FAMILIAL HEPATIC COPPER STORAGE DISEASE: A VARIANT OF WILSON'S DISEASE

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Wilson's disease is one form of cirrhosis affecting young people that is often amenable to treatment. It is therefore important to pick out patients with this condition from the whole group of juvenile cirrhotics. We here report a patient who suffered from a familial cirrhosis. He showed some but not all of the biochemical features of Wilson's disease and had copper deposition in the liver much in excess of that usually found in this condition. The relation of this patient to sufferers from classical Wilson's disease will be discussed.

Case Report

A boy of 14 years, complained of recurrent abdominal colic; appendectomy in June 1961 gave no relief. Physical examination at this time is said to have been normal, but there was biochemical evidence of liver disease: serum glutamic oxalacetate transaminase (S.G.O.T.) 130 units, serum glutamate pyruvate transaminase (S.G.P.T.) 150 units, and alkaline phosphatase 21 King-Armstrong units. He was referred to the Royal Free Hospital in January 1962. On examination a firm liver edge was palpable 2 cm. below the right costal margin, and the spleen could be felt 4 cm. below the left costal margin. There were no other stigmata of chronic liver disease. Neurological examination was normal and slit-lamp examination did not show Kayser-Fleischer rings in the cornea.

Family History. The patient is one of four children of non-consanguineous parents of Irish extraction. In 1953 his sister, aged 11 years, was admitted to hospital in Northern Ireland with a history of abdominal pain and swelling of one week's duration. On the basis of gross ascites, mild jaundice, spider naevi, distended abdominal wall veins and a striking bleeding tendency, a clinical diagnosis of cirrhosis was made. Investigation at this time included a serum bilirubin of 2.2 mg./100 ml., serum albumin 1.8 g./100 ml., serum globulins 2.7 g./100 ml. with an increase in β and γ fractions, a prothrombin concentration of 13% and gross aminoaciduria 'compatible with cirrhosis'. Following brief

initial improvement her clinical course was progressively downhill and she died 13 months after the onset of her illness. There was no autopsy.

In 1961, a younger brother, aged 12 years, was admitted to the Royal Berkshire Hospital, Reading. He complained of severe vomiting lasting for five days and progressive swelling of his abdomen during the 36 hours before his admission. On examination he was jaundiced and had hepatic fetor, gross ascites and distended abdominal wall veins. Investigations included a serum bilirubin of 4.2 mg./100 ml., which increased within 72 hours to 15.6 mg./100 ml., plasma proteins 5.1 g./100 ml. with reversal of the albumin/globulin ratio, S.G.O.T. 70 units, alkaline phosphatase 24 King-Armstrong units and a moderate aminoaciduria. His clinical course was progressively and rapidly downhill with severe gastro-intestinal bleeding, and he died in hepatic coma within two weeks of the apparent onset of his illness. At autopsy the liver was firm and irregular and weighed 900 g. Microscopically it showed a post-necrotic type of cirrhosis.

An elder brother, aged 16, is well and, apart from his small stature, is normal on physical examination.

Investigations. Results of investigations are set out in the Table. Serum bilirubin level was normal and aspartate transaminase and alkaline phosphatase values moderately increased. Serum urea, uric acid, electrolytes, calcium and phosphorus values were normal. Urinary phosphate, uric acid and amino acid excretion were not increased. A radiological skeletal survey was unremarkable.

Serum showed low copper and caeruloplasmin levels. D-penicillamine resulted in a great increase in the urinary copper output but without such stimulus the urinary copper was consistently low. Serum copper and caeruloplasmin levels and routine liver function tests were essentially normal in the patient's parents and surviving sibling. The serum copper and caeruloplasmin levels of his father were 123 $\mu\text{g.}/100\text{ ml.}$ and 162 $\mu\text{l. O}_2/\text{ml./hour}$ respectively, of his mother 93 $\mu\text{g.}/100\text{ ml.}$ and 154 $\mu\text{l. O}_2/\text{ml./hour}$, and of his brother 83 $\mu\text{g.}/100\text{ ml.}$ and 185 $\mu\text{l. O}_2/\text{ml./hour}$.

TABLE
RESULTS OF INVESTIGATIONS

Estimation	Normal	Wilson's Disease	This Case			
			January 1962	August 1962	January 1963	March 1963
Serum bilirubin (mg./100 ml.)	1.0		0.5	0.5	0.5	0.5
Serum alkaline phosphatase (K.-A. units/100 ml.)	15		19	43	17	24
Serum aspartate transaminase (K.-A. units/100 ml.)	40		56	69	60	26
Serum copper (μg./100 ml.)	100	10-70	67; 56			
Serum caeruloplasmin (mg./100 ml.)	20-50	20	8	8.5		
Serum caeruloplasmin (μl. O ₂ /ml./hr.)	95-180	85	59			
Urine copper (μg./24 hrs.)*	50	150	27; 66			
Urine copper after penicillamine (μg.)	200-700	2,000-4,000	2,900	3,490		
Liver copper (μg./g. wet wt.)	3.52	50-100		230		

* Mean three days' collection.

No oesophageal varices were demonstrable on barium swallow, but a splenic venogram revealed a left gastric collateral circulation. The intrasplenic pressure was raised to 23 mm. Hg. Liver biopsy (Figure) showed cirrhosis with some preservation of lobular structure, fairly severe fatty change and some nuclear vacuolation. A rubeanic acid preparation for copper was 'ambiguous'.

In spite of the atypical features a diagnosis of Wilson's disease was made. Before beginning D-penicillamine treatment, however, it was thought essential to establish that copper was indeed present in excessive amounts in

the liver. A biopsy of the liver was obtained through a small surgical incision and revealed that macroscopically the liver was nodular and histologically there was post-necrotic cirrhosis with marked fatty change. A rubeanic acid preparation was again negative, but on chemical analysis the copper content of the organ was found to be over 60 times that of normal (Table).

Progress. Therapy with D-penicillamine (450 mg. four times a day) was started. He has now been treated for 10 months and has greatly improved. He looks well

FIGURE.—Liver biopsy shows a post-necrotic type of cirrhosis. Liver cells show degenerative and fatty change and, some of them, infiltration of their nuclei. There is a predominantly mononuclear infiltration. (Haematoxylin and eosin $\times 120$.)

and no longer complains of abdominal pain. His liver is not palpable and his spleen is slightly reduced in size. His liver function tests are seen in the Table and show a return to normal values.

Discussion

In the published reports there are many examples of Wilson's disease without neurological involvement. Bramwell (1916), who once had Kinnier Wilson as his house physician, noted fulminant liver disease in four siblings and suggested that this might be the preliminary stage of Wilson's disease. A purely hepatic form of the disease was reported briefly by Jendralski (1922), and in 1923 Rystedt described a patient who presented with 'juvenile cirrhosis' and five years later developed progressive neurological changes. Barnes and Hurst (1925) reported a family of four children with cirrhosis; in three the hepatic disease preceded the neurological features by about two years and the other developed no neurological signs. Only one had Kayser-Fleischer rings and these were detected by slit-lamp examination three years after the appearance of the neurological dysfunction.

More recently family studies of patients with Wilson's disease have led to the diagnosis of the asymptomatic sufferer, who shows typical biochemical features but no physical signs (Sternlieb and Scheinberg, 1963; Lygren, Sørensen and Bernhardsen, 1959; Lange, 1962; Stillhart, Richterich and Jeandet, 1962).

The case reported here adds yet another band to the spectrum of Wilson's disease. It is appreciated that the patient with cirrhosis may have a low serum copper level, but this is usually only in the stage of hepatic failure (Walshe and Briggs, 1962) and excessive copper deposition (Butt, Nusbaum, Gilmour and DiDio, 1958). But our patient did not seem to suffer from 'acute juvenile cirrhosis' (Read, Sherlock and Harrison, 1963); clinically he did not have very active liver disease; he was not jaundiced and had no ascites; the serum transaminase values were only moderately raised and the serum globulins were unremarkable. The histology of the liver with post-necrotic cirrhosis, fatty change and glycogenic nuclear degeneration was characteristic of that described in Wilson's disease (Schaffner, Sternlieb, Barka and Popper, 1962). It is perhaps the family history that is most against the diagnosis of 'acute juvenile cirrhosis' in this patient. On the other hand it is clear that we are not dealing with classical Wilson's disease, even of the pure hepatic form. A normal urinary excretion of copper is said not to be found in a patient with clear clinical evidence of Wilson's disease (Bearn, 1960); furthermore,

the degree of copper deposition in the liver of our patient was considerably greater than that found in the classical form of the condition. The problem, however, is obviously one of exaggerated copper storage and the case is probably best considered as yet another variant of Wilson's disease.

Whether or not this patient would have developed neurological symptoms if untreated will never be known. Certainly the family history suggests that time would not have so permitted. It does seem important, however, to realize that any child with cirrhosis who gives a family history of liver disease may have increased copper deposition in the liver and that this can be present without any obvious clinical abnormalities and with biochemical features incompatible with a diagnosis of Wilson's disease. Diagnosis is exceedingly difficult in these cases, but any abnormality in the serum copper or caeruloplasmin or in the urinary copper excretion, however inconsistent, should arouse suspicion. The increase in urinary copper after a provocative dose of D-penicillamine may be a useful screening test. If doubt exists then chemical analysis of liver tissue for copper is essential. This may necessitate a limited laparotomy to obtain a biopsy of sufficient size for analysis, although Sternlieb and Scheinberg (1963) have found routine aspiration biopsy adequate. Such patients should receive D-penicillamine treatment, but it is unjustifiable to embark upon long-term treatment with such an expensive remedy (£15 a week) without diagnostic proof. Patients with a predominantly hepatic form of Wilson's disease may derive considerable benefit from this treatment (Sherlock, 1961), and our patient has done so.

Summary

A child is described with cirrhosis of the liver and brief reference made to two siblings who had died of the same condition. No neurological disturbance or Kayser-Fleischer rings were found in any of these children. Serum caeruloplasmin and copper levels were reduced in the patient to levels found in Wilson's disease, but urinary copper excretion was normal and copper deposition in the liver considerably greater than that found in classical Wilson's disease. The patient is improving on D-penicillamine treatment.

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