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Review article

Paradigm shift in treatment of Wilson's disease: Zinc therapy now treatment of choice

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Abstract

Zinc therapy has replaced penicillamine as first-line therapy for Wilson's disease. New guidelines reflect the paradigm shift in treatment that has occurred in recent years. In the old paradigm, Wilson's disease was seen as genetic disorder associated with the accumulation of copper in the liver and in other organs once the liver had become overloaded with copper. When left untreated, the disease was regarded as uniformly fatal. The old treatment guidelines advised, 'decoppering' with penicillamine because this chelating agent was considered effective in restoring most patients to health. Before the start of treatment, patients were warned that their symptoms could worsen during the first weeks or months of therapy, so as to prevent them from abandoning penicillamine therapy in dismay. In the new paradigm, Wilson's disease is seen as a hereditary disorder associated with copper intoxication. The essence of symptomatic Wilson's disease is poisoning by free copper in the blood, that is, by copper that is not bound to ceruloplasmin. This form of copper is toxic, whereas accumulated copper and copper that is bound to ceruloplasmin or metallothionein is not. The treatment of symptomatic Wilson's disease is no longer aimed at 'decoppering', the removal of accumulated copper, but at the normalization of the free copper concentration in blood, to reverse the copper poisoning. This can be achieved safely and effectively with zinc therapy. Zinc induces metallothionein, a highly effective detoxification protein that binds copper. Oral zinc therapy leads to storage of metallothionein-bound copper in the mucosa of the gut and to the excretion of copper via the stools. New treatment guidelines advise against the use of chelating agents as initial treatment because they may aggravate copper intoxication and cause iatrogenic deterioration.

Keywords: Wilson's disease; Penicillamine; Zinc therapy; Paradigm shift; Copper

1. Introduction

In his book, 'The structure of scientific revolutions', Thomas Kuhn introduced the concept of the scientific paradigm (Greek: paradygma = model) [1]. Kuhn considered 'paradigm' to represent a collective term for assumptions and theories which practitioners of a scientific discipline regard as incontestable. Theories found in scientific textbooks are often more-or-less paradigmatic. Kuhn's ideas about scientific revolution can be applied to the changing theories on the treatment Wilson's disease. Such changes may result in a paradigm shift in how the disease is treated [2]. In this article, I discuss the changes that have occurred in the guidelines for the treatment of Wilson's disease (Table 1). Former guidelines can be found in the monograph on Wilson's disease in the series major problems of internal medicine [3]; the new guidelines can be found in the monograph on Wilson's disease in the series major problems in neurology [4]. In the Department of Neurology at the University in Utrecht, such a paradigmatic shift in ideas on the cause and treatment of Wilson's disease has taken place. Since 1979 [5] all patients with Wilson's disease treated in our department have been given zinc sulfate.

The paradigm shift has major implications for the management of patients with Wilson's disease. I will illustrate this with four case histories. The first two cases concern treatment in accordance with the former guidelines of two patients who were not treated in our hospital. The last two cases are examples of zinc treatment according to the new guidelines.

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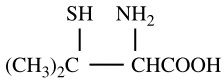
Table 1
Change of opinion regarding Wilson's disease:

- From noxious copper accumulation to free copper intoxication
- From penicillamine as treatment of choice to zinc as treatment of choice
- From negative copper balance as treatment aim to normal free-copper level as aim
- From free-copper excretion via urine to metallothioneine-bound copper excretion via stools
- From serendipity-based medicine to best-evidence-based medicine

From old paradigm to new paradigm

Old paradigm:	New paradigm:
• Impaired excretion of copper in bile	• Impaired excretion of copper in bile
• Deficiency of serum ceruloplasmin	• Deficiency of serum ceruloplasmin
• Symptoms caused by copper accumulation	• Symptoms caused by toxic free-copper level
• If untreated invariably fatal	• Copper chelation: danger of deterioration
• Treatment aim: copper excretion via urine	• Treatment aim: normal free-copper level
• Treatment method: chelation therapy	• Treatment method: zinc therapy
• Penicillamine: treatment of choice; especially for decoppering at start of therapy.	• Zinc induces detoxifying metallothionein
	• Zinc therapy: effective, safe
Penicillamine treatment:	Zinc therapy:
Aim:	**Aim:**
1. Increase urinary copper excretion;	1. Normal free plasma copper level
2. Induction negative copper balance;	2. Decrease copper absorption in gut
3. Decrease copper accumulation	3. Increase copper excretion via gut
Effect:	**Effect:**
1. Excretion of copper-chelate via urine	1. Induction of metallothionein in mucosa
2. Negative copper balance	2. Binding free-copper to mucosal cells and protein-bound-copper excreted via gut
3. Decrease accumulated copper	3. Decrease of plasma free-copper level
4. Clinical improvement	4. Clinical improvement
5. Fading Kayser–Fleischer rings	5. Fading Kayser–Fleischer rings
Iatrogenic 'paradoxic' deterioration:	**Iatrogenic 'paradoxic' deterioration:**
• At start of treatment: major problem	• None
Side effects:	**Side effects:**
• Early side effects: major problem	• None
• Late side effects: major problem	
Overall judgement: Problematic; contraindicated at start	**Overall judgement:** Evidence-based; effective; safe and cheap



PENICILLAMINE

Fig. 1. Penicillamine. Molecular formula: C5H11NO2S. Molecular weight 149. Potentially toxic chelating agent. Used in Wilson's disease to produce a negative copper balance. It mobilizes copper from copper complexes in the liver producing a water-soluble complex, which is excreted in urine. Effectivity is based on production of negative copper balance. The low-molecular-weight penicillamine-copper complex can pass the blood-brain barrier, producing a paradoxic clinical deterioration.

2. Case reports

2.1. Patient 1

About 8 years ago, a 37-year-old woman was admitted to a neurology department suffering from delusions, indistinct speech, and tremor of both hands. Her speech was dysarthric, and she had a coarse wing-beating tremor, dystonic gait, and Kayser-Fleischer rings in the corneas. The diagnosis Wilson's disease was made.

Urine copper, serum ceruloplasmin, and total serum copper concentrations were determined. The urine copper concentration was high at 0.30 mg/l (normal value below 0.10 mg/l). The ceruloplasmin concentration was very low at 30 mg/l (normal range of 200–500 mg/l). Since ceruloplasmin contains 0.3% copper [3], the serum contained 0.09 mg/l ceruloplasmin-bound copper. Although the total serum copper was very low (0.30 mg/l; normal range of 0.80–1.20 mg/l), the non-ceruloplasmin-bound ('free') copper concentration was increased: 0.30 minus 0.09 = 0.21 mg/l (normal value, less than 0.10 mg/l). There were no signs of liver disease. In accordance with the former guidelines, treatment was started with penicillamine (3 × 250 mg/day) (Fig. 1). Contrary to the guidelines, the patient was not warned that symptoms could worsen during the first weeks or months of penicillamine therapy [3]. Ten days later, the neurological signs worsened dramatically and the patient became akinetic mutistic. The urinary excretion of copper was 1.40 mg/24 h (normal value below 0.10 mg/24 h). The patient was still in this condition 5 months later.

The dramatic course of events led to a deep crisis in the relationship between the patient's relatives and the treating physicians. The relatives lost their trust in the medical care provided and stated that they had not been informed that starting treatment with penicillamine could be dangerous and aggravate symptoms, causing so-called 'paradoxical deterioration' [3]. Moreover, they stated that they had not given their informed consent to chelating therapy.

2.2. Patient 2

A 16-year-old girl presented with anemia, jaundice, vomiting, and nosebleed. She had acute hepatic failure and hemolytic anemia. Urine copper was increased to

about 10 times the normal value (1.0 mg/l; normal value <0.10 mg/l). Wilson's disease was diagnosed. In accordance with then current guidelines, the therapeutic options for Wilson's disease were chelating therapy and liver transplantation. Because the patient had acute liver failure due to Wilson's disease, orthotopic liver transplantation was considered the treatment of choice, and the patient duly underwent successful liver transplantation. This case was reported in a national general journal without mention being made of the good results achieved with drug therapy in the setting of acute liver failure [6].

2.3. Patient 3

An 18-year-old woman was admitted to the department of neurology of a university hospital. She had a slight rigidity of both arms and Kayser-Fleischer rings in the corneas of both eyes. Hereditary copper poisoning (Wilson's disease) was diagnosed. The urine copper concentration was increased to 0.30 mg/l, or about three times the normal value. The serum copper concentration was 0.90 mg/l and the ceruloplasmin concentration was 180 mg/l. The free (non-ceruloplasmin-bound) serum copper concentration was calculated to be 0.30 mg/l.

The patient was informed that copper poisoning could effectively be treated with oral zinc therapy and that treatment with penicillamine was inadvisable because it could aggravate symptoms. The patient gave informed consent to start treatment with zinc sulfate (3×200 mg, containing 3×45 mg elementary zinc). Treatment was monitored by measuring the free serum copper concentration and the urine copper concentration, both of which normalized. The patient's symptoms and signs vanished, and 3 years after the start of zinc therapy she gave birth to a healthy child [4].

2.4. Patient 4

A 19-year-old woman was admitted to the Department of Hepatology of our university hospital. She had acute hepatic failure and hemolytic anemia. Liver transplantation was proposed but a liver was not directly available. The patient's urine copper concentration was measured when she was waiting for a donor and found to be high. The free serum copper concentration was 0.30 mg/l. Wilson's disease with copper intoxication was diagnosed. The patient was told of the dangers of starting treatment with penicillamine or trientine [7,8] and subsequently gave her informed consent to treatment with zinc sulfate (3×200 mg/day). She made a rapid recovery and was removed from the transplant waiting list.

3. History of therapy of Wilson's disease

In 1912, Wilson described a familial progressive neurodegenerative disorder that was invariably fatal [9]. The disorder was characterized pathologically by bilateral, symmetrical softening in the lenticular nucleus and by cirrhosis of the liver. He hypothesized that a toxin generated by the liver cirrhosis caused the disease. Therapy was not available. In 1948, Cumings reported finding high copper levels in the brain and liver of patients with Wilson's disease and postulated that copper had an etiological role in Wilson's disease [10].

3.1. Chelation therapy

In 1951, Cumings described the successful treatment of a patient with Wilson's disease with intramuscular injections of the chelating agent British Anti-Lewisite (BAL) [11], and in 1956 the biochemist Walshe published an article in *The Lancet* advocating the treatment of Wilson's disease with the new oral chelator, penicillamine [12]. The effectiveness of penicillamine was discovered by chance. Walshe argued that penicillamine was effective in promoting the urinary excretion of copper to such an extent that the copper balance became negative (Fig. 1). He did not comment on the fact that an increased urinary copper excretion could also be a sign of severe copper poisoning. He also stated that adverse effects did not seem to be a major problem of oral copper chelation therapy. In 1966, on the occasion of the International Symposium of Wilson's disease in Tokyo, Walshe presented a summary of his experience, as clinical biochemist, with penicillamine treatment in 33 patients with Wilson's disease, declaring that "serious toxic symptoms have not been seen, though some patients have chronic thrombocytopenia" and even that "all patients will benefit from treatment with penicillamine once a negative copper balance has been established and maintained". The most remarkable last sentence of Walshe's report was as follows: "it seems probable that therapeutic failures reported in the literature are due more to shortcomings on the part of the physician than on the drug" [13].

In 1964, the clinical neurologist Denny Brown reported his experience with chelating agents [14]. His experience was not at all encouraging. He stated: "Though treatment by chelating agents can have the most remarkable results in relieving tremor for many years in some cases and in improving dystonia for a time in some, it has been a most frustrating experience in many others."

3.2. Zinc therapy

Zinc has long been used as a pharmacological agent. In 1771, Hieronymus David Gaubius (1705–1780) wrote an article on the use of zinc therapy for spasms [15]. In the 19th century oral zinc therapy became popular in Europe as an antiepileptic treatment. These earlier experiences have been important for investigations in modern times because they indicate that zinc has an extremely low toxicity.

In 1961, Schouwink published his doctoral thesis on the influence of zinc supplementation in Wilson's disease [16].

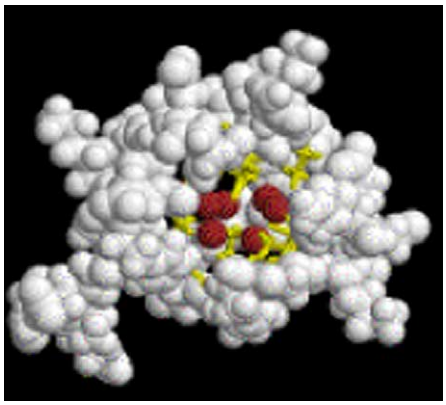


Fig. 2. Metallothionein: macromolecule, molecular weight 40,000. Metal-binding protein. Its synthesis is induced by zinc. This induction is used in oral zinc therapy for patients with Wilson's disease in order to bind and detoxify free, that is unbound, copper, and to store copper, bound to metallothionein, in the mucosal cells of the gut and to promote the excretion of copper via the gut in the stools.

After reading that high dosages of zinc sulfate led to decoppering in sheep, he performed copper balance studies in two patients with Wilson's disease, demonstrating that the copper balance became negative when zinc sulfate was administered in a dosage of 200 mg three times a day.

The disappearance of Kayser-Fleischer rings during long-term treatment with zinc sulfate was proof for me that zinc therapy had been effective in decoppering a patient with Wilson's disease [5]. This finding, and the knowledge that the use of zinc salts is not accompanied by severe side effects, formed the basis for my study of the use of zinc therapy as treatment for Wilson's disease. In 1996, I summarized the results for a series of 50 patients treated with zinc therapy [4].

4. Mechanism of action of zinc therapy

Zinc induces metallothionein, a metal-binding protein with a molecular mass of about 40,000 (Fig. 2). Oral zinc induces this copper-binding protein in the mucosal cells of the gut. In the gut, zinc antagonizes the absorption of copper by increasing the concentration of metallothionein in the mucosa [17]. It is probable that zinc protects against copper toxicity in the liver by promoting the sequestration of free serum copper in a non-toxic metallothionein-bound form [18].

5. The former paradigm [3] (Table 1)

According to this paradigm, Wilson's disease is considered to be caused by an impaired excretion of copper in the bile, which leads to progressive accumulation of copper in the liver. Copper overload causes hepatic dysfunction, but overt liver disease is almost never seen before the age of five. Extrahepatic copper toxicity occurs when the liver is overloaded and non-ceruloplasmin-bound copper is released into the bloodstream, from where it can diffuse into the brain. Without treatment the disorder inevitably results in death. Wilson's disease is diagnosed on the basis of increased amounts of copper in the liver and urine and low levels of ceruloplasmin. Examination of the eye reveals a Kayser-Fleischer ring in many patients with hepatic disease but in all patients with neurological Wilson's disease. The copper balance is positive in Wilson's disease, and the aim of treatment is to induce a negative copper balance, which can be achieved by administering chelating agents that induce the urinary excretion of copper. Penicillamine is the treatment of choice, and this chelator has turned Wilson's disease from an invariably fatal disease into one of the very few forms of serious hepatic, neurological, or psychiatric disease for which specific effective pharmacological therapy is available. However, a recent study has shown that copper is stored in a complex with metallothionein in the liver and that penicillamine can lead to the release of copper from this complex, which could lead to a potentially toxic increase in free copper levels.

6. The new paradigm [4] (Table 1)

In the new paradigm, the central feature of Wilson's disease has shifted from copper accumulation to copper poisoning. The accumulation of copper in the tissues can best be understood as a sign of detoxification of free copper in the liver by metallothionein. If treatment aimed at lowering free copper concentrations in blood is started early, and if treatment is monitored correctly to ensure that free copper concentrations normalize, the symptoms may be completely reversible. If treatment is started late, the severe liver disease and severe cerebral lesions may become irreversible. The essential diagnostic indices of hereditary copper poisoning (Wilson's disease) are Kayser-Fleischer rings, low ceruloplasmin concentration, high urinary copper excretion, and high hepatic copper content. In the new paradigm, treatment of symptomatic Wilson's disease should aim at the normalization of the free serum copper concentration. Treatment of copper poisoning with chelating agents is contraindicated because it may lead to an increase in serum levels of free copper and iatrogenic clinical deterioration.

New treatment guidelines [4] now advise physicians to start patients on zinc. This new emphasis on zinc therapy is a major difference from the old guidelines, which advised the use of penicillamine or trientine as initial therapy. The new guidelines reflect the paradigm shift in treatment that has occurred in recent years. Zinc sulfate is an effective, lowly toxic, and cheap therapy for Wilson's disease. A dose of 3×200 mg zinc sulfate a day, given in the form of tablets, capsules, or liquid, is given before meals.

Compliance with therapy is monitored by determination of the serum 'free' copper concentration, which should be maintained at or near 0.10 mg/l [3,4]. The FDA has approved zinc therapy for the treatment of Wilson's disease [19]. The new guidelines stipulate that although liver transplantation may be needed and may be life saving for some patients with decompensated liver disease [20], liver transplantation is not a suitable method for the treatment of copper poisoning in Wilson's disease [7].

For an update on the most recent developments in our knowledge of Wilson's disease, the reader is referred to the review by Aoki [21]. According to Aoki, the disorder results from a dysfunction of homologous copper-transporting ATP-ases. In hepatocytes, ATP-ase is needed for the incorporation of copper into ceruloplasmin and for the excretion of copper into the bile. In Wilson's disease, this ATP-ase is dysfunctional. Indeed, a large number of different mutations occur in the genes of patients with Wilson disease. As a result, the biliary excretion of copper is impaired, leading to the accumulation of copper in the liver [22]. When the capacity for hepatic storage is exceeded, cell death ensues, and copper is released into the blood, which results in hemolysis and deposition of copper in extrahepatic tissues. In this way, the signs and symptoms of patients with Wilson's disease arise when accumulated copper is released, in unbound form, into the blood. Copper-chelating drugs and zinc are effective in most patients. Zinc can be given as sulfate or acetate, which appear to be equally effective. Unfortunately, zinc sulfate is becoming increasingly difficult to obtain from pharmacies, which is not the case for the more expensive zinc acetate formulation [19].

A recent study has reported on long-term zinc therapy in 22 children with Wilson's disease [23]. Zinc sulfate was administered continuously for 10 years: in a dose of 25 mg elemental zinc twice a day until the age of 6 years, 25 mg three times a day between the ages of 7 and 16 years or until the child attained a body weight of 125 lb, and 50 mg three times a day thereafter. The authors concluded that zinc is the treatment of choice in presymptomatic pediatric patients. The study appeared 27 years after our first report on zinc sulfate therapy [24], 26 years after our report of the long-term treatment of a child with zinc sulfate [5], and 7 years after the editorial in which I warned against starting treatment with penicillamine or trientine [25]. The study of Marcellini et al. [23] is another indication that the treatment of Wilson disease is changing worldwide from chelation therapy to the use of zinc [8].

Over the last century, Wilson disease has changed from a uniformly fatal disease [12] to an eminently treatable disease. This evolution is an example of the remarkable advances of modern medicine [20]. However, this success is counterbalanced by the apparent failure of marketing and post-marketing surveillance regarding the serious adverse effects of chelation therapy. It is surely time that the instances responsible take measures to prevent the initial treatment of patients with Wilson's disease with chelation therapy.

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References

[1] Kuhn TS. The structure of scientific revolutions. Chicago: University of Chicago Press; 1962.
[2] Horton R. Second opinion. Doctors, diseases and decisions in modern medicine. London: Granta Books; 2003.
[3] Scheinberg IH, Sternlieb I. Wilson's disease. In: major problems of internal medicine. Philadelphia: W.B.Saunders; 1984. vol 23.
[4] Hoogenraad TU. Wilson's disease. In: major problems in neurology. London: W.B.Saunders; 1996. vol 30.
[5] Hoogenraad TU, Koevoet R, de Ruyter Korver EG. Oral zinc sulphate as long-term treatment in Wilson's disease (hepatolenticular degeneration). Eur Neurol 1979;18:205–11.
[6] Santos Silva EE, Sarles J, Buts JP, Sokal EM. Successful medical treatment of severely decompensated Wilson disease. J Pediatr 1996; 128:285–7.
[7] Hoogenraad TU. From gene to disease; Wilson disease: copper storage due to mutations in ATP7B. Ned Tijdschr Geneeskd 2003; 147:1386–7.
[8] Brewer GJ. Penicillamine should not be used as initial therapy in Wilson's disease. Mov Disord 1999;14:551–4.
[9] Wilson SA. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Lancet 1912;i:1115–9.
[10] Cumings JN. The copper and iron content of brain and liver in the normal and in hepatolenticular degeneration. Brain 1948;71:410–5.
[11] Cuming JN. The effect of BAL in hepatolenticular degeneration. Brain 1951;74:10–22.
[12] Walshe JM. Wilson's disease. New oral therapy. Lancet 1956;i:25–6.
[13] Walshe JM. Some observations on the treatment of Wilson's disease with penicillamine. Birth Defects Orig Article Ser 1968;4: 126–9.
[14] Denny Brown D. Hepatolenticular degeneration. Wilson's disease: two different components. N Engl J Med 1964;270:49–56.

[15] Gaubius HD. Luna fixata Ludemanni. In: adversariorum varii argumenti. Leiden:Luchtmans; 1771.
[16] Schouwink.G. De hepatocerebrale degeneratie, met een onderzoek naar de koperstofwisseling. University of amsterdam MD thesis; 1961.
[17] Janssens AR, Bosman FT, Ruiter DJ, Van den Hamer CJ. Immunohistochemical demonstration of the cytoplasmic copper-associated protein in the liver in primary biliary cirrhosis: its identification as metallothionein. Liver 1984;4:139–47.
[18] Koizumi M, Fujii J, Suzuki K, Inoue T, Inoue T, Gutteridge JM, et al. A marked increase in free copper levels in the plasma and liver of LEC rats: an animal model for Wilson disease and liver cancer. Free Radic Res 1998;28:441–50.
[19] Brewer GJ. Zinc acetate for the treatment of Wilson's disease. Expert Opin Pharmacother 2001;2:1473–7.
[20] El-Youssef M. Wilson's disease. Mayo Clin Proc 2003;78: 126–36.
[21] Aoki T. Genetic disorders of copper transport—diagnosis and new treatment for the patients of Wilson's disease. No To Hattatsu 2005; 37:99–109.
[22] Suzuki KT, Someya A, Komada Y, Ogra Y. Roles of metallothionein in copper homeostasis: responses to Cu-deficient diets in mice. J Inorg Biochem 2002;88:173–82.
[23] Marcellini M, Di Ciommo V, Callea F, Devito R, Comparcola D, Comparcola MR, et al. Treatment of Wilson's disease with zinc from the time of diagnosis in pediatric patients: a single-hospital, 10-year follow-up study. J Lab Clin Med 2005;145:139–43.
[24] Hoogenraad TU, Van den Hamer CJ, Koevoet R, Korver EG. Oral zinc in Wilson's disease. Lancet 1978;ii:1262.
[25] Hoogenraad TU. Editorial. Oral zinc in Wilson's disease. J Lab Clin Med 1998;132:240–1.