Original Paper

European Neurology

Eur Neurol 2003;50:48–52
DOI: 10.1159/000070858

Received: October 7, 2002
Accepted: February 25, 2003

Clinical Presentation and Treatment of Wilson's Disease: A Single-Centre Experience

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Key Words
Wilson's disease · Clinical presentation · Penicillamine · Zinc sulphate

Abstract
Thirty patients with Wilson's disease (WD) were observed at a movement disorder clinic between 1970 and 2000. Disease onset was at the mean age (SD) of 14.5 (±5.9) years. Presentation with hepatic disease occurred in 12 of 30 patients and with neurologic disease in 15. Three patients were asymptomatic at the time of diagnosis. The mean (SD) delay to diagnosis was 5.9 (±5.7) years. Five patients diagnosed in an advanced stage of disease died before initiating treatment. Eighteen patients were followed and treated with *D*-penicillamine alone or in combination with zinc sulphate. Treatment improved most of neurological symptoms. Dystonic postures, behavioural disturbances and dysarthria were the most resistant neurological signs. 'Pseudo-sclerotic' neurologic involvement predicted a good outcome, whereas hepatic onset and 'classic' neurologic involvement were associated with a poorer prognosis. Two of the 18 treated patients died of hepatic failure due to voluntary discontinuation of therapy. Both *D*-penicillamine and zinc sulphate were well tolerated. No teratogenic effect of *D*-penicillamine was observed throughout 5 pregnancies. Our results suggest that *D*-penicillamine or a combination of *D*-penicillamine and zinc sulphate is a safe and effective long-term treatment in patients with WD.

Introduction

Wilson's disease (WD) is an autosomal recessive disorder of copper accumulation due to mutations in copper-binding ATPase (ATP7B), primarily expressed in the liver [1]. It is one of the very few forms of serious, degenerative neurological diseases for which specific, effective therapy is available [2]. The greatest experience of treatment of WD has been obtained with *D*-penicillamine, introduced by Walshe in 1956 [3]. Since then, the prognosis of patients with WD has dramatically improved. In the following years, other drugs, such as zinc, trientine dihydrochloride and tetrathiomolybdate, have been introduced in the treatment of WD [4].

In the present study, we reviewed the clinical data of 30 consecutive patients with WD observed at our movement disorder clinic over the last 30 years and evaluated the clinical courses of 18 of them. These patients had been followed closely and treated with *D*-penicillamine alone or in combination with zinc sulphate.

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0014–3022/03/0501–0048$19.50/0

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Patients and Methods

Thirty patients (15 males, 15 females) with WD have been diagnosed at the movement disorder clinic of the 'Federico II' Medical School since 1970. The diagnosis was confirmed by low levels of plasma ceruloplasmin, increased levels of urinary copper and increased copper contents in liver biopsy specimens.

Five of these patients died before treatment. Seven patients have been followed in other movement disorder clinics. Eighteen patients were followed in our centre and were treated with daily doses of *D*-penicillamine ranging from 600 to 3,000 mg. The drug was gradually introduced over a period of 2–3 weeks and the dose was then adjusted individually according to urinary copper excretion. Daily doses ranging from 1,200 to 3,000 mg were used in the first months of treatment to obtain an adequate copper excretion (at least 800–1,000 μg/24 h). After clinical improvement or stabilisation, a maintenance dose (600–900 mg/day) was given. The total overall treatment period was 182.5 years (mean: 10.1 years). Pyridoxine (50 mg per os weekly) was also administered. We introduced the use of oral zinc in our centre in 1983; 11 of 18 patients also received zinc sulphate (daily dose: 600 mg), with a total overall treatment period of 71.5 (mean: 6.5) years. All patients were placed on a copper-reduced diet. Liver transplantation was performed in 1 patient with severe cirrhosis. To assess the severity of neurologic involvement, a scale ranging from zero to 3 (0 = asymptomatic; 1 = slight; 2 = moderate; 3 = severe neurologic involvement) was used. Follow-up brain magnetic resonance imaging (MRI) was performed in 5 patients.

Results

The clinical features of 30 patients diagnosed with WD since 1970 are summarised in table 1. We observed 27 symptomatic patients, 14 with neurologic presentation and 13 with hepatic presentation. Three patients were 'pre-symptomatic' at the time of diagnosis and were identified on family screening. Neurologic involvement suggested the classic, dystonic form of WD in 22 patients and the 'pseudo-sclerotic' (Westphal) type in 5 [5]. The patients were from 25 families. Consanguinity was present in 1 family. There were 25 singletons and 5 couples. Eighteen families came from Southern Italy, 4 from Sicily, and the remaining 3 families were from Northern Italy.

Disease onset was at the mean (SD) age of 14.5 (±5.9) years. Onset with hepatic signs (12.9 ± 7.2 years) was slightly earlier than onset with neurological signs (15.9 ± 4.5 years). Patients with hepatic onset typically had a classic neurologic involvement. The mean (SD) delay to diagnosis was 5.9 (±5.7) years. Delay to diagnosis was not related with neurological score at diagnosis. Two of the 3 symptomatic couples were concordant for type of disease onset and neurologic involvement, the third couple was discordant for both features.

Neurologic outcome of the 18 patients treated at our movement disorder clinic is shown in table 1. Figure 1 shows duration of treatment with *D*-penicillamine alone and in combination with zinc sulphate in our patients. Seven patients were treated with penicillamine alone and 11 with the combination therapy. Improvement began a few months after initiation of therapy and continued for up to 5 years, although improvement was more evident in the first 2 years of treatment.

Six patients had an excellent response to treatment and became symptom-free (neurological score = 0). Six patients had a good recovery but were left with minor neurologic deficits (neurological score = 1). Kinetic tremor and dysmetria were the most responsive neurological signs, whereas dysarthria, dystonic postures and behavioural disturbances were the more resistent neurological features. All 5 patients with 'pseudo-sclerotic' neurologic involvement had a good or excellent recovery. Five of the 12 patients (41.7%) with classic neurologic involvement had a poor response and were left with major disabilities (neurological scores = 2, 3). They had the most severe presentation at the time of diagnosis. Nine of the 11 patients (81.8%) with neurologic onset compared with 3 of the 6 patients (50%) with hepatic onset had a good or excellent recovery. One asymptomatic relative (table 1, patient 30) continued to be asymptomatic after 4 years of penicillamine treatment. Delay to diagnosis was not related with neurological score. Four of the 6 symptomatic patients (66.7%) treated with penicillamine alone and 8 of the 11 patients (72.7%) treated with penicillamine and zinc had a good or excellent neurologic outcome. Mean (SD) improvement of neurological score was 1.45 (±0.93) in patients treated with the combination therapy and 0.67 (±0.82) in patients treated with penicillamine alone ($p = 0.104$).

Two patients (patients 15 and 26) voluntarily discontinued their therapy after they had obtained a good recovery and died of hepatic failure 2 years later. One patient with behavioural disturbances (patient 20) was murdered. One patient (patient 3) showing progressive hepatic failure had successful hepatic transplantation after 6 months of *D*-penicillamine treatment, but she was left with upper-limb dystonia and behavioural disturbances.

Side effects of *D*-penicillamine therapy were mild and occurred in 2 patients (11%). One patient (patient 3) developed skin rash and leukopenia in the first months of treatment. One patient (patient 8) developed cutaneous elastosis of the neck after several years of penicillamine treatment. Initial neurologic deterioration with *D*-penicillamine was observed in 10 out of 18 patients (55%) and

Table 1. Clinical data of 30 patients with WD

Pt.	Sex	Age at onset years	Family history	Initial feature of WD	Type of neurologic involvement	Delay to diagnosis years	Neurological score		Clinical outcome
							pre	post	
1	F	5	–	hepatic	classic	9	2	0	symptom-free
2	M	7	–	hepatic	absent	6	0		*died pre-therapy*
3	F	7	parents were first cousins	hepatic	classic	13	3	2	dystonic postures and behavioural disturbances
4	F	9	–	hepatic	classic	4	3	3	poor recovery
5	M	9	brother of 13	hepatic	classic	1	1		followed elsewhere
6	M	10	–	hepatic	classic	1	1		followed elsewhere
7	M	11	brother of 15	hepatic	classic	0	1		*died pre-therapy*
8	M	12	–	neurologic	classic	12	2	0	symptom-free
9	F	12	–	neurologic	pseudo-sclerotic	12	3	1	good recovery, mild dysarthria and action tremor persist
10	M	12	–	hepatic	classic	5	3		*died pre-therapy*
11	M	13	–	neurologic	pseudo-sclerotic	10	2	0	symptom-free
12	F	13	sister of 14	neurologic	classic	3	3		*died pre-therapy*
13	M	13	brother of 5	hepatic	classic	3	2		followed elsewhere
14	M	14	brother of 12	neurologic	classic	0.5	1	1	good recovery
15	F	14	sister of 7	neurologic	pseudo-sclerotic	4	2	1	good recovery, died due to therapy discontinuation
16	F	14	–	neurologic	classic	1	3		*died pre-therapy*
17	M	15	–	hepatic	classic	2	3		followed elsewhere
18	F	16	–	neurologic	classic	1	2	0	symptom-free
19	F	16	–	neurologic	pseudo-sclerotic	3	2	0	symptom-free
20	M	17	–	hepatic	classic	9	2	2	poor improvement, murdered
21	M	17	–	neurologic	classic	1	1		followed elsewhere
22	M	17	–	neurologic	classic	0.5	2	1	good recovery, behavioural disturbances persist
23	F	18	–	neurologic	classic	2	3	3	generalised dystonia
24	M	19	brother of 30	neurologic	classic	13	3	3	dystonic postures and dysarthria
25	F	24	sister of 28	hepatic	classic	3	1	0	symptom-free
26	M	29	–	hepatic	classic	17	2	1	good recovery, died due to therapy discontinuation
27	F	30	–	neurologic	pseudo-sclerotic	7	3	0	good recovery
28	F	–	sister of 25	asymptomatic	–	–	0		followed elsewhere
29	F	–	[1]	asymptomatic	–	–	0		followed elsewhere
30	F	–	sister of 24	asymptomatic	–	–	0	0	asymptomatic

pre = Pre-therapy; post = post-therapy; classic = characterised primarily by extrapyramidal dysfunction, especially dystonia; pseudo-sclerotic = characterised by kinetic tremor and dysarthria of the cerebellar type [5]. Severity of neurologic involvement: 0 = asymptomatic; 1= slight; 2 = moderate; 3 = severe.

[1] Patient 29 had an affected brother diagnosed in Germany.

was characterised by a worsening of the pre-existing neurological signs, particularly tremor and dysarthria. It reversed within 2–4 months in all patients. No side-effects have been observed in association with zinc sulphate. We treated 3 women throughout 5 pregnancies with *D*-penicillamine (mean dosage: 1 g; mean therapy duration: 10 years), and no teratogenic effects were observed in the new-borns.

Follow-up MRIs were performed in 5 of the patients with good or excellent recovery on treatment and showed almost complete resolution of hyperintense lesions on T_2 in the basal ganglia, thalamus and brainstem (fig. 2). Four of these patients had been treated with penicillamine and zinc sulphate, and 1 with penicillamine alone.

Discussion

Penicillamine is a controversial treatment for WD because of its reported side-effects and potential initial neurological worsening [6, 7]. It was reported that about 50% of patients with neurological signs of WD have an initial deterioration after *D*-penicillamine introduction and that 50% of them do not recover after this initial deterioration [7]. However, long-term studies showed that penicillamine, when used by an experienced physician, is a safe and effective treatment for WD and initial deterioration of neurological symptoms, if it occurs, does not alter the final outcome unfavourably [8, 9]. Walshe [8] reported that only 3 patients in his total series of 300

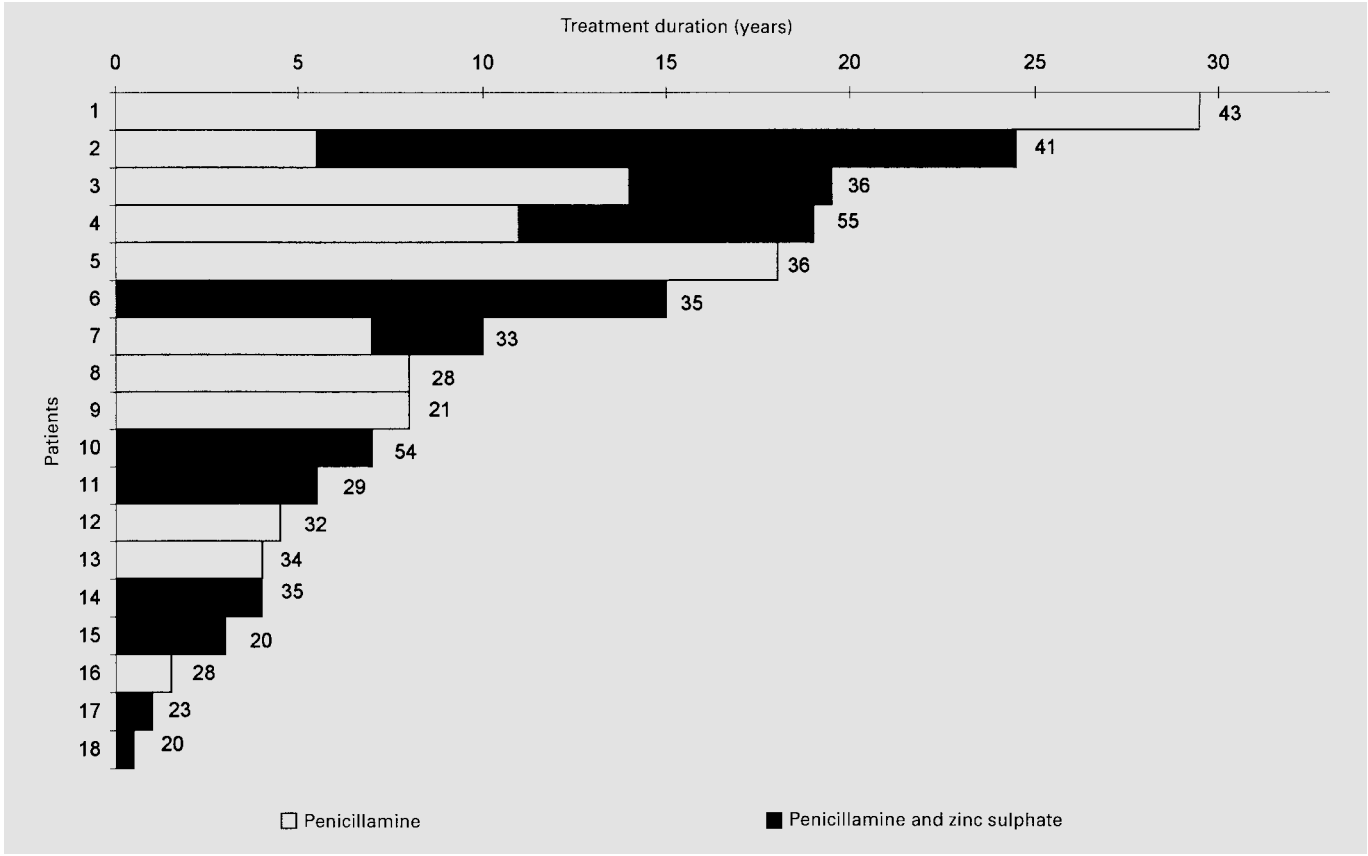

Fig. 1. Duration of treatment with *D*-penicillamine alone or in combination with zinc sulphate in 18 patients. Age at last examination is indicated at the top of the column.

showed rapid, irreversible deterioration. We observed an initial deterioration in a considerable number of patients, but it did not modify the final neurologic outcome. We successfully used penicillamine as a maintenance therapy in WD and we found a lower incidence of penicillamine-related side-effects than in previous studies, where they occurred in up to 30% of patients [10, 11].

D-penicillamine therapy during pregnancy is a controversial matter. *D*-penicillamine has a teratogenic effect according to some authors [12, 13], but other studies reported uncomplicated pregnancies and no teratogenic effects in the new-borns of several women [14, 15]. In our experience, *D*-penicillamine is a safe drug during pregnancy.

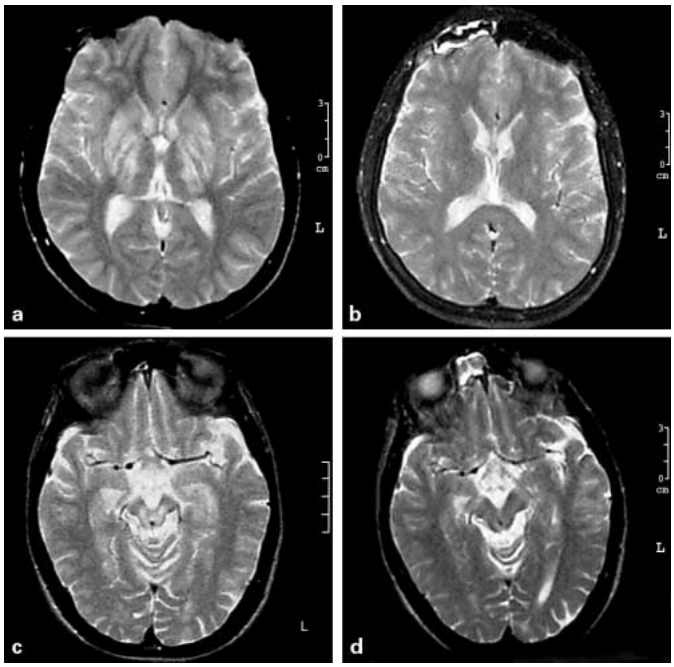

Fig. 2. T_2-weighted MRIs showing hyperintense lesions in the basal ganglia and thalamus (**a**) and midbrain (**c**) that disappeared after treatment with penicillamine and zinc sulphate in two different patients (**b**, **d;** patients 9 and 22). **c** Note the typical 'face of the giant panda'.

Zinc is a non-toxic drug, but it is rather slow in inducing a negative copper balance in patients with WD [4]. It is largely used in pre-symptomatic patients with WD and in maintenance therapy, but it also has a value as adjunctive therapy for the treatment of symptomatic patients [16, 17]. Combination therapy using a chelating drug and zinc has been recently proposed for all symptomatic patients with liver or neurologic disease [10, 18], although an antagonistic effect of these drugs in the gastrointestinal tract was postulated [19]. We used a combination therapy of *D*-penicillamine and zinc in 11 patients because of the potential additive effects. In fact, *D*-penicillamine acts by reductive chelation and increasing urinary excretion of copper, while zinc acts by inducing intestinal cell metallothionein and blocking the absorption of copper from foods and endogenous secretions, promoting its excretion into the stools [4]. In our patients, the two drugs were administered at different times during the day to avoid interaction in the gastrointestinal tract, which could reduce the efficacy of both *D*-penicillamine and zinc. Our patients received therapeutic doses of zinc for up to 19 years without gastric discomfort or any other side-effect. MRI follow-up in patients with good clinical outcome showed that penicillamine alone or in combination with zinc sulphate can reverse brain damage. The combination therapy was slightly more effective than penicillamine alone, but the analysed data are retrospective and the two groups too small to draw conclusions.

At the time of diagnosis, patients with most severe neurological disability, especially of the classic type, had poorest prognosis. Even though some recovery occurred, they were left with significant disabilities. Pseudo-sclerotic neurologic involvement was always associated with good clinical outcome. Moreover, it appeared that hepatic onset was associated with poorer prognosis than neurologic onset. In our series all patients who died (7 out of 30) had been diagnosed in an advanced stage of disease or voluntarily discontinued their treatment. In our study, neither disease severity at the time of diagnosis nor neurologic outcome appeared to be related with delay to diagnosis. It is likely that genetic differences influence the type and severity of clinical presentation in WD.

A lifelong WD therapy also causes major compliance problems. Many patients with little or no symptoms during their maintenance phase are prone to discontinue their treatment. The rate of serious problems with compliance amounts to about 10% in a large series [6]. In our series, 2 of 18 patients (11%) died of hepatic failure due to treatment discontinuation.

Overall, our experience with WD was very satisfactory: we obtained good or excellent clinical outcome in 66% of our patients, restoring them to a normal life. In fact, at present, 50% of them are working full time and 33% are married.

References

1 Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW: The Wilson's disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 1993;5:327–337.
2 Scheinberg I, Sternleib I: Wilson's disease; in Smith LH (ed): Major Problems in Internal Medicine. Philadelphia, WB Saunders, 1984, pp 126–155.
3 Walshe JM: Penicillamine, a new oral therapy for Wilson's disease. Am J Med 1956;21:487–495.
4 Brewer GJ: Practical recommendations and new therapies for Wilson's disease. Drugs 1995;50:240–249.
5 Denny Brown D: Hepatolenticular degeneration (Wilson's disease). Two different components. N Engl J Med 1964;270:1149–1156.
6 Brewer GJ: The treatment of Wilson's disease. Adv Exp Med Biol 1999;448:115–126.
7 Brewer GJ: Penicillamine should not be used as initial therapy in Wilson's disease. Mov Disord 1999;14:551–554.
8 Walshe JM: Penicillamine: The treatment of first choice for patients with Wilson's disease. Mov Disord 1999;14:545–550.
9 Walshe JM, Yealland M: Chelation treatment of neurological Wilson's disease. Q J Med 1993;86:197–204.
10 Brewer GJ, Yuzbasiyan-Gurkan V: Wilson's disease. Medicine 1992;71:139–164.
11 Stremmel W, Meyerrose KW, Niederau C, Hefter H, Kreuzpaintner G, Strohmeyer G: Wilson disease: Clinical presentation, treatment and survival. Ann Int Med 1991;115:720–726.
12 Mjolnerod OK, Dommerud SA, Rasmussen K, Gjeruldsen ST: Congenital connective tissue defect probably due to *D*-penicillamine treatment in pregnancy. Lancet 1971;1:673–675.
13 Solomon L, Abrams G, Dinner M, Berman L: Neonatal abnormalities associated with *D*-penicillamine treatment during pregnancy. N Engl J Med 1977;296:54–55.
14 Walshe JM: Pregnancy in Wilson's disease. Q J Med 1977;46:73–83.
15 Scheinberg IH, Sternlieb I: Pregnancy in penicillamine-treated patients with Wilson's disease. N Engl J Med 1975;293:1300–1302.
16 Shimizu N, Yamaguchi Y, Aoki T: Treatment and management of Wilson's disease. Pediatr Int 1999;41:419–422.
17 Brewer GJ: Zinc acetate for the treatment of Wilson's disease. Expert Opin Pharmacother 2001;2:1473–1477.
18 Schilsky ML: Treatment of Wilson's disease: What are the relative roles of penicillamine, trientine, and zinc supplementation? Curr Gastroenterol 2001;3:54–59.
19 Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V, Dick RD, Wang Y: Treatment of Wilson's disease with zinc. 12. Interaction with other anticopper agents. J Am Coll Nutr 1993;12:26–30.