Skin fragility and abnormal liver function tests

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A 53-year-old man, a worker in a plastic factory, presented with a 12-month history of a non-itchy skin rash on the dorsum of both hands, associated with increased skin fragility and tendency to recurrent scar formation. The biochemical profile revealed an isolated elevation of serum alanine aminotransferase 55 IU/l (normal 5–36 IU/l). Clinical examination did not reveal any stigmata of chronic liver disease. He denied any history of jaundice, blood transfusions, intravenous drug use or family history of skin or liver disease. His alcohol intake was in the range of three bottles of wine a week. Hepatitis B surface antigen and hepatitis C antibodies (ELISA) were not detected. Serum copper, caeruloplasmin and alpha-1-antitrypsin levels were normal. No serum auto-antibodies were detected. Subsequently, a liver biopsy was performed (figure).

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Figure Liver biopsy (Perls stain, orig $\times 400$)

Questions

- 1 What does the liver biopsy show ?
- 2 What is the underlying skin disorder ?
- 3 How is the condition treated ?

Answers

QUESTION 1

The figure is a high-power view of a portal tract with the adjacent hepatic parenchyma. The striking feature is the presence of dark-staining granules, representing haemosiderin deposition, both in the parenchymal and the stromal cells. There is no evidence of cirrhosis. The overall appearance is consistent with haemochromatosis.

QUESTION 2

The underlying skin disorder is sporadic porphyria cutanea tarda (PCT).

QUESTION 3

Phlebotomy is the treatment of choice. Abstinence from alcohol is an important adjunct measure. An alternative but less effective form of treatment is low-dose chloroquine.

Further investigations

The features of iron overload were confirmed in our patient. Serum ferritin was 1878 µg/l (normal 30–400), serum iron 41 µmol/l (8–34) and serum transferrin 1.9 g/l (2–3.2). Porphyrin investigations revealed the following. In urine, markedly elevated uroporphyrin levels at 3244 nmol/24 h (0–50), and normal coproporphyrin levels at 414 nmol/24 h (0–430). In faeces, a normal protoporphyrin level at 80 nmol/g dry weight (0–200), and marginally raised coproporphyrins at 80 nmol/g dry weight (0–76). Thin-layer chromatography of urine and faecal extracts revealed similar changes. In addition, the presence of 5,6,7-carboxylic porphyrins (urine, faeces) and isocoproporphyrins (faeces) was detected. A test for erythropoietic protoporphyria was negative.

Discussion

The porphyrias are metabolic disorders arising from enzymatic defects in the haem biosynthetic pathway.¹ Their clinical presentation depends on the predominant form of porphyrin precursor accumulation. They may present as isolated cutaneous lesions, neuropsychiatric disorders, or both.

PCT is probably the commonest type of porphyria worldwide. However, there are striking geographical variations. There are three types: the common sporadic (type I) or the familial types (types II and III). The underlying metabolic defect is a reduction in the activity of the enzyme uroporphyrinogen decarboxylase. In the familial types, the reduction in enzyme activity is seen in all tissues. In the more common sporadic type, the reduction in enzyme

activity is confined to the liver. Clinical and experimental studies suggest that this enzyme is reversibly inactivated by an iron-dependent process. The cutaneous manifestations of PCT include photosensitivity, recurrent blister formation, hypertrichosis, hyperpigmentation and scarring. This may result in a pseudo-sclerodermatous appearance. Features suggestive of acute intermittent porphyria such as severe abdominal pain and drug sensitivity (apart from alcohol and oestrogens) are notably absent. Hepatomegaly, raised serum bilirubin and aminotransferase levels may occur, especially in alcoholics. A striking association with hepatitis C has been noted in some but not all studies.² The presence of hepatitis C may explain some of the pathological changes encountered in the liver, but the role of the hepatitis C virus in the pathogenesis of sporadic PCT is uncertain.

Mild-to-moderate hepatic iron overload is often present in patients with PCT. In less than 10% of patients, this may be in the range usually associated with hereditary haemochromatosis. The relationship between sporadic PCT and hereditary haemochromatosis has been re-examined in the light of the discovery of the probable haemochromatosis gene (HLA-H).³ Indeed, a significant association has been noted between one of the causative mutations (Cys282Tyr) in the HLA-H gene and sporadic PCT.⁴ This mutation is responsible for much of the iron overload in populations of European descent.⁵ It has been suggested that, in countries where this mutation is common, patients with PCT should be screened for its presence.⁵ Homozygotes thus identified should be treated and their families should be screened for haemochromatosis.

Phlebotomy is the treatment of choice in patients with PCT. This achieves a reduction in the hepatic iron stores. The iron 'load' in PCT is not usually marked (in the range of 3–5 g). Phlebotomy is performed once or twice weekly initially. Lasting clinical remission is often achieved after only five or six sessions of phlebotomy. Serum ferritin should be monitored to prevent the development of iron deficiency. Low-dose chloroquine (125 mg) is an alternative form of treatment for patients who cannot tolerate phlebotomy. Avoidance of precipitating factors like alcohol and oestrogens is important.

Final diagnosis

Sporadic porphyria cutanea tarda and haemochromatosis.

Keywords: porphyria cutanea tarda; haemochromatosis; skin fragility

1 Anderson KE. The porphyrias. In: Williams WJ, Beutler E, Ersler AJ, *et al*, eds, *Hematology*. New York: McGraw-Hill, 1990; pp 722–42.

2 Fargion S, Piperno A, Cappellini MD, *et al*. Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. *Hepatology* 1992;16:1322.

3 Feder JN, Gnirke A, Thomas W, *et al*. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399–408.

4 Roberts AG, Whatley SD, Morgan RR, Worwood M, Elder GH. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet* 1997;349:321–3.

5 Elder GH, Worwood M. Mutations in the hemochromatosis gene, porphyria cutanea tarda, and iron overload. *Hepatology* 1998;27:289–91.

Syncope, the head ruling the heart

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A previously fit 53-year-old man was referred for investigation of episodes of syncope and pre-syncope. There was no history of convulsions and after one such episode his pulse rate was noted to be 44 beats/min. Examination was unremarkable. An electrocardiogram and echocardiogram were normal. Repeated 24-hour Holter monitoring did not show an arrhythmia during a collapse although his resting pulse rate fell to 39 beats/min.

Over the next few weeks he deteriorated, complaining of unsteadiness, poor short-term memory and frequent headaches. The attacks continued on a daily basis and were associated with urinary incontinence. His gait became broad-based and unsteady but otherwise neurological examination remained normal.

He was admitted after a further attack followed by confusion. On admission he had a Glasgow Coma Score of 14/15, was afebrile, had a pulse rate of 84 beats/min and a blood pressure of 120/70 mmHg. Papilloedema was noted but there were still no focal neurological signs. Over the next 24 hours he deteriorated to a Glasgow Coma Score of 8. His pulse rate decreased to 40 beats/min and his blood pressure increased to 150/100 mmHg. A computed tomography (CT) scan (figure 1) and subsequent gadolinium-enhanced magnetic resonance imaging (MRI) scan (figure 2) were performed.

Figure 1 Axial brain CT scan

Figure 2 Coronal gadolinium-enhanced MRI

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Questions

- 1 Where is the lesion and what effect is it having?
- 2 What are the ways in which lesions in this area might present?
- 3 What is the differential diagnosis?
- 4 Describe the cardiovascular response to his decreased conscious level.