satisfactory steady state is achieved by eight hourly administration. Houghton *et al* showed that administration of the drug as a suppository provides a sustained plateau of serum concentration extending from eight to 16 hours after administration,⁶ which suggests that 12 hourly administration may be adequate. The much greater systemic availability of metronidazole from the paediatric (500 mg) suppository than from the 1.0 g suppository⁶ implies that a regimen of 500 mg given as a suppository every 12 hours may be adequate in most patients. Selkon suggested that the dosage of metronidazole recommended at present is excessive and that more metronidazole is being given to patients than is necessary.⁶ Further studies are planned to define the optimum treatment regimen.

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Wilson's disease: a diagnostic dilemma

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Abstract

A 13 year old boy presented with headache, sore throat, myalgia, and fever and subsequently developed haemolytic anaemia and acute liver failure. Wilson's disease, a rare cause of acute liver failure, was diagnosed at necropsy.

In such cases Wilson's disease must be diagnosed at an early stage for treatment to be effective. The most reliable indications are increased urinary and hepatic copper concentrations.

Introduction

Acute liver failure in children is usually the consequence of fulminant viral hepatitis, but if serological tests do not confirm a viral aetiology other causes must be considered. Of these, the

most important is Wilson's disease, whose features mimic a wide range of acute and chronic liver disease,¹ not only because specific treatment may reverse liver damage but also because of the implications of this diagnosis for other members of the family. We report a case in a child in whom Wilson's disease could not be confirmed in life but in whom the postmortem liver copper content established this diagnosis.

Case report

A 13 year old white boy with unremarkable medical and family histories presented with headache, sore throat, myalgia, and intermittent fever (up to 40°C) and rigors that did not respond to treatment with amoxycillin and soluble aspirin. Ten days later he developed a mild jaundice with pharyngitis and generalised lymphadenopathy but without hepatomegaly. He had an evanescent morbilliform rash. In the third week his condition deteriorated with a swinging fever and hepatosplenomegaly. The serum bilirubin concentration was 77 µmol/l (6.6 mg/100 ml) (mostly conjugated), alanine aminotransferase activity 450 IU/l, alkaline phosphatase activity 118 IU/l, total protein concentration 50 g/l (500 mg/100 ml), and albumin concentration 22 g/l (220 mg/100 ml). He became anaemic (haemoglobin concentration 8.6 g/dl) and had a persistent neutrophil leucocytosis (up to 45 × 10⁹/l (45 000/mm³)) and thrombocytopenia (84 × 10⁹/l (84 000/mm³)).

Cultures of urine, blood, cerebrospinal fluid, and bone marrow were sterile. There was no serological evidence of hepatitis A or B infection, cytomegalovirus infection, glandular fever, leptospirosis, brucellosis, toxoplasmosis, or streptococcal infection on repeated

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testing. A technetium-99m hepatoscintiscan showed poor liver uptake with increased splenic and vertebral uptake; ultrasonography showed no focal lesion within the liver.

On admission to this hospital during the sixth week of his illness he was still febrile with a temperature rising to 38.5°C despite full courses of penicillin, gentamicin, and metronidazole. He was jaundiced with ascites, ankle and scrotal oedema, and splenomegaly but had no other signs of chronic liver disease. His liver was impalpable, and he was intermittently confused.

Initial investigations showed haemoglobin concentration 9 g/dl with a reticulocyte count of 5.6%, white cell count $21.4 \times 10^9/l$ ($21\,400/mm^3$) with 95% neutrophilia, and thrombocytopenia ($33 \times 10^9/l$ ($33\,000/mm^3$)). A Coombs test was negative. The prothrombin time was 65 seconds with a control of 13 seconds. His serum bilirubin concentration had risen to 198 $\mu mol/l$ (11.6 mg/100 ml) and aspartate aminotransferase activity to 1560 IU/l. Total protein concentration was 44 g/l (440 mg/100 ml) and albumin concentration 21 g/l (210 mg/100 ml); serum IgM concentration was raised (6.1 g/l), but IgG and IgA concentrations were normal. Tissue autoantibodies were absent; α_1 -antitrypsin phenotype was normal.

Slit lamp examination did not show Kayser-Fleischer rings. Serum concentrations of copper (16 $\mu mol/l$ (101.9 $\mu g/100$ ml); normal 12-19 $\mu mol/l$ (76-121 $\mu g/100$ ml)) and caeruloplasmin (0.3 and 0.6 g/l; normal 0.2-0.6 g/l) were normal. Initially 24 hour urine copper excretion was raised at 45 $\mu mol/24$ h (286.6 $\mu g/24$ h) (normal < 1.25 $\mu mol/24$ h (7.96 $\mu g/24$ h)), but a penicillamine challenge could not be completed because of clinical deterioration. Three subsequent estimations of urine copper excretion obtained while he was receiving prednisolone and artificial liver support with charcoal haemoperfusion were normal (0.4, 0.9, and 0.6 $\mu mol/24$ h).

SUBSEQUENT COURSE

The haemolytic anaemia was unaffected by prednisolone at a dose of 2 mg/kg/24 h. Haemoperfusion carried out on three consecutive days using a Haemocol 100 charcoal perfusion column (Smith and Nephew Pharmaceuticals, Welwyn Garden City, Herts) did not prevent further deterioration of consciousness and the development of rigidity of the right arm and leg. A computed tomogram showed no evidence of cerebral oedema or a focal lesion. The prothrombin time remained prolonged up to 90 seconds; he died of a massive gastrointestinal haemorrhage in the eighth week of the illness.

Necropsy showed 12 superficial ulcers along the greater curve of the stomach. There were no varices. The liver was small and scarred, and on histological examination features of confluent necrosis with extensive bridging and multilobular collapse were present. There was prominent cholestasis with pronounced regeneration within small areas of the remaining parenchyma. The postmortem liver copper content was 82.5 mg/100 g dry weight compared with the normal value of < 30 mg/100 g dry weight; this result is in the range for Wilson's disease.

FAMILY STUDIES

Both parents and two of the four surviving siblings had caeruloplasmin concentrations in the heterozygote range.

Discussion

The prevalence of fulminant hepatic failure in Wilson's disease is unknown.² Wilson's disease has been diagnosed in only eight of 422 (1.9%) cases of fulminant hepatic failure admitted to this unit over the past 10 years (unpublished data). The clinical presentation with acute haemolysis and pyrexia³ led us to suspect the diagnosis, but this could not be confirmed in life. The absence of Kayser-Fleischer rings does not exclude the diagnosis, and neither does a normal serum caeruloplasmin concentration as this occurs in 5-10% of cases.^{1 4}

The single high value for urinary copper excretion followed by three values in the normal range while the patient was receiving artificial liver support and corticosteroids is less easily explained in the context of Wilson's disease, although normal urine copper excretion has been recorded in other cases. No studies of copper clearance by the Haemocol charcoal column

were carried out in this case. The high liver copper content at necropsy and the caeruloplasmin concentrations in the heterozygote range in the parents and two siblings would support the diagnosis of Wilson's disease.

According to a recent report a high serum copper concentration together with a high hepatic copper concentration is the most reliable means of differentiating Wilson's disease from other causes of fulminant hepatic failure. In our case, however, the serum copper concentration was within the normal range even though the hepatic copper concentration was appreciably increased and within the range reported in that series.² Thus the only reliable criterion of Wilson's disease presenting as fulminant hepatic failure appears to be a raised hepatic copper concentration. The determination of hepatic copper content in a biopsy specimen might have enabled the diagnosis to be made in life. In similar circumstances, when the prothrombin time is too prolonged to allow percutaneous liver biopsy, obtaining a liver biopsy sample via the transjugular route should be considered, even though the specimens may be small and multiple biopsies may be necessary to obtain sufficient tissue for copper estimation.

Although penicillamine is the drug of choice in Wilson's disease it may be ineffective in both fulminant hepatic failure³ and decompensated chronic liver disease,⁶ which is a conclusion reinforced by our experience of 50 children with Wilson's disease who presented with hepatic abnormalities. Of these, nine died, seven having received penicillamine, albeit for less than 72 hours in three cases. The newer chelating agent triethylene tetramine might be a more effective drug in advanced liver disease, and its use warrants further investigation.

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ONE HUNDRED YEARS AGO A few months ago, we drew attention to a grave public danger, which is daily increasing in London and other busy places, in the telephone and telegraph wires which are being stretched over streets in all directions. The reality of the peril received an unfortunate exemplification last Saturday in London. Some workmen were engaged in removing certain overhead wires, extending across Gresham Street, when one of the wires slipped through the hands of the man who had charge of it before it was properly secured by a guiding rope, and it fell with a crash in that crowded locality. Several gentlemen were struck on the head, and it is stated that "several persons had narrow escapes," owing to the wire having "twisted and turned in serpent-like fashion in the air." An elderly lady was badly cut across the head and face. This accident happened when workmen were changing some telephone wires. It is obvious that, in course of time, the wear and tear of overhead wires will make them likely to fall when they are subjected to unusual strain, as in a violent storm. It has been frequently urged that these wires should be placed under-ground; and some day this precaution against accident will probably be enforced by legislation, when a few more "accidents" have demonstrated over again the danger of the present system. (*British Medical Journal*, 1883;ii:883.)