Primary hypothyroidism masquerading as hepatic encephalopathy: case report and review of the literature

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Abstract

A 74 year old woman with hepatitis C of long duration was admitted to hospital in hyperammonaemic coma. Despite aggressive treatment of hepatic encephalopathy, there was no clinical improvement. As part of her evaluation for other causes of altered mental status, she was found to be profoundly hypothyroid. Treatment with thyroid replacement hormone was accompanied by prompt normalisation of her mental status and hyperammonaemia. Hypothyroidism may exacerbate hyperammonaemia and portosystemic encephalopathy in patients with otherwise well compensated liver disease. Hyopthyroidism should be considered in the differential diagnosis of encephalopathy in patients with liver disease.

(*Postgrad Med J* 2000;**76**:424–426)

Keywords: hypothyroidism; cirrhosis; hyperammonaemia; coma

Although the liver is considered to be a hormone independent organ, it is hormone responsive and endocrine alterations affect hepatic function. We present a case of metabolic coma due to hyperammonaemia and myxoedema in a patient with well compensated cirrhosis and primary hypothyroidism. Coma developed after discontinuation of thyroid hormone replacement and it appears that hypothyroidism precipitated hyperammonaemia.

Case report

A previously healthy, functional 74 year old women was admitted in coma after being found unresponsive in her flat. Several days before she had fallen and struck her head without loss of consciousness. Since then, she had exhibited slurred speech and did not seem herself. Her past medical history as reported at the time of admission was remarkable for well compensated hepatitis C of approximately 20 years' duration. A search of the patient's flat found no prescription medication. She neither smoked nor drank.

Examination revealed a thin female in coma with shallow, irregular respirations. Her pulse was 95 beats/min, blood pressure was 120/50 mm Hg, and respirations were 6–8/min. A healing contusion was noted on her forehead. Examination of the abdomen showed the liver to be of normal span with a firm edge. There was no splenomegaly or ascites noted. There was no oedema or spider angiomas, but palmar erythema was noted. Neurologically, she was unresponsive. Her Glasgow coma score was 3.

A complete blood count, electrolytes, urinalysis, and prothrombin time were within normal limits. Results of liver chemistry were (normal limits): aspartate aminotransferase (AST) 156 U/L (11–35), alanine aminotransferase (ALT) 53 U/l (7–46), alkaline phosphatase 113 U/l (46–139), total bilirubin 37.6 μmol/l (3.4–20.5), direct bilirubin 10.3 μmol/l (0–5.1), and albumin 34 g/l (34–48). The serum ammonia concentration was 124 μmol/l (10–47). Computed tomography of the head revealed no evidence of intracranial haemorrhage or cerebrovascular accident. Lumbar puncture revealed a normal opening pressure, no gross or microscopic blood, and normal concentrations of glucose and protein. An echocardiogram showed no valvular abnormalities, pericardial effusion, thrombus, or vegetations. Ultrasound examination of the abdomen disclosed a small, echogenic liver and splenomegaly. An electroencephalogram revealed severe generalised slowing with triphasic waves.

A diagnosis of hepatic coma was made and the patient started on lactulose. Within 24 hours, the ammonia level decreased to 52 μmol/l, but her mental status was unchanged. Because of the poor clinical response, other aetiologies for metabolic encephalopathy were sought. A morning cortisol was normal and a serum toxin screen was negative. Her serum thyroid stimulating hormone was 104 mU/l (0.47–6.90).

Intravenous levothyroxine 0.05 mg was administered intravenously every six hours. Over the next day, the patient gradually regained consciousness and her mental status returned to normal over the following days. Once alert, she informed the staff that she had a long history of hypothyroidism treated with levothyroxine. She had discontinued it two months before admission at the urging of her chiropodist who had instead recommended a herbal preparation to stimulate the thyroid. She was discharged to home shortly thereafter on levothyroxine and is euthyroid with no evidence of hepatic dysfunction.

Discussion

This unusual case demonstrates the complex interactions of liver and thyroid. It shows that hyperammonaemia may accompany profound hypothyroidism in patients with coexisting liver disease and that the presence of

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Submitted 30 July 1999
Accepted 22 November 1999

hyperammonaemia, particularly in the absence of other evidence of hepatic decompensation, should prompt a search for hypothyroidism.

Thyroid test abnormalities are common in both acute and chronic liver disease, but most patients remain euthyroid. The most common abnormalities are increases of total thyroxine and thyroxine binding globulin in association with normal free thyroxine and thyroid stimulating hormone concentrations.[1 2] Increased concentrations of total thyroxine appear due to increased thyroxine binding globulin, which have been variously attributed to release by damaged hepatocytes, decreased thyroxine binding globulin catabolism, or increased synthesis by regenerating hepatocytes.[3] Serum triiodothyronine concentrations in chronic liver disease are variable but generally decrease with increasing hepatic dysfunction.[4]

Thyroid dysfunction may also occur in association with chronic liver disease most commonly in immune mediated liver disorders, particularly autoimmune chronic active hepatitis, primary biliary cirrhosis, and hepatitis C.[5 6] Hypothyroidism is more common than hyperthyroidism. Antithyroglobulin and antimicrosomal antibodies are often positive even in the absence of thyroid dysfunction. Thyroid antibodies are detected in 36%–72% of patients with autoimmune chronic active hepatitis and primary biliary cirrhosis and in 6%–14% of patients with chronic hepatitis C.[6 7]

Conversely, both hyperthyroidism and hypothyroidism can adversely affect hepatic structure and function. Hyperthyroidism is associated with increases in serum transaminases, alkaline phosphatase, and serum bilirubin concentrations.[8] Liver biopsy specimens in hyperthyroid patients most often show non specific changes including hepatocyte degeneration, cholestasis, and Kupffer cell hyperplasia.[8] Although hyperthyroidism may alter hepatic histology and biochemistry, the clinical picture is usually dominated by the signs and symptoms of hyperthyroidism and diagnosis is not difficult.

Differentiation of hypothyroidism from hepatic dysfunction can be difficult, particularly in patients with coexisting liver disease as symptoms of hypothyroidism and chronic liver disease are similar. In both, patients may present with fatigue or mental status changes, as well as weakness, myalgias, and dyspnoea on exertion. Oedema, ascites, and pleural effusion are seen in both disorders. Transaminase increases are common, often with AST raised out of proportion to ALT, as was seen here. While these increases may be caused by the steatosis which has been reported in hypothyroidism, AST increases may also be caused by myopathy.

While myxoedema may cause coma, it may not have been the sole cause of coma in this patient. Profound hyperammonaemia was noted at the time of admission without other evidence for hepatic dysfunction, such as coagulopathy, jaundice, or ascites. The effect of thyroxine on ammonia metabolism is not well understood. Although protein synthesis is decreased in hypothyroidism,[9] urea production and the activities of urea cycle enzymes are increased in rats with experimental hypothyroidism.[10 11] These observations would suggest that hypothyroidism may increase ammonia production. There is only one other reported case of hypothyroidism, hyperammonaemia, and apparent portosystemic encephalopathy in a patient in a patient with cirrhosis.[12] In that report, a patient with altered mental status and decompensated liver disease, including hyperammonaemia, failed to respond to protein restriction and lactulose. Further investigation disclosed hypothalamic hypothyroidism and the patient's mental status was restored after administration of thyroxine. Interestingly, the electroencephalograms in both this and the previous reports disclosed generalised slowing and triphasic waves suggestive of hepatic encephalopathy. While this pattern is seen in a variety of metabolic encephalopathies, including hyperthyroidism, it is uncommon in hypothyroidism which more often demonstrates only diffuse slowing.[13]

In summary, differentiating hypothyroidism from hepatic dysfunction may occasionally be difficult, particularly in the setting of preexisting liver disease. Hyperammonaemia and mental status changes in chronic liver disease may be due to hypothyroidism. If suspected portosystemic encephalopathy does not respond to therapy, clinicians should evaluate for coexistent hypothyroidism.

Learning points

- Thyroid and liver disease may coexist.
- Differentiation of hyperthyroidism from chronic liver disease may occasionally be difficult.
- Hyperammonaemia may be precipitated by hyperthyroidism in patients with liver disease.
- Altered mental status and hyperammonaemia in patients with coexisting liver disease may be caused by hyperthyroidism in the absence of primary hepatic decompensation.

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Turkish pepper (extra hot)

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Abstract
A 38 year old female office worker was admitted with a newly discovered blood pressure of 250/110 mm Hg. Evaluation for secondary forms of hypertension was negative and treatment was begun. Sodium excretion was markedly reduced, plasma aldosterone was normal, and plasma renin activity was low. Therefore, presence of an aldosterone-like activity was suspected. Eventually, the patient confessed to abusing "Turkish Pepper", a brand of Scandinavian liquorice candies and "Fisherman's Friend", another brand of liquorice candies, concurrently. After eliminating liquorice from her diet, the hypertension disappeared thus allowing her antihypertensive treatment to be stopped.
(*Postgrad Med J* 2000;**76**:426–428)

Keywords: liquorice; hypertension

Hypertension is among the most frequently encountered medical problems. Having excluded secondary forms of hypertension such as renal artery stenosis, hyperthyroidism, phaeochromocytoma, mineralocorticoid and cortisol excess, clinicians commonly assign their patients the label of "essential" hypertension. Dietary causes of hypertension such as excessive liquorice consumption are often overlooked. Clinicians often fail to ask about liquorice ingestion and patients are unaware of liquorice as a potential health hazard. We present a case of liquorice "abuse", a common form of hypertension in industrialised countries, and provide a brief review of the disorder.

Case report

A 38 year old office worker presented with worsening headache and decreased appetite. She had suffered from migraine for years. The remainder of her previous medical history was unremarkable. She received no regular medication except for an oral contraceptive preparation. On admission, she appeared distressed but not acutely ill. Her blood pressure was 230/130 mm Hg and a trace of pitting pedal oedema was present. Grade 1 hypertensive retinopathy was noted. The remainder of the physical examination was unremarkable.

Serum creatinine, urine analysis, arterial blood gas values, and thyroid hormones were normal. Her serum potassium concentration was 3.9 mmol/l. Urinary catecholamines and plasma cortisol were normal. Electrocardiography, chest radiography, and a duplex scan of the renal arteries were normal. Urine sodium excretion was reduced to 17 mmol/day. Urinary cortisol was 196 nmol/24 hour (high normal), urinary aldosterone was 1.3 nmol/24 hour (low), and plasma renin activity was 0.15 ng/l (very low) suggesting presence of an aldosterone-like substance.

Further inquiries revealed daily consumption of large amounts of "Turkish Pepper" (Karl Fazer Ltd, Helsinki, Finland, fig 1), a brand of liquorice candies containing 200 mg glycyrrhicinic acid and 1.5 g of sodium/100 g. Moreover, to our astonishment, the patient was incidentally seen ingesting "Fisherman's Friend" (Lofthouse Ltd, Fleetwood, UK, fig 2) liquorice lozenges containing 200 mg glycyrrhicinic acid and 60 mg sodium chloride/100 g.

Figure 1 "Turkish Pepper": a strong brand of liquorice candies manufactured in Finland.

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Submitted 26 April 1999
Accepted 26 April 1999