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

BY

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(RECEIVED FOR PUBLICATION JULY 29, 1963)

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 oxalacetic 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 μg./100 ml. and 162 μl. O₂/ml/hour respectively, of his mother 93 μg./100 ml. and 154 μl. O₂/ml/hour, and of his brother 83 μg./100 ml. and 185 μl. O₂/ml/hour.
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TABLE
RESULTS OF INVESTIGATIONS

<table>
<thead>
<tr>
<th>Estimation</th>
<th>Normal</th>
<th>Wilson's Disease</th>
<th>This Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg./100 ml.)</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (K.-A. units/100 ml.)</td>
<td>15</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>Serum aspartate transaminase (K.-A. units/100 ml.)</td>
<td>40</td>
<td>10-70</td>
<td>67, 56</td>
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<tr>
<td>Serum copper (ug./100 ml.)</td>
<td>20-50</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td>Serum caeruloplasmin (ul. O2/ml./hr.)</td>
<td>95-180</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Urine copper (ug./24 hrs.)*</td>
<td>50</td>
<td>150</td>
<td>27, 66</td>
</tr>
<tr>
<td>Liver copper (ug./g. wet wt.)</td>
<td>200-700</td>
<td>2,000-4,000</td>
<td>2,900</td>
</tr>
</tbody>
</table>

* 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

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**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 × 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 involve-
ment. 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 bio-
chemical features but no physical signs (Sternlieb
and Scheinberg, 1963; Lygren, Sörensen and Bern-
hardsen, 1959; Lange, 1962; Stillhart, Richterich

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 (Barn, 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-peni-
cillamine 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 dis-
turbance 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.

We wish to thank Professor J. N. Cumings and Dr.
J. M. Walshe for help with the biochemical investiga-
tions in this patient and Dr. D. Stone for kindly referring
the patient.

Dr. M. M. Fisher was a Medical Research Fellow of
the Medical Research Council, Canada, during the
preparation of this work.
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