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LESSON OF THE WEEK

An unusual cause of jaundice

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Patients with jaundice of unknown cause need their thyroid function tested to exclude an underlying thyroid problem

We report on a patient with Graves' thyrotoxicosis, whose presentation with jaundice and hepatic dysfunction led to unnecessary investigations and a delay in management. We suggest patients with jaundice of unknown cause should have thyroid function tests performed as a part of their routine investigation.

Case report

A 36 year old labourer was referred to the gastroenterology department at his local hospital with a three month history of general malaise, myalgia, and painless jaundice. He reported a 25 kg weight loss and a change of bowel habit with pale diarrhoea and steatorrhoea, passing stools up to 20 times daily, with some darkening of his urine.

He had no medical history of note, was a non-smoker, consumed around 5 units of alcohol a week, and lived with his wife and teenage daughter. He had not travelled abroad recently and had had no occupational exposure to hepatitis or hepatotoxic chemicals or drugs. In addition, he had not received any blood products, undergone body piercings, or experienced any previous episodes of jaundice.

On clinical examination he was markedly cachetic and icteric (fig 1), with no signs of chronic liver disease or tattoos evident. He had no fever and a pulse rate of 78 beats/min, blood pressure of 134/78 mm Hg, respiratory rate of 14 breaths/min, and BMI of 23.9. We

detected no lymphadenopathy or testicular atrophy or organomegaly on abdominal examination.

Results of full blood count and tests for urea, electrolytes, and random glucose were all within normal limits. Inflammatory markers were raised with the erythrocyte sedimentation rate of 47 mm in the first hour and C reactive protein of 52 mg/l. Results of routine hepatic function tests were 581 (normal range 1-22) µmol/l for bilirubin, 184 (30-115) U/l for alkaline phosphatase, 26 (5-48) U/l for γ-glutamyltransferase, 146 (5-40) U/l for alanine aminotransferase, 69 (5-45) U/l for aspartate aminotransferase, and 33 g/l (35-50) for albumin. Results of clotting and coagulation studies, and hepatitis investigations were normal, and autoantibody testing showed positive smooth muscle antibody of low titre (1:40), with negative results for other autoantibodies (IgA antitransglutaminase, antinuclear, antidouble stranded DNA, antineutrophil cytoplasmic, and anti-mitochondrial antibodies).

Abdominal ultrasonography showed normal liver, biliary tree, and gall bladder with no evidence of biliary obstruction; computerised tomography of the abdomen also showed normal liver size and texture. Percutaneous liver biopsy showed evidence of cholestasis, and subsequent magnetic resonance cholangiopancreatography found no abnormality in the bile and pancreatic ducts.

Because of his unresolving jaundice and ongoing hepatic dysfunction with an undefined cause the initial medical team investigating his condition considered liver transplantation. He was subsequently referred to the gastroenterology department at our tertiary centre for a further opinion.

On review at our hospital by the gastroenterologists

Fig 1 | The patient showing signs of jaundice and cachexia

Fig 2 | The patient a year after treatment

he was icteric and cachectic and reported a poor appetite with frequent bowel motions, and stool examination confirmed steatorrhoea. Thyroid function tests were requested as part of the routine investigation into weight loss and subsequently showed a free thyroxine (FT4) concentration of 24.8 (normal 9.8-23.1) pmol/l, free triiodothyronine (FT3) concentration 9.8 (3.5-6.5) pmol/l, and a thyroid stimulating hormone (TSH) concentration of 0.07 (0.35-5.5) mU/l, consistent with a diagnosis of thyrotoxicosis.

He was referred to the endocrinologists for further investigations and management. On examination he was not tachycardic, and there was no evidence of sweating, tremor, goitre, thyroid eye disease, or skin changes. Test results for thyroperoxidase and thyroid stimulating hormone receptor antibodies (TSAB) were both positive, 97.9 kU/l (normal <32.0) and 8.7 IU/l (<1.5) IU/l, respectively. We diagnosed Graves' thyrotoxicosis and treated the patient with carbimazole. He began to improve clinically with resolution of his liver function over the next few weeks. He gained weight, his bowel frequency reduced, and his jaundice subsided with normalisation of his thyroid function.

He remained on a block and replace regimen with carbimazole and levothyroxine for six months. A year after his original diagnosis he remains euthyroid and well (fig 2). He has regained his original weight and test results for thyroid stimulating hormone receptor antibodies are now negative (<1.5 IU/l).

Presently he is kept under regular review at the thyroid clinic and will be treated with radioiodine if there is a relapse of his thyrotoxicosis.

Discussion

Thyrotoxicosis may be associated with various abnormalities in liver function¹ and can be a cause of profound cholestasis,² which may be associated with steatorrhoea. In this case the malabsorption caused by steatorrhoea augmented the weight loss caused by hyperthyroidism.

Thyroid hormone concentrations are important for normal hepatic function and metabolism of bilirubin.³ Lack of knowledge of the association between thyroid and liver abnormalities can lead to misdiagnosis, mistakes in management of patients, and consequent under-reporting of those patients affected. Published case series in those with hyperthyroidism show that results of liver tests can be severely abnormal and modest abnormalities are common.⁴⁻⁵ In certain individuals this can lead to serious morbidity and even mortality.

The liver has an important role in metabolism of thyroid hormone, and autopsies have shown hepatic inflammation, fibrosis, and centrilobular necrosis in patients with hyperthyroidism.⁶ The pathogenesis of hepatic dysfunction is unknown; one theory suggests the liver is damaged by the systemic effects of excess thyroid hormone. Hyperthyroidism induces an increased metabolic rate, which is associated with increased oxidative capacity and oxidative damage of tissue.⁷

Thyroid hormones are also known to increase production of insulin-like growth factor within the liver⁸

and can cause changes in fatty acid and lipid synthesis. This hypermetabolic state makes the liver more susceptible to injury, and, in addition, thyroid hormones might also have a direct toxic effect on hepatic tissue.

Other associations between liver dysfunction and thyroid disease per se or its management are also well described. Autoimmune hepatitis is associated with autoimmune thyroid disease, and raised aminotransferase concentrations may be seen before thyroiditis is diagnosed.⁹ If these persist after correction of thyroid dysfunction, liver biopsy may be required to differentiate autoimmune hepatitis from liver involvement secondary to thyroid disease as immunosuppressive therapies are usually indicated for autoimmune hepatitis.

A strong association exists between Hashimoto's thyroiditis and primary biliary cirrhosis.¹⁰ In those affected, autoimmune thyroid failure might occur associated with the presence of thyroid microsome, thyroperoxidase, and thyroglobulin antibodies in addition to the presence of goitre. Patients with these antibodies or hypothyroidism (either clinical or biochemical), or both, may be found in a considerable number of those with primary biliary cirrhosis.

Drug induced hepatotoxicity should be considered in those who present with hepatic dysfunction after initiation of thionamide therapy. The estimated incidence of antithyroid associated hepatotoxicity with both carbimazole and propylthiouracil is about 0.5%.¹¹ Propylthiouracil induced hepatotoxicity, although rare, can be severe enough to cause hepatic failure with associated morbidity and mortality¹²; hepatic function should therefore be monitored routinely during treatment.

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