LIVER, BILIARY, AND PANCREAS

Wilson's disease in Scotland

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Abstract

The prevalence and clinical features of Wilson's disease in Scotland were investigated. Thirty three cases were identified but adequate information was available on only 28. In 1989, the prevalence rate was 4 per million. Ten patients with a mean (SEM) age of 18 (1·9) years presented with neurological symptoms, 12 patients aged 14 (1·7) years presented with hepatic symptoms, and six patients aged 12 (0·9) years were asymptomatic siblings of patients with Wilson's disease. Nine (56%) of the 16 patients who underwent liver biopsy on presentation were found to have cirrhosis. Penicillamine treatment was stopped in nine patients because of: abnormal peripheral blood count (6), rash (2), and patient's own choice (1). Nineteen patients were alive in 1989 – 12 were well, one had chronic liver failure, four chronic neurological disabilities, and two had both chronic liver failure and neurological disabilities. Twelve patients died from: complications of chronic liver failure (2), acute liver failure (4), pneumonia associated with immobility (4), and other causes (2). Several patients who died had received incomplete medical supervision.

In 1912 Kinnier Wilson concluded that progressive lenticular degeneration was a rare disease. He had found only seven cases in the published reports for that time, to which he added another four.[1] In 1968, Sternlieb and Scheinberg estimated the prevalence of Wilson's disease to be five per million.[2] Since then they have raised their estimated worldwide prevalence to 30 per million,[3] basing this on studies from the USA,[4] East Germany,[5] and Japan.[6] Using this estimate, Parkes argued that there could be 1500 cases in Great Britain,[7] with at least 1000 unrecognised cases.[7,8] The increased estimated prevalence for Wilson's disease produced an uncomfortable concern in the minds of many gastroenterologists and neurologists who were apparently failing to detect the majority of cases of this treatable disorder.[9]

Despite much quoted worldwide prevalence data,[3] very few complete epidemiological studies have been carried out,[10–12] most studies being restricted to groups of patients to determine the gene frequency.[13–16] To date the only mention of the prevalence of Wilson's disease in Scotland has been in a letter commenting on the seemingly low prevalence in the north of Scotland.[9] In 1981, Walshe found only 24 cases in East Anglia, (population 3 376 981) giving a prevalence of 7·1 per million.[8]

This study aimed to determine the prevalence of Wilson's disease in Scotland and the clinical features of the disease and to audit the clinical management of the patients.

Methods

Patients were considered to have Wilson's disease if the following criteria were met: a plasma copper concentration <10 μmol/l (normal range 15–25 μmol/l) with at least two other features including urinary copper >1·5 μmol/l (normal <0·8 μmol/l), serum caeruloplasmin <80 mg/l (normal 150–300 mg/l), hepatic copper >250 μg/g dry weight of tissue (normal 15–60 μg/dry weight of tissue), or the presence of Kayser-Fleischer rings.

Patients with Wilson's disease were identified from three sources. Firstly, from computerised records of the Scottish Hospital Inpatient Statistics (SHIPS) over the 15 year period 1974–89.[17] Secondly, from a review of death certificates during the same period of time. Thirdly, by postal questionnaire to all gastroenterologists, neurologists, and paediatricians working in Scotland (questionnaire response rate 73%). We had initially thought that the SHIPS figures would be the most accurate method of detecting patients in Scotland as we presumed that each patient would require at least one hospital admission. There were, however, several errors in the information from SHIPS, resulting partly from the diagnostic coding. Wilson's disease, in the *International Code for Diagnosis* (ICD 8) appears under section 273·3 'other and unspecified congenital disorders of metabolism' and in the 1977 revision (ICD 9) under section 275·1 'disorders of mineral metabolism'.[18,19] Other disease were commonly wrongly coded as Wilson's disease, indicating the importance of accurate input of information.

Results

PATIENT IDENTIFICATION

During the study period to 1989, 33 cases (20 female) were identified in Scotland (1989 population 5 090 700).[20] In 1989, 21 of the 33 patients were still alive, giving a point prevalence of 4 per million Adequate information was available for 28 of the 33 patients (16 females). Further discussion, apart from data available from death certificates of two other patients, will

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TABLE I *Demographic details of patients on presentation (results mean (SEM))*

	Sex F/M	Age at onset of symptoms (yrs)	Age at presentation (yrs)	Time to diagnosis (yrs)
Hepatic group (n=12)	4/8	13·9 (1·7)	14 (1·7)	0·7 (0·3)
Neurological group (n=10)	6/4	17 (2·1)	18 (1·9)	2·0 (0·8)
Asymptomatic group (n=6)	6/0	-	12 (0·9)	-

TABLE II *List of initial misdiagnoses*

Psychiatric	Mental retardation (2)
	Hysteria (1)
	Personality disorder (1)
	Frontal lobe syndrome (1)
Neurological	Multiple sclerosis (1)
Hepatic	Cryptogenic cirrhosis (2)
	Viral hepatitis (1)

be limited to these 28 patients, 19 of whom were still alive in 1989. Twenty four patients (15 female) were born in Scotland and continued to stay locally, two patients were born in England, and two were born in Pakistan.

TABLE III *Year of diagnosis*

Date of diagnosis	No of patients
1940–44	1
1945–49	0
1950–54	0
1955–59	2
1960–64	0
1965–69	4
1970–74	3
1975–79	11
1980–84	4
1985–89	3
Total	28

CLINICAL PRESENTATION

Ten patients presented with neurological or psychiatric symptoms, 12 with hepatic symptoms, and six were asymptomatic siblings of Wilson's disease patients. (Table I). In nine patients (32%) there was a family history of Wilson's disease. Patients in the hepatic group presented at an earlier age than patients who had neurological symptoms. (Table I) The time taken to reach a diagnosis was shorter in patients from the hepatic group than in those in the neurological group (Table I). The mean (SEM) time taken to reach the diagnosis for both groups was 1·3 (0·4) years. There was considerable delay (>1 year) in reaching the diagnosis in nine of the patients (three in the hepatic group and six in the neurological group) (Table II). One patient attended several psychiatrists and neurologists for two years before the diagnosis of Wilson's disease was made, despite having a family history of Wilson's disease. Most cases have been diagnosed since 1975 (Table III).

METHODS OF DIAGNOSIS

At presentation all symptomatic patients had abnormal clinical signs. Kayser-Fleischer rings were present in 20, absent in four, and not looked for in another four (Table IV). Six patients (21%) were asymptomatic siblings of patients with Wilson's disease. All patients had routine blood tests including liver function tests (LFTs), which were abnormal in 79% of the total group. All the hepatic group patients had abnormal LFTs, and surprisingly all the asymptomatic patients had considerably raised transaminase activities (three to four times normal). Serum copper was low in all patients except the two who presented with acute liver failure. In 75% of all patients, urinary copper excretion was also estimated. Serum caeruloplasmin values were checked in 20 patients (71%) and were uniformly low. On presentation, the peripheral blood count was abnormal in 32% of all patients.

Fourteen patients had a liver biopsy performed on presentation, two patients at necropsy after presentation with acute liver failure, two patients at necropsy after chronic liver failure, and in 10 patients a liver biopsy was never performed (Table V). At presentation, all of the patients in the hepatic group who had had a liver biopsy were found to have either fibrosis or cirrhosis, four of seven in the neurological group had cirrhosis, and all three asymptomatic patients were found to have either mild fibrosis or normal liver histology. Hepatic copper was measured in eight patients on presentation (one in a necropsy sample) and was found to be mean (range) 1386 (136–4177) μg/g dry weight of tissue (normal reference range 15–60 μg/g dry weight of tissue) (Table VI).

TABLE IV *Clinical signs and investigations on presentation*

	Total group	Hepatic group	Neurological group	Asymptomatic group
Abnormal clinical signs (n=28) (%)	85	100	100	33
Kayser-Fleischer rings (n=24) (%)	83	89	100	40
Abnormal liver function tests (n=28) (%)	79	100	40	100
Mean (SEM) serum copper (μmol/l) (n=26)*	4·5 (0·6)	4·5 (0·3)	4·2 (0·2)	5·1 (0·3)
Mean (SEM) urinary copper (μmol/l) (n=21)*	6·9 (0·8)	4·7 (0·6)	10·3 (1·2)	5·9 (0·7)
Mean (SEM) serum caeruloplasmin (mg/l) (n=20)*	29 (7)	22 (4)	37 (5)	28 (7)
Abnormal peripheral blood count (n=28) (%)	32	50	20	17
Anaemia (n=28) (%)	7	17	0	0
Thrombocytopenia (n=28) (%)	14	25	0	17
Pancytopenia (%)	11	8	20	0

*Normal ranges for serum copper 15–25 μmol/l, urinary copper <0·8 μmol/l, and serum caeruloplasmin 150–300 mg/l. Expressed as mean (SEM).

TABLE V *Liver histology before and after treatment (values, no (%))*

Histology	Total group	Hepatic group	Neurological group	Asymptomatic group
On presentation	*(n=28)*	*(n=12)**	*(n=10)*	*(n=6)*
Normal	3 (11)	0 (0)	2 (20)	1 (17)
Abnormal	13 (47)	6 (50)	5 (50)	2 (33)
Fatty change	1 (4)	0 (0)	1 (10)	0 (0)
Fibrosis	3 (7)	1 (8)	0 (0)	2 (33)
Cirrhosis	9 (32)	5 (42)	4 (40)	0 (0)
Not performed	12 (42)	6 (50)	3 (30)	3 (50)
On follow up	*(n=26)*	*(n=10)**	*(n=10)*	*(n=6)*
Normal	3 (12)	0 (0)	1 (10)	2 (33)
Abnormal	9 (34)	5 (50)	4 (40)	0 (0)
Fatty change	1 (4)	0 (0)	1 (10)	0 (0)
Fibrosis	0 (0)	0 (0)	0 (0)	0 (0)
Cirrhosis	8 (31)	5 (50)	3 (30)	0 (0)
Not performed	14 (54)	5 (50)	5 (50)	4 (67)

*Results from the necropsy histology of two patients in the hepatic group who presented in acute liver failure were included in the presentation data, and not the follow up data. The follow up histology of three of the five patients in the hepatic group was from necropsy samples.

TREATMENT

All patients except the two who presented with fulminant liver failure were begun on penicillamine. This was stopped in nine patients because of an abnormal peripheral blood count (6), rash (2), and patient's own choice (1). Four of the six patients who developed an abnormal blood count had a moderate thrombocytopenia (platelet count 80–150 000 × 10^6/l) that seemed to have been the result of drug therapy, and two patients had a pancytopenia that was probably caused by hypersplenism rather than drugs. Seven patients were established on trientine without any further problems.

Only one patient had received a short course of oral zinc therapy. Five patients did not comply with regular drug treatment and could therefore be considered to have been inadequately treated.

One patient who defaulted from follow up and

TABLE VI *Hepatic histology, liver function tests (LFTs), and hepatic copper (μg/g dry weight) values of individual patients before and after treatment*

Patient no	Histology		Copper concentration*		Abnormal LFTs	
	Before	After	Before	After	Before	After
Hepatic group						
2	–	Cirrhosis	–	–	Yes	Yes
5	Cirrhosis	Cirrhosis	–	–	Yes	No
6	Cirrhosis	Cirrhosis	–	–	Yes	Yes
10	–	–	–	–	Yes	No
11	–	–	–	–	Yes	No
14	Fibrosis	–	–	–	Yes	No
15	Cirrhosis	–	840	–	Yes	–
18	Cirrhosis	–	–	–	Yes	–
22	–	Cirrhosis	–	–	Yes	Yes
23	Cirrhosis	Cirrhosis	720	709	Yes	Yes
24	–	–	–	–	Yes	Yes
27	–	–	–	–	Yes	No
Neurological group						
1	Fatty change	Fatty change	–	473	Yes	No
3	–	–	–	–	No	No
7	–	–	–	–	No	Yes
9	Cirrhosis	–	230	–	Yes	No
13	–	–	–	–	No	No
19	Cirrhosis	Cirrhosis	–	132	No	Yes
20	Normal	Normal	4177	1162	No	No
21	Cirrhosis	Cirrhosis	–	–	Yes	Yes
26	Normal	–	463	–	No	No
28	Cirrhosis	Cirrhosis	–	–	Yes	Yes
Asymptomatic group						
4	Normal	Normal	1976	1260	Yes	No
8	–	–	–	–	Yes	No
12	–	–	–	–	Yes	No
16	Fibrosis	Normal	2542	1514	Yes	No
17	Fibrosis	–	136	–	Yes	No
25	–	–	–	–	Yes	No

*Reference range for hepatic copper 15–60 μg/g dry weight of tissue.

subsequently presented with acute liver failure required a liver transplant, but died two months afterwards. One other patient had surgery for portal hypertension.

LIVER HISTOLOGY/COPPER AFTER TREATMENT

Liver biopsies were performed after treatment in nine patients and liver histology was examined in a further three patients at necropsy after a follow up of 10·3 years (range 2–25 years) (Table VI). The liver histology was unchanged in six patients with known cirrhosis and in two patients with normal histology. One patient's histology continued to show fatty change. In one of the asymptomatic patients, repeat biopsy specimen was normal after having shown fatty change with fibrosis two years previously. Necropsy histology was available for three patients who were all found to have cirrhosis.

Follow up hepatic copper concentrations were available for six patients, although only four of them had had a pretreatment estimation. All four showed a mean (SEM) decrease of 37 (14)% from their pretreatment values. The concentrations after treatment were, however, still very high. All four patients have shown an excellent clinical response to treatment and three of the patients had normal LFTs at the time of the second biopsy. The hepatic copper concentrations of the other two patients who did not have a previous biopsy were noticeably raised seven and 25 years after treatment despite a satisfactory clinical response.

TABLE VII *Hospital supervision for Wilson's disease patients**

Type of hospital	No of patients
Teaching hospital	17
District General	3
Teaching and district general	3
No hospital follow up	5

*Six patients had also attended a teaching hospital outside Scotland.

TABLE VIII *Cause of death in patients with Wilson's disease*

Complications of chronic liver disease (2)
Acute liver failure (4)
Pneumonia associated with immobility (4)
Pulmonary aspiration during a seizure (1)
Acute pancreatitis (1)

OTHER CLINICAL CONDITIONS

Two patients developed epilepsy (one Jacksonian seizures) one and two years after diagnosis. Both patients had a normal brain computed tomogram. Two patients developed symptomatic gall stones. One of them required a cholescystectomy. Other clinical conditions included alcoholism (1), recurrent abortions (1), and acute pancreatitis (1).

HOSPITAL SUPERVISION

At the time of the study (1989) or at the time of death, 23 patients were or had received adequate hospital supervision and follow up, but five patients had not attended a hospital clinic for several years (Table VII).

FOLLOW UP

Twelve of the 33 patients identified have died, 10 of conditions directly attributable to Wilson's disease and two from other disorders (Table VIII). One of the patients who died from chronic liver failure complicated by massive variceal bleeding had been advised inappropriately by a general physician to stop penicillamine four months before his death as he was thought to have drug induced thrombocytopenia rather than the true cause of hypersplenism. Another unfortunate patient, an asymptomatic case, had stopped penicillamine on her own accord 18 months before presenting in acute liver failure.

Nineteen of the 28 patients were alive at the end of the study and had been followed up for a mean of 13·7 years (range 2–33 years). Twelve were well and symptom free, four were disabled by neurological problems, one had chronic liver failure, and two had both severe chronic liver failure and neurological disability.

Discussion

We have found from this epidemiological study that the prevalence rate for Wilson's disease in Scotland is 4 per million, which is considerably lower than the previous estimation of 30 per million.[3] There are several explanations for this discrepancy. Firstly, there may be a variation in the prevalence rates in different geographical areas, although a difference of this magnitude would be unusual. Secondly, we may have failed to pick up the majority of cases in Scotland. Lastly, the previous estimations have been incorrect. We believe that the last explanation is the most likely and that there has been widespread confusion and misquotation over the

epidemiological data and definitions in the previous studies.

In 1984, Scheinberg and Sternlieb raised their 1968 prevalence estimate for Wilson's disease from 5 per million to 30 per million.[3] Their estimation was based on three sources. Firstly, data from the mortality figures for the USA for the years 1968–78 showed that the average number of deaths from Wilson's disease was 13·21 per million.[4] Scheinberg and Sternlieb felt that the rate probably represented half the true value. Secondly they quoted a study by Bachman from East Germany[5] whom they claimed had found an 'incidence rate for WD to be 29 per million – about six times the prevalence rate we had estimated in 1968'. Bachman, however, actually reported an annual 'incidence rate' of 2·9 per 100 000 live births. In fact, Bachman found 78 patients who were alive in 1974 (population of East Germany 16·9 million), which gave a prevalence rate of 4·6 per million. Lastly, Scheinberg and Sternlieb used data from a Japanese study by Saito involving 287 families,[6] and stated that he had found the prevalence to be 33 per million. Saito's study assessed the value of screening for Wilson's disease using serum caeruloplasmin and was not an epidemiological study of the prevalence of Wilson's disease in Japan. Saito used only 162 families to estimate the gene frequency and hence the 'disease frequency'. There are also major methodological errors, in particular his use of Dahlberg's formula to calculate the gene frequency from a retrospective study (personal communication, Professor J M Connor). It is not clear how many patients were alive during the period of the study and the hypothetical value for 'disease frequency' of one in 30 000 for homozygotes (33 per million) is not equivalent to disease prevalence. Unfortunately, many articles on Wilson's disease written since 1984 have used Scheinberg and Sternlieb's estimate and their sources.[3] Giagheddu's study from Sardinia found a high gene frequency rate and a prevalence rate of 16·4 per million for 1981.[12]

Our study has confirmed the frequent delay (mean 1·3 years) in reaching a diagnosis of Wilson's disease,[12 22 23] and that the initial misdiagnosis was usually psychiatric.[23] As in other studies, our patients with hepatic disease presented at an earlier age compared with the patients presenting with neurological or psychiatric problems (Table I).[22 23] Unlike other studies, including two British ones,[8 16] that have shown a high proportion of men (around 52–65%)[10 12 15 24] we found that only 40% of our group were male.

Some 43% of our patients presented with predominantly hepatic problems, and one patient developed fulminant hepatic failure complicated by intravascular haemolysis and renal failure.[25] Roche-Sicart *et al*,[26] and subsequently McCulloch *et al*,[27] have documented the clinical features of these patients and have suggested that those with fulminant hepatic failure caused by Wilson's disease have higher serum copper concentrations, a less pronounced increase in serum transaminase activities, a higher concentration of total bilirubin, and lower haemoglobin concentrations than patients with idiopathic fulminant hepatic failure. Patients with Wilson's disease who present with or develop acute fulminant hepatic failure should be considered for immediate liver transplantation.

The diagnosis of Wilson's disease can be difficult if serum caeruloplasmin values are not particularly low and Kayser-Fleischer rings are absent. Sternlieb has also suggested that urinary copper excretion is often misleading because of inaccurate collection.[28] All of our patients had unequivocally raised urinary copper excretion values and we have found urinary copper estimations to be useful.

It is surprising that hepatic histology was available for only 50% of the 12 patients who presented with hepatic disease. (Histology was available for 58% of the whole group.) Clinicians may be reluctant to submit their patients for liver biopsy if they feel confident about making a diagnosis of Wilson's disease based on clinical findings and other laboratory tests, and when it is known that standard light microscopic examination of hepatic tissue is rarely pathognomonic for this disorder.[3] We feel that biopsy is an important investigation as pathognomonic changes to the hepatic mitochondria can be found using electron microscopic techniques,[3] and the liver copper concentration can also be measured. Moreover, Wilson's disease patients presenting with chronic active hepatitis have a poor outcome and should be considered for early liver transplant.[29] Lau *et al* found a good correlation between serum caeruloplasmin values and the severity of the liver damage, and suggested that serum caeruloplasmin may be a useful prognostic marker.[30] We have not been able to assess this finding because of the small number of patients who had a liver biopsy. However, both patients who died from complications of chronic liver disease had higher serum caeruloplasmin values than the rest of the group.

Hepatic copper was measured after treatment in only six patients, and unfortunately in only four of them was there a pretreatment value for comparison. Despite good clinical response and improvement in the LFTs, all six patients still had grossly raised copper values, although in four these had fallen by 37 (14)% (mean (SEM)). In 1987, Scheinberg *et al* reported very high hepatic copper values in patients successfully treated with penicillamine and suggested that the mode of action of penicillamine was not its decoppering effect but one of detoxification, possibly by induction of metallothioneins in the liver.[31] Further histological studies have shown that copper is complexed with metallothionein in patients with Wilson's disease.[32] Mason *et al* found that both penicillamine and trientine did not reduce the copper values of ^{35}S labelled copper metallothionein in preparations of rat liver cytosol as compared with thiomolybdate which stripped the copper from the cytosol proteins and may have a 'true' decoppering effect.[33]

In 1960 Bearn reported that before treatment for Wilson's disease was available the average age at death was 30·6 years.[15] Our study has shown a high mortality for patients with Wilson's disease in Scotland, all of whom had received treatment

after presentation. Of the 33 patients identified, 12 had died during the period 1975–89. The average age at death was 29·2 years, range 8–49.

Several patients were not adequately treated as a result of non-compliance. Tragically, an asymptomatic patient decided to stop treatment and developed acute liver failure 18 months later. Scheinberg *et al* have found that patients who do not comply with their treatment are well for 2 to 3 years then develop rapid liver failure,[34] as shown by case reports by Walshe[35] and Breen.[36] Giagheddu *et al* found that the median survival of patients who received inadequate treatment was only 6 years 4 months, but of 45 patients who received adequate treatment, only three died.[12] Several patients in our study did not receive optimal hospital supervision and it is of some concern that at the end of the study period five patients were not attending a hospital clinic on a regular basis. Many of those attending hospital, however, did not receive ideal treatment, especially specialised supervision of their chronic liver disease from which many patients died. To ensure the best prognosis, patients with Wilson's disease should attend a specialist hospital clinic for regular review. This is of particular importance for asymptomatic patients detected by screening, as adequate treatment ensures an excellent long term prognosis.[37]

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