Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine

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Abstract

Background—Wilson's disease, heralded by severe hepatic insufficiency, is a rare disorder for which emergency liver transplantation is considered to be the only effective therapy.

Aims—To report the features of Wilson's disease with severe hepatic insufficiency in a series of 17 patients and, during the second period of the study, to assess the efficacy of a policy consisting of early administration of D-penicillamine.

Patients—Seventeen consecutive patients with Wilson's disease were studied. During the first period of the study (up to 1979), none of the patients received D-penicillamine. During the second period (after 1979), all patients without encephalopathy at admission received D-penicillamine.

Results—The four patients observed during the first period who did not have encephalopathy at admission and did not receive D-penicillamine progressed to encephalopathy and died. Among the 13 consecutive patients observed during the second period, two patients with encephalopathy at admission did not receive D-penicillamine and were transplanted. The 11 remaining patients all received D-penicillamine. Ten of these patients survived without the need for transplantation and returned to compensated liver disease without liver insufficiency. In one patient, liver insufficiency progressed and transplantation had to be performed.

Conclusions—In most patients with Wilson's disease heralded by severe hepatic insufficiency and without encephalopathy at admission, early administration of D-penicillamine was associated with survival without transplantation. These results suggest the importance of early diagnosis of this form of Wilson's disease before the onset of encephalopathy, and favour early administration of D-penicillamine which could avoid the need for transplantation in most cases.

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Keywords: Wilson's disease; acute liver failure; liver transplantation; hepatic encephalopathy

Wilson's disease is usually diagnosed in patients presenting with either neuropsychiatric disorders or manifestations related to chronic liver disease. Rarely, the first manifestations

mimic those of an acute liver injury.^{1–4} It is noteworthy that the outcome of patients in whom Wilson's disease is first manifested by severe hepatic insufficiency is poor. In these patients, massive liver cell necrosis may lead to acute liver failure within a few days or weeks. In addition to acute liver failure, liver cell necrosis results in massive release of copper into the bloodstream and, as a consequence, acute haemolytic anaemia.

D-penicillamine, which is the treatment of choice in patients presenting with manifestations of chronic liver disease, is generally considered to be ineffective in patients with acute liver failure for whom emergency liver transplantation is recommended.^{5–9} However, strong evidence for this assumption is lacking.

The purpose of this study was to analyse the clinical features and outcome of Wilson's disease with severe hepatic insufficiency in a consecutive series of 17 patients, as well as to assess the results of a policy consisting of systematic administration of D-penicillamine in patients with this form of Wilson's disease and without encephalopathy.

Patients

Seventeen patients (five males and 12 females), admitted from January 1969 to May 1999, were included in this study. Fourteen patients were admitted to Hôpital Beaujon, France. Two patients were admitted at Hadassah University Hospital, Israel, and then referred at Hôpital Beaujon. One patient was admitted to Hôpital Cantonal de Genève, Switzerland. These patients met the following three criteria. Firstly, manifestations appeared less than two months before admission. Secondly, regenerative haemolytic anaemia, defined as haemoglobin lower than 11 g/dl and a reticulocyte count >150 000/mm³, was present during hospitalisation. Thirdly, prothrombin at admission was less than 50% of normal.

The diagnosis of Wilson's disease was based on the following criteria. In all patients, other causes of liver injury were excluded. In particular, serological markers of infection with hepatitis A, B, and C viruses were absent (in all patients with available test results) and anti-organellar antibodies were absent. Ceruloplasmin concentration was low in 12 patients and normal in the remaining five patients. Cupruria was above 5 µmol/24 hours (normal <0.5 µmol/24 hours) in all patients. Kayser-Fleischer ring was present in 13 patients. Family history was suggestive of Wilson's disease in nine patients with first degree parental consanguinity in five, and established Wilson's disease

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Table 1 Diagnostic criteria for Wilson's disease in the 17 patients in our series

Patient No	Cupruria ($>5 \mu\text{mol/day}$)	Kayser-Fleisher ring	Parental consanguinity	Wilson's disease in siblings	High hepatic copper ($>3 \mu\text{mol/g dry weight}$)	Low serum ceruloplasmin ($<0.2 \text{ g/l}$)
1	Yes	Yes	No	No	ND	Yes
2	Yes	Yes	No	No	ND	Yes
3	Yes	Yes	No	No	ND	Yes
4	Yes	Yes	No	No	ND	Yes
5	Yes	No	Yes	Yes	Yes	Yes
6	Yes	No	Yes	No	Yes	Yes
7	Yes	Yes	No	No	Yes	No
8	Yes	Yes	No	Yes	ND	No
9	Yes	Yes	No	No	Yes	No
10	Yes	Yes	Yes	No	Yes	Yes
11	Yes	Yes	No	No	Yes	No
12	Yes	Yes	Yes	Yes	Yes	Yes
13	Yes	No	Yes	No	Yes	No
14	Yes	Yes	No	No	Yes	Yes
15	Yes	No	No	Yes	Yes	Yes
16	Yes	Yes	No	No	Yes	Yes
17	Yes	Yes	No	No	Yes	Yes

ND, not done.

in siblings in four patients. Hepatic copper concentration was high (above $5 \mu\text{mol/g dry weight}$) in the 12 patients who were tested. Individual results are given in table 1.

Mean age was 16.6 years (range 8–22). Mean time interval between the first manifestations and admission was 14 days (range 1–60). The first manifestations included asthenia, anorexia, abdominal pain, fever, and jaundice. At admission, jaundice was present in all patients. Ascites was present in four patients, fever in eight, and encephalopathy in two. Five of 15 patients who did not have encephalopathy at admission subsequently developed encephalopathy. At admission, two patients (Nos 16 and 17) had acute renal failure with serum creatinine levels of 234 and $203 \mu\text{mol/l}$, respectively. Seven additional patients developed acute renal failure thereafter (Nos 1–6, and 14). Individual features are shown in table 2.

Histological examination of the liver showed cirrhosis in 13 of 17 patients. In the four patients who did not have cirrhosis, histological features were consistent with chronic active hepatitis with mild fibrosis in three and extensive fibrosis in one. In all patients, inflammatory infiltrates, steatosis, and hepatocyte necrosis were present.

During the first period of this study, before 1979, patients with Wilson's disease heralded by severe hepatic insufficiency admitted to our institution were not given D-penicillamine

because it was considered (as generally accepted in the literature) that this drug would be ineffective. During the second period of this study (from 1979 to 1999), in order to assess the potential efficacy of D-penicillamine, we systematically administered the drug to patients with Wilson's disease heralded by severe hepatic insufficiency, provided they did not have encephalopathy at the time of admission. Indeed, in patients with hepatic encephalopathy, emergency liver transplantation was systematically considered. Thus two groups of patients were identified. Group 1 included four patients (Nos 1–4) admitted during the first period and who were not given D-penicillamine; and group 2 included 13 patients (Nos 5–17) admitted during the second period. Two of these 13 patients (Nos 5 and 6) with hepatic encephalopathy at admission did not receive D-penicillamine and in accordance with our policy were considered for emergency liver transplantation. The remaining 11 patients (Nos 7–17) received high doses of D-penicillamine within the first 48 hours after admission. The initial dosage was 300 mg/day and progressively increased up to 2400 mg/day within 20 days.

Results are presented as mean (SD). Statistical analysis was performed using the Student's *t* and Fisher's exact tests. A *p* value less than 0.05 was defined as statistically significant.

Results

Patients were significantly younger in the first group (12.7 (3.3) years) than in the second group (17.8 (3.1) years; $p < 0.05$). Mean prothrombin level at admission (21.7 (11.7) and 33.7 (9.4)% of normal in groups 1 and 2, respectively), mean haemoglobin concentration (10 (0.8) and 8.8 (2.7) g/dl in groups 1 and 2, respectively), and mean serum bilirubin (159.7 (32.2) and 326.8 (361.1) $\mu\text{mol/l}$ in groups 1 and 2, respectively) were not significantly different between the two groups.

The four patients in group 1 did not have hepatic encephalopathy at admission. These four patients had a decrease in coagulation factors after admission as a result of worsening hepatic insufficiency. All progressed to encephalopathy within a few days or weeks and

Table 2 Features and outcome of the 17 patients in our series. Group 1, patient Nos 1–4; group 2, patient Nos 5–17

Patient No	Year	Age (y)	Sex	Encephalopathy at admission	D-penicillamine administration	Liver transplantation	Outcome
1	1969	8	F	No	No	No	Dead
2	1970	13	M	No	No	No	Dead
3	1971	15	F	No	No	No	Dead
4	1972	15	F	No	No	No	Dead
5	1987	19	M	Yes	No	Yes	Dead
6	1989	10	F	Yes	No	Yes	Alive
7	1979	21	M	No	Yes	No	Alive
8	1983	17	M	No	Yes	No	Alive
9	1983	20	F	No	Yes	No	Alive
10	1985	16	F	No	Yes	No	Alive
11	1988	17	F	No	Yes	No	Alive
12	1988	17	F	No	Yes	No	Alive
13	1989	22	F	No	Yes	No	Alive
14	1990	16	F	No	Yes	Yes	Alive
15	1990	21	F	No	Yes	No	Alive
16	1991	19	M	No	Yes	No	Alive
17	1999	17	F	No	Yes	No	Alive

Table 3 Individual features in 11 patients who did not have encephalopathy at admission and received D-penicillamine

Patient No	Interval between first manifestations and admission (days)	Prothrombin (% of normal)			Bilirubin ($\mu\text{mol/l}$)		Renal failure during hospitalisation	Haemoglobin at admission (mg/dl)	In hospital stay (days)
		Admission	Nadir	1 month	Admission	1 month			
7	30	45	45	52	24	13	No	7	41
8	60	30	30	33	37	35	No	10	25
9	10	44	40	57	46	27	No	10	35
10	7	35	34	42	83	31	No	7	34
11	2	42	42	47	288	63	No	7.4	22
12	30	32	30	39	70	40	No	12	12
13	4	29	15	40	269	110	No	12	60
14 ^a	21	13	9	9	217	— ^a	Yes	4.7	— ^a
15	30	28	27	48	476	75	No	11	40
16	7	46	27	54	234	66	Yes	7.8	52
17	8	39	18	37	1064	102	Yes	5.2	26

^aLiver transplantation.

died. In accordance with the policy we defined during the second period of this study, the two patients in group 2 who had hepatic encephalopathy at admission did not receive D-penicillamine and were listed for emergency liver transplantation. These two patients were transplanted and one died immediately after transplantation. The remaining 11 patients in group 2 were given D-penicillamine. In one of these patients (No 14), severe haemolytic anaemia persisted with the need for repeated transfusions of red blood cell units. Despite D-penicillamine administration, prothrombin time decreased to 10% of normal and remained constant for one month. Eventually, she developed hepatic encephalopathy 36 days after admission. Plasmapheresis was performed without significant improvement of neurological status and she was listed for emergency liver transplantation. The patient was transplanted and survived. The remaining 10 patients in this group survived without the need for transplantation with a mean follow up of 6 years (range 3 months to 12 years). It is interesting to note that within the first seven days after D-penicillamine was started, prothrombin time continued to decrease from 31 (11)% to a nadir of 26 (11)% of normal. Thereafter, a progressive increase in prothrombin time was observed with an average of 41 (13)% of normal one month after admission. In parallel, mean serum bilirubin decreased from 298 (318) $\mu\text{mol/l}$ at admission to 56 (32) $\mu\text{mol/l}$ one month after admission. Patients were discharged from hospital on average 36 (15) days after admission (range 12–60 days). In all patients, prothrombin time was above 80% of normal within six months after admission. It is noteworthy that all returned to a state of compensated liver disease without hepatic insufficiency. Individual features are listed in table 3.

Overall, the proportion of patients who survived without transplantation was significantly higher in group 2 (10/13) than in group 1 (0/4) ($p=0.01$). No significant side effects were observed in patients who received D-penicillamine and in this series there was no need for discontinuation of treatment and/or switch to trientine.

Discussion

All patients in this series were asymptomatic two months or less before admission, and all had a

clinical presentation resembling acute liver injury. Standard diagnostic criteria (that is, low serum ceruloplasmin, high urinary copper, Kayser-Fleischer ring, familial history suggestive of Wilson's disease, and high hepatic copper concentrations) provided evidence that acute-like liver injury was in fact related to Wilson's disease. However, it is important to note that all of these patients had underlying chronic liver lesions, with cirrhosis in the majority.

It is generally accepted that, except for patients in whom Wilson's disease is first manifested by severe hepatic insufficiency receiving a specific therapy or who are transplanted, the outcome may be rapidly fatal.^{1 4 10–13} Thus it is not surprising that the four patients in the first period of this study who did not receive D-penicillamine and who were not transplanted died within one month after admission. Interestingly, hepatic encephalopathy was absent at admission in all which suggests that whatever the initial severity, the natural history in such patients is marked by progressive deterioration of liver function, which results in the occurrence of encephalopathy and death if a specific treatment is not given or transplantation is not undertaken. In these patients with Wilson's disease, the presence of underlying chronic liver lesions may be an important limiting factor for rapid liver regeneration, a necessary condition for recovery.

The most important finding in this study is that, in contrast with those observed during the first period, patients observed during the second period had a favourable outcome in most cases. Indeed, 10 of 11 patients who received D-penicillamine survived without the need for emergency transplantation. It must be noted that in our series, mean prothrombin, mean haemoglobin concentration, and mean serum bilirubin, as well as the proportion of patients with encephalopathy at admission, were not significantly different in the two groups. These results strongly suggest that D-penicillamine played an important role in the rapid improvement of patients in group 2. Theoretically, a controlled study would be the only way to determine unequivocally the efficacy of D-penicillamine in this form of Wilson's disease. However, because it is a rare condition, a controlled study would be particularly difficult to conduct. Furthermore, taking into account the favourable influence of

D-penicillamine observed in this series, a controlled study would be ethically questionable.

D-penicillamine is a copper chelator which decreases the body pool of copper by increasing urinary copper excretion. As this process is slow, the body pool of copper is significantly depleted only several weeks or months after the treatment has been initiated. Therefore, copper depletion by itself seems to be too slow to account for the rapid improvement observed after D-penicillamine administration. Besides the chelation properties of D-penicillamine, it has been suggested that the efficacy of this drug could be related to a rapid reduction in cellular toxicity of copper to the hepatocytes.^{14,15} A recent experimental study conducted in Long-Evans cinnamon rats, which have a mutation in the gene homologous to the human Wilson's disease gene leading to copper accumulation, gave important insights on the properties of D-penicillamine.¹⁶ Long-Evans cinnamon rats spontaneously develop acute hepatic injury within the first months after birth and half die of fulminant liver failure. In this experimental study, administration of D-penicillamine to either healthy or diseased animals prevented or reversed hepatic injury. The authors showed that D-penicillamine prevented the formation or induced solubilisation of lysosomal copper-rich granules, a form of copper which seems to be especially toxic for hepatocytes. In parallel, this drug had only minor effects on copper bound to metallothionein in the cytosol, a form which even at relatively high concentrations seems to be well tolerated. The results of this experimental study strongly support the findings we observed in the present series.

Obviously, patients in whom Wilson's disease is heralded by severe hepatic insufficiency and who improve after D-penicillamine administration are left with irreversible chronic liver lesions (cirrhosis in most cases) after liver insufficiency has recovered. Therefore, these patients may be exposed to delayed complications of cirrhosis and consequently they may remain potential candidates for liver transplantation several months or years after the initial episode. However, it must be noted that in our series, none of the patients who improved after D-penicillamine administration had to be transplanted thereafter, with a follow up of six months to 12 years, and this seems to reflect the absence of progression of chronic liver lesions due to Wilson's disease when continuously treated with copper chelators. In addition, even if elective liver transplantation had to be performed after initial improvement, it would carry a lower risk than emergency transplantation.⁹

Surprisingly, none of the 10 patients who improved with D-penicillamine had to be withdrawn or temporarily discontinued this drug because of side effects. Indeed, the good tolerance observed in this series contrasts with a 10–20% rate of complications reported in other series¹⁷ and there is no other explanation than chance for this apparent discrepancy. None the less, in other series a significant proportion of patients may exhibit complications. Such patients should be switched temporarily

or indefinitely to other copper chelating agents such as trientine or tetrathiomolybdate which seem to have different side effect profiles.¹⁸ However, even if these agents were shown to be effective copper chelators, there is no evidence that they have detoxifying properties comparable with those of D-penicillamine.

In conclusion, the results of this study indicate that the majority of patients with Wilson's disease heralded by severe hepatic insufficiency may progress to encephalopathy and death if not given D-penicillamine or liver transplantation. Recognition of the disease at an early stage, before the occurrence of encephalopathy, is crucial as early administration of high doses of D-penicillamine may be associated with rapid improvement, avoiding the need for emergency transplantation. However, when the diagnosis is delayed after the onset of first manifestations or when the course of the disease is too short, severe encephalopathy, acute renal failure, or sepsis may be present at admission. In such cases, D-penicillamine is likely to be ineffective. In parallel with the criteria used for the decision to perform transplantation in patients with acute liver failure,¹⁹ we suggest a decrease in prothrombin time below 20% of normal and the occurrence of encephalopathy should lead to emergency liver transplantation.

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