Failure of Prophylactic Zinc in Wilson Disease

DEVENDRA MISHRA
VEENA KALRA
RACHNA SETH

ABSTRACT

Early institution of prophylactic therapy of asymptomatic Wilson disease patients can prevent the expression of the disease. Zinc is currently preferred therapy for presymptomatic patients. We report onset of symptomatic disease in a presymptomatic patient and deterioration of biochemical parameters in another, despite appropriate zinc therapy.

Key words: *Copper metabolism, Wilson disease, Zinc.*

INTRODUCTION

Wilson disease is a rare, treatable, autosomal recessive disorder of copper metabolism leading to brain and liver damage. As the disease is 100% penetrant, prophylactic therapy of presymptomatic affected patients either with penicillamine(1) or zinc(2), prevents the onset of symptomatic disease. Toxicity of penicillamine(3) has led to the use of zinc as the preferred mode of therapy for presymptomatic Wilson disease(2). Deterioration following zinc use has been reported rarely in patients of Wilson disease(4-6). We report progression from presymptomatic stage to symptomatic disease and biochemical deterioration, respectively in two siblings, despite treatment with zinc.

From the Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029, India.

Correspondence to: Prof. Veena Kalra, Chief, Child Neurology Division and Head, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. E-mail: kalra_veena@hotmail.com

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CASE REPORT

We made a diagnosis of Wilson disease in an 8-year old boy, who presented with progressive dysarthria, poor school performance, raised 24-hour urinary copper (577.5 µg/L), positive slit-lamp examination for Kayser-Fleischer (KF) rings, low serum ceruloplasmin levels of 0.068 OD units (normal 0.2-0.5), and suggestive MRI of brain. Treatment was initiated with copper-free diet, D-penicillamine (25mg/kg/day in three divided doses, two hour after meals), pyridoxine (10 mg/kg/day, single dose) and zinc (25 mg twice-a-day, one hour before meals). The family was non-consanguineous and had two asymptomatic siblings aged 6 and 11 years. Genetic studies, liver function tests and copper studies of the index patient and siblings were advised. Follow-up, one year later, revealed therapy compliance and significant symptomatic and biochemical improvement in the index case.

Both siblings had high 24-hour post-penicillamine urinary copper levels. Serum ceruloplasmin, liver function tests and renal biochemistry were normal in both. Both siblings received treatment with zinc (25 mg thrice a day orally) in addition to a copper-free diet, and followed over the next two years. Clinical and biochemical findings are summarized in ***Table* I**. Non-compliance was ruled out on the basis of history from the parents and also crosschecking with the two elder children. Urinary zinc level estimation was not possible due to financial constraints. Failure of zinc monotherapy in preventing the progression to symptomatic disease in the first sibling and the increased urinary copper excretion in second sib, prompted initiation of D-penicillamine therapy in both the children. Follow-up hematological and biochemical profile of both children eleven months after penicillamine are normal and no new symptoms have appeared.

DISCUSSION

Early diagnosis of affected presymptomatic siblings and prophylactic therapy prevents the onset of symptomatic disease in Wilson disease(1). Penicillamine is known to cause deterioration or onset of neurological disease in both presymptomatic and symptomatic patients(3). Brewer, *et al.*(7) reported benefit of zinc as maintenance therapy of

symptomatic and prophylaxis of presymptomatic Wilson disease(2). The high efficacy and few side effect of zinc resulted in making zinc a standard therapy for prophylaxis in presymptomatic patients(2). Wu, *et al*.(8) used zinc sulfate as the sole therapy for up to five years in presymptomatic Wilson disease. None of the children developed clinical disease but three others who refused zinc therapy became symptomatic during the period.

For the follow up of presymptomatic patients not receiving a copper chelator, lack of clinical illness is not the primary criterion for evaluating treatment; the primary copper intervening variable that is recommended for assessing therapy is urine copper level(2). Followed over three years, the urinary copper in both sibs increased from the pre-therapy level and sib I developed KF rings within a year of therapy. Sib II had an episode of acute hepatitis. Based on epidemiological considerations, sporadic jaundice in our country is most likely to be viral but the possibility of it being due to Wilson disease in this child remains, as the patient was not investigated. Thus, despite adequate zinc prophylaxis, the clinical/ biochemical profile progressed in both siblings.

Review of literature shows quite a few reports of failure of zinc therapy in symptomatic Wilson disease but only one report concerns its use in presymptomatic patients. Symptomatic adult patients have been reported to deteriorate clinically after the initiation of zinc sulfate(4,5). A Wilson disease patient with raised transaminases has been reported to develop acute hepatitis (negative serology for infective causes of hepatitis) after start of treatment with oral zinc. She became asymptomatic with normalization of liver enzymes, after withdrawal of zinc and start of D-penicillamine(6). Although the authors considered this to be acute hepatitis after starting zinc therapy, this could very well have been a hepatic presentation of Wilson disease that did not respond to zinc due to the well-known delayed onset of anti-copper action of zinc therapy.

The explanation for the apparent failure of zinc therapy in these two children remains difficult. Our experience with zinc sulfate in other presymptomatic siblings has been satisfactory. However, failure in two children within the same family may suggest a genetic basis. Wilson disease occurs due to a mutation in the gene coding for the copper transport protein ATP7B. Multiple mutations in the gene have been described to lead to Wilson disease. There may be pheno-genotypic differences in the ability to induce metallothionein based on the mutations; this needs to be explored in future. Given the low incidence of side effects, reported efficacy, and low cost, zinc still remains the drug choice for initial treatment of presymptomatic siblings. We caution for regular clinical and biochemical follow up of such patients.

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TABLE I CLINICAL AND BIOCHEMICAL PROFILE OF THE TWO SIBLINGS OF THE INDEX PATIENT

Patient profile (year)	Sib I: 11 year female			Sib II: 6 year male		
	2001	2002	2003	2001	2002	2003
Symptoms	none	none	none	none	none	none
KF Rings	absent	present	present	absent	absent	absent
History of hepatitis	no	no	no	no	no	yes
Serum ceruloplasmin*	0.31 OD units	–	30.9 mg/dL	0.35 OD units	–	38.5 mg/dL
24-hr urinary Cu # (μg/24hr)						
baseline	6	205	200.1	4	350	387.6
post-penicillamine	191.4	–	–	155.8	–	–
Liver function tests	N	N	N	N	N	abnormal
Renal function tests	N	N	N	N	N	N

*N=Normal, – =Not done; *Normal value: 0.2-0.5 OD units; 20-46 mg/dL, # Normal value: <100 μg /24hr*

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