LESSON OF THE WEEK

Hypothyroidism in a patient with non-alcoholic fatty liver disease

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Consider hypothyroidism as a cause of non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is increasingly recognised as a cause of chronic liver disease (affecting in some series 30-40% of the population[1]) and the commonest cause of abnormal liver function tests. The disease spans a spectrum of histopathological abnormalities, ranging from simple hepatic steatosis and steatosis with necroinflammation to steatosis with necroinflammation accompanied by varying degrees of fibrosis (which may progress to cirrhosis and its complications, including liver failure and hepatocellular carcinoma).[2]

Non-alcoholic fatty liver disease is characterised by a bright liver echo pattern on abdominal ultrasonography, and although it is often accompanied by raised liver enzymes, in many cases liver biochemistry is normal.[3] Most patients are asymptomatic, with liver disease identified incidentally from abnormalities discovered in routine biochemistry tests or imaging performed for other reasons.

Although obesity is the commonest and primary metabolic cause, non-alcoholic fatty liver disease may arise secondary to several other endocrine disorders, including thyroid dysfunction, growth hormone deficiency, adrenal insufficiency, and polycystic ovary syndrome.[4] It is important to consider and screen for underlying conditions in the diagnostic approach to non-alcoholic fatty liver disease.

We report the case of a young man diagnosed with non-alcoholic fatty liver disease in whom an underlying cause was discovered.

Case report

A 33 year old, previously healthy man presented to his general practitioner with a hot swollen ankle of recent onset. He had no other joint involvement and no systemic symptoms apart from general lethargy, which he attributed to his shift work. He did not drink alcohol and was not taking any prescribed medication or over the counter drugs. He had a history of untreated obstructive sleep apnoea. His general practitioner diagnosed gout and recommended treatment with non-steroidal anti-inflammatory drugs but arranged to check renal function and liver function. These initial investigations showed abnormal liver biochemistry (aspartate aminotransferase 91 (normal range 13-42) U/L, alanine aminotransferase 60 (11-55) U/L, and gamma-glutamyl transferase 31 (0-55) U/L). Renal function showed a raised creatinine concentration of 143 (0-135) µmol/L and an estimated glomerular filtration rate of 54 mL/min/1.73m^2. Over the following three months his liver and renal function remained abnormal, and he was therefore referred to the gastroenterology clinic for further investigation and management.

Clinical examination at the hospital was unremarkable. Initial laboratory investigations confirmed his abnormal

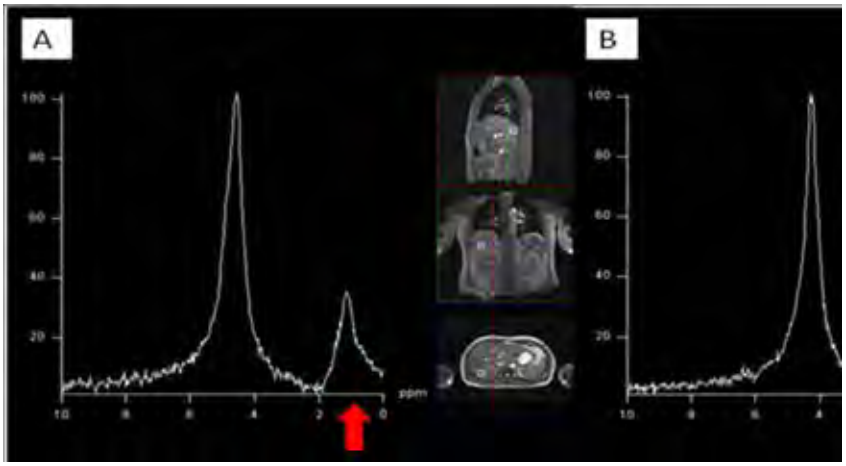

Fig 1 | Pretreatment (A) and post-treatment (B) measurements of liver fat showing a reduction in hepatic triglyceride content from 12.7% at baseline to 5.9% after treatment. By means of proton magnetic resonance spectroscopy, areas of resonances from protons of water (large peak) and of methylene groups in the fatty acid chains of hepatic triglyceride (smaller peak, red arrow) were quantified and converted to percentages by a validated computer algorithm (Java based software jMRUI v.3.0)[5]

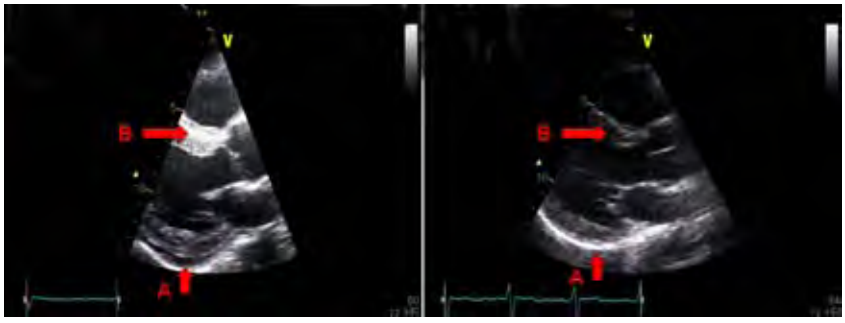

Fig 2 | Parasternal long axis views before (left) and after (right) thyroxine replacement. A 1.2 cm pericardial effusion (A) and moderate (1.7 cm) septal hypertrophy (B) were noted before treatment, both of which resolved on follow-up scanning

liver biochemistry. Liver specific auto-antibody screen was negative with normal immunoglobulin electrophoretic pattern. There were normal concentrations of α_1 antitrypsin, ferritin, transferrin saturations, copper, and ceruloplasmin. Markers for chronic viral hepatitis B and C were negative. He also had hyperlipidaemia (total cholesterol 9.2 mmol/L, triglyceride 7.1 mmol/L, and high density lipoprotein cholesterol 1.5 mmol/L; low density lipoprotein cholesterol could not be calculated). Liver ultrasonography showed a bright liver echo pattern consistent with steatosis but no evidence of established cirrhosis. Non-alcoholic fatty liver disease was diagnosed on the basis of the clinical information.

The patient subsequently consented to participate in a research study investigating the effects of supervised exercise in non-alcoholic fatty liver disease. At entry into the study the patient weighed 97 kg, with a body mass index of 31 (weight (kg)/(height (m)^2)). Non-invasive quantification of liver fat by proton magnetic resonance spectroscopy[5] confirmed the clinical diagnosis of non-alcoholic fatty liver disease with a hepatic fat content of 12.7% (normal range <5.6%, fig 1A). As part of his cardiovascular screening before exercising, echocardiography showed a small pericardial effusion (fig 2). Further biochemical investigations, undertaken to explain the pericardial effusion, uncovered profound hypothyroidism, with a thyroid stimulating hormone concentration of 151 (0.4-4.5) mU/L and a free thyroxine concentration of 2.6 (8-21) pmol/L. Thyroid microsomal antibodies were markedly raised at 269 (<80) IU/mL. Further questioning in the endocrine clinic found no further symptoms apart from profound lethargy, and he had no family history of thyroid or other autoimmune disease. Examination showed coarse facial features and a mild bradycardia but no other clinical signs. Replacement therapy with thyroxine was started (50 µg daily, increased to 100 µg daily after one week), and after informed consent, investigations were repeated after six weeks. At this time the patient's weight had fallen to 90 kg and his thyroid stimulating hormone concentration had decreased to 2.82 mU/L, indicating biochemical euthyroidism. Liver function tests were normal (aspartate aminotransferase 37 U/L, alanine aminotransferase 45 U/L, and gamma-glutamyl transferase 27 U/L) and his lipid profile had dramatically improved (total cholesterol 4.4 mmol/L, triglyceride 1.8 mmol/L, high density lipoprotein cholesterol 0.8 mmol/L, low density lipoprotein cholesterol 2.8 mmol/L). The pericardial effusion resolved (fig 2), and liver fat had more than halved to 5.9%, indicating almost complete resolution of his non-alcoholic fatty liver disease (fig 1B).

Discussion

This case illustrates a common scenario: coincidental presentation of non-alcoholic fatty liver disease with abnormal liver biochemistry performed for an unrelated reason, in this case presenting with an episode of acute gout. Most importantly, however, this case shows that primary hypothyroidism may mimic liver disease and in particular drive the development of non-alcoholic fatty liver disease and associated obesity and dyslipidaemia. Gout in this instance may have been precipitated by the patient's hypothyroid state.[6]

General practitioners and hospital specialists should be alert to the possibility of thyroid dysfunction in any patient with unexplained liver biochemistry or with a clinical suspicion of non-alcoholic fatty liver disease. In our patient, primary hypothyroidism was discovered only opportunistically, through his participation in a clinical research study and the discovery of the clinically silent small pericardial effusion. His clinical and biochemical abnormalities would otherwise have been attributed solely to non-alcoholic fatty liver disease. Treatment of the primary hypothyroidism resulted in normalisation of liver biochemistry and reduction in liver fat and probably reduced the risk of long term hepatic or cardiovascular sequelae of non-alcoholic fatty liver disease.

The diagnostic investigations for any patient with suspected non-alcoholic fatty liver disease include serology for hepatitis B and C, autoantibodies, iron studies, serum ceruloplasmin, fasting glucose and lipids, and liver ultrasonography.[7] The diagnosis of non-alcoholic fatty liver disease is often a diagnosis of exclusion, made when the tests mentioned above are normal and when the patient has other concomitant features of the metabolic syndrome such as central obesity, dyslipidaemia, hypertension, and glucose intolerance. The possibility of hypothyroidism as an underlying cause is rarely considered in the assessment of non-alcoholic fatty liver disease despite the common clinical and biochemical features of central obesity, abnormal liver transaminases,

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and hypertriglyceridaemia observed in both non-alcoholic fatty liver disease and hypothyroidism.

The many clinical associations between hypothyroidism and liver diseases are unsurprising given the multiple effects of thyroid hormones on liver function, cholesterol regulation, and insulin sensitivity.[8 9] The prevalence of hypothyroidism in patients with non-alcoholic fatty liver disease is twice that in patients with other chronic liver diseases (15% *v* 7.2%),[10] and even in patients with non-alcoholic fatty liver disease whose thyroid function is normal, free thyroxine and triiodothyronine concentrations are significantly lower than in controls.[7] Rodent models of non-alcoholic fatty liver disease support a direct hepatic, therapeutic effect of thyroid hormones with regression of hepatic steatosis using either thyroid hormones or liver specific thyroid hormone receptor agonists.[11-13] Mild hypothyroidism may also cause increased gamma-glutamyl transferase and alanine aminotransferase and promotes gallstone disease.[7] The incidence of hypothyroidism is also higher in patients with hepatocellular carcinoma.[14]

Although obesity has independent effects on liver fat, hepatic steatosis in hypothyroidism is likely to be the result of additional factors. The link between non-alcoholic fatty liver disease and features of the metabolic syndrome (including insulin resistance) and type 2 diabetes mellitus is well described.[15] However, other endocrinopathies are increasingly implicated in the aetiology of non-alcoholic fatty liver disease. Patients with hypopituitarism have an increased incidence of non-alcoholic fatty liver disease, particularly patients with growth hormone deficiency,[16 17] and growth hormone levels are lower in men with non-alcoholic fatty liver disease than in normal controls.[18] Growth hormone replacement normalised steatosis with necroinflammation and hypercholesterolaemia in a single case report. Non-alcoholic fatty liver disease is said to be more prevalent in both polycystic ovarian syndrome and adrenal insufficiency.[4] Secondary endocrine causes of non-alcoholic fatty liver disease are increasingly recognised, and some specialists have suggested such causes should be systematically considered in all patients in whom non-alcoholic fatty liver disease is diagnosed.[19]

This case illustrates that primary hypothyroidism and other endocrinopathies are important conditions to consider as possible underlying causes in patients with non-alcoholic fatty liver disease or with abnormalities of liver biochemistry. The diagnosis of non-alcoholic fatty liver disease is not an end in itself but should provoke consideration of underlying conditions.

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