Lethargy in a patient with cirrhosis

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In December 1983, a 53-year old Chinese woman presented with a one-year history of generalised pruritus. Various members of her family, extending over four generations, had autoimmune thyroid disorders. On examination, she had bilateral xanthelasmata but no stigmata of chronic liver disease nor jaundice. Her liver was just palpable but she had neither splenomegaly nor ascites. Serum bilirubin was 7 $\mu\text{mol/l}$, total alkaline phosphatase 710 IU/l, aspartate transaminase 98 IU/l, alanine transaminase 108 IU/l and albumin 39 g/l. Erythrocyte sedimentation rate was 110 mm/h and her total cholesterol was 6.1 mmol/l. Serum IgM level was elevated at 404 mg/dl (normal range: 100–206) but IgG and IgA levels were both within normal limits. Antinuclear factor and anti-smooth muscle antibody were both negative but anti-mitochondrial antibody was positive. A liver biopsy was done (figures 1, 2).

She was started on a gradually increasing dose of penicillamine and attained a maximum dose of 600 mg/day in just over six months. Because of her strong family history of autoimmune thyroid disorders, her thyroid status was checked. She was clinically and biochemically euthyroid but antimicrosomal antibody and antithyroglobulin were detected at titres of 1 in 1600 and 1 in 20, respectively. About a year after the onset of illness, she was started on cholestyramine as her itching had persisted. Her serum bilirubin had by now risen to 30 $\mu\text{mol/l}$ but her alkaline phosphatase, aspartate transaminase and alanine transaminase were 313, 115 and >108 IU/l, respectively.

Six months later, her pruritus had improved remarkably but she noticed gradual onset weakness in both upper limbs over a six-week period and blurring of vision. These symptoms tended to worsen towards the evening. She complained of diplopia on looking to the left but this was not present on formal testing. A diagnosis was made and she was treated medically. Her weakness gradually improved and within a year, she was off treatment.

Four years after the initial diagnosis she presented with lethargy, palpitations and weight loss of about 8 kg in 10 months despite a normal appetite. In January 1990 she complained of eye irritation. Ursodeoxycholic acid was started five years after her initial presentation. It has been 12 years since she first presented and she remains relatively well with a serum bilirubin of 25 $\mu\text{mol/l}$, total alkaline phosphatase 441 IU/l, aspartate transaminase 114 IU/l, alanine transaminase 130 IU/l, albumin 36 g/l and a total cholesterol of 10.6 mmol/l.

Figure 1

Figure 2

Questions

- 1 What did the biopsy show and what was the diagnosis?
- 2 What was the cause of her weakness and visual disturbances?
- 3 How would you confirm this diagnosis?
- 4 What was the cause of her lethargy, palpitations and weight loss?
- 5 What test would you do for her eye irritation and what was the diagnosis?

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Answers

QUESTION 1

Liver biopsy revealed inflammation, predominantly of the portal tracts (figure 1), with portal – portal fibrous and bile ductule proliferation (figure 2), consistent with primary biliary cirrhosis.

QUESTION 2

Myasthenia gravis

QUESTION 3

Tensilon test was positive and acetylcholine receptor antibody was detected.

We believe that our patient had penicillamine-induced myasthenia gravis, as complete resolution of symptoms occurred when the drug was discontinued.^{1,2} Penicillamine has been used successfully to treat conditions as varied as rheumatoid arthritis and Wilson's disease. In the case of primary biliary cirrhosis, it has been shown to improve survival and biochemical profile, lower hepatic copper content, reduce inflammation and piecemeal necrosis.³ However, these favourable responses have not all been borne out in six subsequent trials.⁴ We now know that the lysosomal copper accumulation in primary biliary cirrhosis is an epiphenomenon and is non-toxic. Furthermore it is associated with an elevated serum caeruloplasmin level. In contrast, caeruloplasmin is decreased in Wilson's disease, resulting in cytosolic and mitochondrial copper accumulation which is toxic.⁵ Penicillamine is currently not recommended in primary biliary cirrhosis because of the high incidence of side-effects, up to 30% in some studies.⁴ It can also trigger acetylcholine receptor antibody formation as in idiopathic myasthenia gravis⁶ and at least 166 cases of penicillamine-induced myasthenia gravis have been reported in the literature.

QUESTION 4

Thyrotoxicosis.

The patient's serum thyroxine was 210 nmol/l (normal range: 55–140) with a free thyroxine index of 31.0 (normal range: 4.1–16.8). Her serum bilirubin was 45 μ mol/l, alkaline phosphatase >350 IU/l, aspartate transaminase 97 IU/l and alanine transaminase 159 IU/l. With antithyroid treatment, her bilirubin remained at 44 μ mol/l, alkaline phosphatase at 998, aspartate transaminase at 96 and alanine transaminase at 130 IU/l. She was treated with carbimazole for 14 months but relapsed six months after stopping treatment. When she relapsed, her bilirubin rose to 62 μ mol/l but her alkaline phosphatase, aspartate transaminase and alanine transaminase remained at 493, 99 and 118 IU/l, respectively. Radioactive iodine (I^{131}) was given and bilirubin returned to 44 μ mol/l. Aspartate transaminase and alanine transaminase also improved transiently to 64 and 79 IU/l, respectively.

Hyperthyroidism in association with primary biliary cirrhosis has only ever been reported in four cases,^{7–10} in three of which

Learning points

- lethargy in a patient with primary biliary cirrhosis may be due to hyperthyroidism
- the effect of hyperthyroidism on liver function in primary biliary cirrhosis not only varies from patient to patient but may also vary from time to time in the same patient
- penicillamine can induce myasthenia gravis

liver function was unaffected. However, in the latest report,¹⁰ hyperthyroidism was accompanied by marked deterioration in liver function and jaundice which subsequently reversed with treatment of the hyperthyroidism. Our patient was treated for hyperthyroidism on two separate occasions. Her serum bilirubin and liver enzymes remained unchanged pre- and post-treatment on the first occasion but subsequent relapse was associated with worsened jaundice. Re-treatment was followed by return of serum bilirubin to pre-relapse value and transient improvement in her liver enzymes. The effect of hyperthyroidism on liver function in primary biliary cirrhosis not only varies from patient to patient but may also vary from time to time in the same patient.

QUESTION 5

Schirmer test for the diagnosis of sicca syndrome. In our patient, after five minutes, the length of wetting on the right was 4 mm and on the left 8 mm. Sicca syndrome was hence diagnosed.

Discussion

Primary biliary cirrhosis may result from a genetically predetermined defect in immunoregulation. A reduction in suppressor T cell number and function is associated with recognition by cytotoxic T cells¹¹ of increased major histocompatibility complex class II antigen expression on biliary epithelium.¹² As such, primary biliary cirrhosis may be considered as a form of hepatic autorejection which runs a chronic course. Other epithelial surfaces with a high concentration of HLA antigens, such as those of the lacrimal, salivary and pancreatic ducts, are also involved. Not surprisingly, sicca syndrome (which may or may not amount to Sjögren's syndrome) is present in approximately 75% of cases of primary biliary cirrhosis.¹³

Final diagnosis

Primary biliary cirrhosis with thyrotoxicosis, penicillamine-induced myasthenia gravis and sicca syndrome.

Keywords: biliary cirrhosis, thyrotoxicosis, myasthenia gravis, penicillamine, sicca syndrome

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An unusual lesion of the penis

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A 53-year-old uncircumcised man presented with a one-week history of a painful swelling on the ventral aspect of the corona of his penis. He had first noticed a nontender swelling in that region one month previously. He denied any urinary symptoms or urethral discharge. On examination the distal third of his penis was grossly swollen and tender, and the foreskin could not be retracted. There was no inguinal lymphadenopathy and tests for sexually transmitted diseases were negative. He was treated initially with intravenous antibiotics followed by local excision. The histology of the lesion is depicted in figure 1.

Figure 1 Haematoxylin and eosin stain

Figure 2 Periodic acid Schiff stain

Questions

- 1 What two abnormalities are shown in figure 1?
- 2 What is the diagnosis?
- 3 Which opportunistic infection (figure 2) may be associated with this condition?
- 4 In which other parts of the body has this condition been described?

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