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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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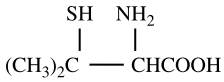
Table 1
Change of opinion regarding Wilson's disease:

- 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