WILSON'S DISEASE

THE PRESENTING SYMPTOMS

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(RECEIVED FOR PUBLICATION JANUARY 22, 1962)

Since the publication of Wilson's classic article (Wilson, 1912) the illness which has come to bear his name has generally been considered to be a neurological disease. Wilson himself referred to the condition as 'Progressive lenticular degeneration; a familial nervous disease associated with cirrhosis of the liver': the liver being relegated to a secondary position which it has largely occupied subsequently. The introduction of the name 'hepatolenticular degeneration' by Hall (1921) did little to alter the general view that this was predominantly a central nervous system disease. Of late years, however, there has been an increasing awareness that Wilson's disease is a genetically determined metabolic disorder (Bearn, 1957) involving many systems; jaundice or other evidence of hepatic disease being particularly common in children (Walshe, 1957). The occurrence of predominantly hepatic examples has resulted in the unfortunate conception of 'abdominal Wilson's disease' (Kehrer, 1930), 'forme fruste' (Bramwell, 1916) and 'incomplete Wilson's disease'. The importance of investigating copper metabolism in all forms of cirrhosis in childhood has recently been stressed by Chalmers, Iber and Uzman (1957). Bony lesions can also be the first to bring the patient to his doctor (Warnock, 1952) as may occasionally haemolytic crises (Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe and Bean, 1954); personality difficulties with 'hysterical behaviour' may also be the presenting symptoms (Boudin and Pepin, 1959).

Analysis of the presenting signs and symptoms in cases personally studied has fully confirmed the pleomorphic manifestations of Wilson's disease and the various guises which it may take.

Case Material

The present series comprises 25 cases, 20 having Kayser-Fleischer rings or typical biochemical findings of Wilson's disease. There were, in addition, five probable examples of the disease; the reason for the inclusion of these patients will be described later.

A summary of the findings in all cases is given in the Table; Cases 1 to 20 are proven cases and 21 to 25 are probable cases.

Hepatic Manifestation. Of the 20 proven cases, six gave a history of jaundice (Cases 1, 2, 4, 5, 7 and 9) as the presenting symptom and one (Case 3, the asymptomatic sibling of Case 2) was found at the age of 8 to have abnormal liver function tests and an abnormal liver biopsy fulfilling the histological criteria for the diagnosis of Wilson's disease of Anderson and Popper (1960). Since the age of 6 he had been known to have abnormally low concentrations of caeruloplasmin and copper in his serum and a high excretion rate of urinary copper. In Cases 1, 2 and 7 there can be little doubt that jaundice was of mixed hepatic and haemolytic origin. Case 1 presented at the age of 6 with jaundice, oedema and ascites, hepatosplenomegaly and excess of urobilin, but no bilirubin in the urine. Twice during her first admission to hospital her haemoglobin fell suddenly from over 90% to below 50%. She died at the age of 14 of haemorrhage from a ruptured oesophageal varix. The only symptom of nervous system involvement observed during the eight years of her illness was occasional Jacksonian epilepsy during the six months before her death. Case 2 was first seen at the age of 7 years with 'anaemia and jaundice'; the anaemia was so severe that a transfusion was required. Open liver biopsy showed 'subacute atrophy with nodular hyperplasia'. Case 7 was first seen at the age of 13 years with jaundice and anaemia (diagnosed as Lederer's anaemia) requiring blood transfusion. In addition to a marked reticulocytosis he also had bile in the urine, a raised serum alkaline phosphatase and hepatomegaly, all suggesting a mixed origin of the jaundice. In three cases (Cases 1, 4 and 5) the course of the illness remained predominantly hepatic. Case 1 has already been mentioned, and Cases 4 and 5 both died rapidly of hepatic failure and terminal haemorrhage from oesophageal varices; in neither case was there neurological involvement. All these three patients were found to have Kayser-Fleischer rings on slit-lamp examination and their serum caeruloplasmin levels were <1, 5 and 7 mg. per 100 ml. respectively, findings which leave little doubt as to the correctness of the diagnosis. The course of the illness in Case 2, originally presenting with jaundice,

TABLE 1

No.	Age of Onset (years)	C.N.S.	Hepatic	Haemolytic	Skeletal	Cause of Death		Remarks
						C.N.S.	Hepatic	
1	6		+	+			+	Predominantly hepatic illness; died 14 years from haemorrhage
2	7		+	+				C.N.S. signs at 11 years
3a	8		+					Biochemical diagnosis a 6 years
4	10		+				+	Duration of illness about five months
5	11		+				+	Duration of illness about three months
6	13		+					C.N.S. signs at 20 years
7	13		+	+				C.N.S. signs at 17 years
8	14				+			C.N.S. and hepatic signs at 18 years
9	18		+					C.N.S. signs at 29 years
10	12	+						Biochemical diagnosis at 9 years
11	12	+						Normal liver biopsy
12	13	+				+		Predominantly C.N.S. illness
13	13	+						Predominantly C.N.S. illness
14	14	+						Predominantly C.N.S. illness
15	15	+						Predominantly C.N.S. illness
16	15	+				+		Predominantly C.N.S. illness
17	15	+						Predominantly C.N.S. illness
18	17	+					+	Died of ruptured varix after four years with C.N.S. signs
19	23	+						Predominantly C.N.S. illness
20	32	+					+	Terminal liver failure
21b	8		+					Hepatosplenomegaly; no symptoms
22c	8		+				+	Subacute hepatic necrosis
23c	8		+				+	Subacute hepatic necrosis
24d	?		+				+	Subacute hepatic necrosis also lenticular degeneration
25	13		+				+	Subacute hepatic necrosis

a = Younger sibling of Case 2; abnormal liver function tests and liver biopsy; no symptoms.
b = Younger sibling of a case not included in this series.
c = Elder siblings of Case 17.
d = Elder sibling of Case 7.

and 7, presenting with hepatosplenomegaly, came eventually to be dominated by tremor and personality difficulties, the evidence of hepatic disease becoming relatively trivial. Case 9 gave a history of a brief illness thought to be infectious hepatitis at the age of 18, after which she remained well until tremor developed at the age of 29 years. Case 6, although not presenting with jaundice, had been investigated for hepatosplenomegaly eight or nine years before there was any clinical evidence of nervous system involvement, but at the time the significance of the finding was not apparent.

Skeletal Manifestation. Case 8 was of particular interest as he first complained of pain in the knees, and at the age of 14 was found by an orthopaedic surgeon to have osteochondritis dissecans. At the age of 16 he developed florid rickets; gall-stones were also diagnosed radiologically at this time (suggesting a previous episode of haemolysis). At the age of 18 years epilepsy developed and this was followed by the typical signs of basal ganglia involvement. At this age also gall-stone colic necessitated cholecystectomy. At operation he was found to have cirrhosis of the liver. Three other cases in this series also have osteochondritis dissecans or other bone disease (Cases 7, 11 and 19), though in two (Cases 11 and 19) the diagnosis is purely radiological and the condition has not yet given rise to symptoms.

Central Nervous System Symptoms. The remaining 11 patients (Cases 10 to 20) all presented with either tremor or disturbances of gait. In general the neurological symptoms followed the classical pattern of basal ganglia involvement described in the literature and need no further elaboration here save to mention that in two cases the tremor was so severe and bizarre at onset that an initial diagnosis of hysteria was made. One patient, Case 18, eventually died of haemorrhage from oesophageal varices and one, Case 20, of hepatic failure and portal hypertension.

Probable Cases of Wilson's Disease. Finally we must consider the five probable examples of Wilson's disease: three (Cases 22, 23 and 24) were older siblings of proven cases and all three had died of cirrhosis or subacute necrosis of the liver; one was found at autopsy to have degeneration of the lenticular nuclei (Case 24). The remaining two cases require mention in greater detail. Case 21, a boy of 12, the sibling of a proven case of Wilson's disease, was found at the age of 8 on routine examination of the family, to have hepatosplenomegaly and a slight increase in his urinary copper, but his serum copper and caeruloplasmin levels were, and still are, normal. The uptake of radio-copper by his liver was 55% of the injected dose, higher than has been found in Wilson's disease but rather below the normal range

(Osborn and Walshe, 1962); the boy is considered as a possible case of the disease. The other patient (Case 25) was seen in 1948. She died of subacute hepatic necrosis after an illness lasting six weeks. Certain features at the time caused comment, her parents were first cousins, she had a very low serum inorganic phosphorus, 1·7 mg. per 100 ml., a persistent glycosuria of renal origin, together with an unusual aminoaciduria. Clinically she showed florid signs of basal ganglia involvement seldom found in hepatic coma (Walshe, 1951, Case 9). Retrospectively, the diagnosis of Wilson's disease seemed probable, and a histological reinvestigation of the liver was undertaken (unfortunately brain tissue was not available). Dr. Hans Popper reported on the liver as follows: 'The liver shows subacute hepatitis with submassive breakdown. Several features suggest Wilson's disease as the aetiology rather than viral hepatitis. There are the clumping of the cytoplasm, the unusually conspicuous pigmentation, the peculiar fatty metamorphosis not usually seen in a patient of that age group, the somewhat lesser inflammatory reaction and the type of collapse which I have seen in Wilson's disease. The last criterion of glycogen nuclei is not present, but it was so in other cases at this stage in the files. I am coding this case as hepatocellular breakdown presumably from Wilson's disease.' This patient also is considered as a presumptive case of Wilson's disease.

Thus, of 25 patients studied, comprising 21 families, there were 11 cases in which jaundice or other evidence of liver disease was the presenting symptom, 11 presented with neurological signs and one with disease of the skeletal system. Two have been found on routine examination of families known to carry the Wilson's disease gene to have evidence of liver disease and abnormal copper metabolism; but they are at present symptom free.

Discussion

These findings clearly emphasize the importance of the liver in the early symptomatology of Wilson's disease, the combination of hepatic and haemolytic jaundice being of particular interest. The mechanism of haemolysis is obscure, but is also known to occur in sheep on a pasture rich in copper and is thought to be associated with a sudden release of the metal from tissue stores (Cartwright *et al.*, 1954). The role of copper in the development of bone lesions is also difficult to explain, but the finding of osteochondritis dissecans in no less than three patients suggests that routine radiological surveys of all patients might have revealed more cases.

It is of interest that cases presenting with an apparently pure hepatic illness may later develop the classical neurological lesions with a corresponding amelioration of the hepatic disease. Instances of this transition may be cited from the present series; Cases 2, 6, 7 and 9 all presented with jaundice and other evidences of liver disease, and after making an apparent recovery later developed signs of central nervous system involvement. It remains to be seen if Cases 3 and 21 will undergo a similar transition. This suggests an identity of the primary gene abnormality, a point further illustrated by the fact that both hepatic and neurological cases can occur in the same family; Case 17 presented at the age of 15 with classical signs of basal ganglia involvement and Kayser-Fleischer rings and has subsequently responded to treatment with B.A.L. and penicillamine, whilst two of his elder siblings had previously both died at the age of 8 of subacute hepatic necrosis. Again, Case 7, who developed a mixed hepatic and haemolytic jaundice before the onset of nervous system signs, also had an elder sibling who had died of hepatic cirrhosis and was found at autopsy to have unsuspected disease of the basal ganglia. This clinical separation seems to occur at about puberty, and in view of the known ability of oestrogens to influence copper metabolism and to raise the blood copper levels during pregnancy (Russ and Raymunt, 1956) and in patients with Wilson's disease (German and Bearn, 1961), and their known ability to influence various metabolic processes in the liver (Ahrens, Payne, Kunkel, Eisenmenger and Blondheim, 1950), it is probable that this is one factor that is at least in part responsible for the occurrence of these differing clinical entities.

It seems probable that environmental factors influence the varying clinical manifestations of Wilson's disease, but a role for the action of modifying genes in the hereditary structure of affected siblings cannot be entirely excluded.

Other points arose from study of the case material. Three cases (Cases 3, 10 and 21) were diagnosed before the onset of symptoms as a result of family studies. Again, in three of the 21 families there was consanguinity between the parents, all being examples of first cousin marriages. The origin of cases was as follows: 11 came from London or the industrial midlands, and were presumably of English stock; six were of Scottish stock, though in four the families had emigrated; one was Hungarian, one Jewish from Poland, one Italian and one mixed Scottish and Polish. The relatively high incidence of the disease in the large cities may simply reflect population distribution throughout this country, or, more probably, the location of the large medical centres in which the diagnosis is likely to be made.

Summary

Twenty proven and five probable cases of Wilson's disease have been studied to ascertain the commonest presenting symptom of the disease.

In 11 this was jaundice or hepatosplenomegaly, including four of the five probable cases of the disease all of whom died of hepatic failure before the onset of neurological symptoms. All except one of these patients presented between the ages of 6 and 14.

Eleven patients presented with symptoms attributable to the nervous system. Their ages ranged between 12 and 32 years.

One patient presented with metabolic bone disease and two (Cases 3 and 21) had clinical or biochemical evidence of hepatic disease, but have remained symptom free to the time of writing.

The possible diagnosis of Wilson's disease should be considered in all children with prolonged jaundice or obscure hepatosplenomegaly.

In conclusion, I must thank all those physicians who have so generously allowed me to study and publish cases under their care. I am particularly grateful to Dr. M. Ashby (Case 13), Dr. E. R. Bickerstaff (Case 19), Dr. D. Brinton (Cases 9 and 18), Dr. G. Hall (Case 10), Professor I. G. W. Hill (Case 8), Professor D. Hubble (Case 21), Dr. R. D. C. Johnstone (Cases 1 and 5), Dr. S. Nevin (Case 17), Dr. J. S. Robson (Case 7) and Dr. S. B. M. Warren (Cases 2 and 3) for their repeated help during the course of these investigations. Cases 2 and 3 are being published in detail elsewhere (Warren, C. B. M. and Broughton, P. M. G. *Arch. Dis. Childh.*, **37**, 242).

Addendum

Since this paper was written two further cases have been seen; one presented with haemorrhage from oesophageal varices, the other with tremor and a previous history of jaundice; she has an asymptomatic younger sibling with a very low serum concentration of caeruloplasmin, presumably also homozygous for the abnormal gene.

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