hypothyroid children.
American journal of diseases of children. 1983;137(1):65-8.

8.Altman DI, Murray J, Milner S, Dansky R, Levin SE.
Asymmetric septal hypertrophy and hypothyroidism in children.
British heart journal. 1985;54(5):533-8.

9.Mancuso L, Lo Bartolo G, Iacona MA, Bondi F, Marchi S, Giambrone F, et al.
[Echocardiography in primary hypothyroidism. Study of 25 patients].
Giornale italiano di cardiologia. 1986;16(6):505-9. Aspetti ecocardiografici nell'ipotiroidismo primario. Studio di 25 pazienti.

10.Shenoy MM, Goldman JM.
Hypothyroid cardiomyopathy: echocardiographic documentation of reversibility.
The American journal of the medical sciences. 1987;294(1):1-9.

11.Gundersen T, Paulsen AQ, Gallefoss F, Aslaksen BB.
[Hypothyroid cardiomyopathy--an underdiagnosed cause of heart failure].
Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 1990;110(15):1948-51. Hypotyreot kardiomyopati--en underdiagnostisert arsak til hjertesvikt.

12.Badano L, Carratino L, Calisi P, Giunta L, Lucatti A.
Concentric left ventricular wall thickening in a patient with primary hypothyroidism. Response to gradual thyroxine replacement.
Giornale italiano di cardiologia. 1991;21(5):553-6.

13.Kotake C, Koya Y, Ikeda Y, Ikeda S, Onaka H, Ichinohe T, et al.
[Two cases of hypothyroidism with echocardiographic features similar to cardiomyopathy: one simulates hypertrophic and the other dilated cardiomyopathy].
Kokyu to junkan Respiration & circulation. 1992;40(11):1129-34.

14.Felices Nieto A, Quero Cuevas J, Gonzalez Barrero A, Cabello Gonzalez A, Lopez Chozas JM, Alvarez Aragon LM.
[Asymmetric septal hypertrophy associated with "subclinical hypothyroidism"].
Revista espanola de cardiologia. 2004;57(8):792-5. Hipertrofia septal asimetrica reversible asociada a "hipotiroidismo subclinico".

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

16.Asvold BO, Vatten LJ, Nilsen TI, Bjoro T.
The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study.
European journal of endocrinology / European Federation of Endocrine Societies. 2007;156(2):181-6.

17.Tokinaga K, Oeda T, Suzuki Y, Matsushima Y.
HMG-CoA reductase inhibitors (statins) might cause high elevations of creatine phosphokinase (CK) in patients with unnoticed hypothyroidism.
Endocrine journal. 2006;53(3):401-5.

18.Qari F.
Severe rhabdomyolysis and acute renal failure secondary to use of simvastatin in undiagnosed hypothyroidism.
Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2009 20(1):127-9.

19.Sekine N, Yamamoto M, Michikawa M, Enomoto T, Hayashi M, Ozawa E, et al.
Rhabdomyolysis and acute renal failure in a patient with hypothyroidism.
Internal medicine. 1993;32(3):269-71.

20.S Kursat TA, HB Colak.
A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivative combination and occult hypothyroidism.
Clinical nephrology. 2005;64(5):391-3.

21.Sousa AA, Kronit HS, Neves Fde A, Amato AA.
Fenofibrate-induced rhabdomyolysis in a patient with chronic kidney disease: an unusual presenting feature of hypothyroidism.
Arquivos brasileiros de endocrinologia e metabologia. 2009;53(3):383-6.

22.Scott KR, Simmons Z, Boyer PJ.
Hypothyroid myopathy with a strikingly elevated serum creatine kinase level.
Muscle & nerve. 2002;26(1):141-4.

23.Danese MD, Powe NR, Sawin CT, Ladenson PW.
Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis.
JAMA : the journal of the American Medical Association. 1996;276(4):285-92.

24.Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al.
American Thyroid Association guidelines for detection of thyroid dysfunction.
Archives of internal medicine. 2000;160(11):1573-5.

25.Rawat A KR, Chandra A, Faruqi TH, Khanduri S, Saxena S.
Screening or aggressive case finding for hypothyroid patients. What is the evidence?
Indian Journal of Community Health. July 2009-June 2010;21(No.2):26-32.

26.Abu-Helalah M, Law MR, Bestwick JP, Monson JP, Wald NJ.
A randomized double-blind crossover trial to investigate the efficacy of screening for adult hypothyroidism.
Journal of medical screening. 2010;17(4):164-9.

27.de Koning HJ, van Ineveld BM, van Oortmarssen GJ, de Haes JC, Collette HJ, Hendriks JH, et al.
Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors.
International journal of cancer Journal international du cancer. 1991;49(4):531-7.

28.Littenberg B, Garber AM, Sox HC, Jr.
Screening for hypertension.
Annals of internal medicine. 1990;112(3):192-202.