

Buona risposta alla monoterapia con acetato di zinco in un'adolescente affetta da grave malattia di Wilson

Good response with zinc acetate monotherapy in an adolescent affected by severe Wilson disease

M. G. Marazzi,^{1,4} S. Giardino,² C. Dufour,² M. Serafino,¹ D. Sperli,³ R. Giacchino⁴

Key words: haemolytic anaemia, Wilson disease, zinc acetate

Riassunto

Descriviamo una ragazza di 17 anni con anemia emolitica, come presentazione di malattia di Wilson. La diagnosi è basata sui risultati della ceruloplasmina sierica < 20 mg/dl, presenza di anello di Kayser-Fleischer e anemia emolitica Coombs-negativa.

I test genetici hanno rivelato la presenza della mutazione H1069Q allo stato eterozigote.

La paziente è stata trattata con acetato di zinco in monoterapia, con buona risposta mantenuta dopo 22 mesi.

Questo caso sottolinea l'importanza di riconoscere atipiche presentazioni cliniche della malattia di Wilson, che deve sempre essere considerata nei pazienti con anemia emolitica con test di Coombs negativo.

La buona risposta clinica, nel nostro caso al trattamento con acetato di zinco in monoterapia, potrebbe prestarsi a considerare l'uso di monoterapia con zinco come terapia iniziale, anche in pazienti con malattia di Wilson sintomatici sotto stretta osservazione clinica. Studi clinici sono necessari per fornire prove dell'uso dello zinco in monoterapia, come terapia iniziale nei pazienti con malattia di Wilson sintomatici.

Abstract

We describe a 17-year-old girl with haemolytic anaemia as presentation of Wilson disease.

The diagnosis was based on the findings of < 20 mg/dl ceruloplasmin serum level, Kayser-Fleischer ring and Coombs-negative haemolytic anaemia. Genetic testing revealed the presence of the H1069Q heterozygous mutation.

The patient was treated with Zinc acetate monotherapy, with good response, maintained after 22 months. This case emphasizes the importance of recognizing atypical clinical presentation of Wilson disease, which must always be considered in patients with Coombs-negative haemolytic anaemia.

The good clinical response to treatment with zinc acetate monotherapy in our case might lend to consider the use of zinc monotherapy as initial therapy also in symptomatic patients with Wilson disease under close clinical observation.

Clinical trials are needed to provide evidence for use of zinc monotherapy as first-line therapy in symptomatic patients with Wilson disease.

Introduction

Wilson disease is a hereditary disorder characterized by a pathological accumulation of copper in tissues and organs, particularly the liver and the brain. Onset of disease may occur from paediatric to adult age, with peak incidence between the second and the third decades of life. Symptoms on presentation usually include extremely variable liver disease, which may develop into cirrhosis, manifestations in the central nervous system, psychiatric symptoms and ophthalmologic signs, namely, the presence of Kayser-Fleischer rings. More rarely, other manifestations at onset include haemolytic disorders, bone injury, amenorrhoea, endocrine gland alterations, as well as renal and cardiac abnormalities.^{1,2}

Several treatment options for Wilson disease have been described, and guidelines have recently been published.³ The most commonly

¹ Department of Paediatrics, University of Genoa, Italy;

² Paediatric Haematology and Oncology Unit, G. Gaslini Children's Hospital, Genoa, Italy;

³ Department of Paediatrics, Azienda Ospedaliera di Cosenza, Cosenza, Italy;

⁴ Infectious Diseases Unit, G. Gaslini Children's Hospital, Genoa, Italy

Indirizzo per la corrispondenza (Corresponding author):

Professor Maria Grazia Marazzi, MD

Department of Paediatrics, University of Genoa

Infectious Diseases Unit

G. Gaslini Children's Hospital

Largo G. Gaslini 5

16147 Genoa, Italy

Tel. 00390105636428

Fax 0039010384323

e-mail: mgraziamarazzi@ospedale-gaslini.ge.it

used pharmacological therapies are chelating agents (penicillamine⁴, trientine⁵), tetrathiomolybdate⁶ or zinc-based treatments.^{7,8} Although initial D-penicillamine treatment is generally recommended in symptomatic patients, numerous, often severe, side effects can occur, requiring discontinuation in up to 30% of cases.^{1,2} Especially, neurologic deterioration may appear during the initial phase of treatment with D-penicillamine.⁹

A valid alternative therapy seems to be zinc, which is often used in combination with or after chelators as maintenance therapy. Zinc administered exclusively as monotherapy in symptomatic patients is controversial: current recommendations call for its use after a period of chelating therapy.³ Nevertheless, there are reports in the literature on its immediate use as monotherapy in these patients.^{7,10,11}

Case report

A previously healthy 17 year old female was admitted to another hospital because of ingravescant jaundice (total bilirubin 10.7 mg/dL, direct 2.9 mg/dL, indirect 7.8 mg/dL), progressive decrease in haemoglobin (Hb) values (to 5.4 g/dL), severe coagulopathy (aPTT at 44 seconds [normal values 24.5-34.5 seconds] and PT ratio 1.64 [normal values 0.82-1.19], not correctable by vitamin K), and decreased antithrombin III (ATIII) 36% (normal values 82-137). She also presented alterations of liver function test values: increased AST/ALT (92/38 IU/L), decreased pseudocholinesterase (PCE) (1789 U/L) and albumin (2.5 g/dL). Direct and indirect Coombs' test were negative and fragmented red cells were found on peripheral blood film. After symptomatic therapy, the girl was referred our hospital for a complete diagnostic workup.

The girl was in quite good general conditions: moderate hepatomegaly and splenomegaly were present, neurological examination was normal, serum liver test showed moderate alterations. (Table) Nevertheless, coagulation screening revealed prolonged PT ratio (1.63) and PTT ratio (1.44), as well as decreased coagulation factors consistent with liver disease: factor II 42% (normal values 70-121), factor V 55.3% (normal values 59-149), factor VII 32.5% (normal values 67-150), factor X 52.9% (normal values 76-138)

and ATIII 30% (normal values 82-137). Factor VIII was normal. Hepatotropic virus and autoimmunity tests were negative. Abdominal ultrasound (US) examination showed increased liver volume with non-homogeneous echostructure and mild splenomegaly (longitudinal diameter: 12.5 cm). Doppler US revealed no portal hypertension.

Specific tests were then performed on the suspected diagnosis of Wilson disease: ceruloplasmin was 9.2 mg/dL (normal values: 18-70); serum copper level was 107 mg/dL (normal values: 85-165), and bilateral Kayser-Fleischer rings were present for 360°. The result of 24-hours urinary copper excretion at admission was not available but fifty days after was 146,5 mcg (normal value < 50 mcg/24 h). Brain MRI was normal. Liver biopsy was not performed to avoid the risk of bleeding.

The coexistence of haemolytic anaemia with liver failure, low ceruloplasmin serum levels and bilateral Kayser-Fleischer rings prompted the diagnosis of Wilson disease. Genetic testing, which revealed the presence of the H1069Q heterozygous mutation, confirmed the diagnosis.

To avoid the risk of neurological deterioration with chelating treatment, the girl was thus started on therapy with zinc acetate at the low dose of 25 mg 3 times a day and a diet with reduced copper content. After four months she was in good general conditions but Kayser-Fleischer rings were unaltered. Laboratory findings showed a decrease of AST, an increase in PCE and improvement in the coagulation pattern. (Table) Serum zinc level was 214 mg/dL (normal values: 52-144), a marker of good compliance with therapy. Hepatic elastography showed an elastographic pattern compatible with F3 fibrosis (stiffness: 10 KPa).

Given the absence of adverse side effects, the zinc acetate dose was increased to 50 mg three times a day. Follow-up at 15 months confirmed improvement of clinical and laboratory findings, with normalisation of platelets, Hb, AST, ALT, albumin, total bilirubin, LDH, PCE, PT ratio and PTT ratio, as well as coagulation factors II (93,2%), V (72,4%), VII (76,5%), and X (75,3%), and antithrombin III (101%). (Table)

Good control of disease was confirmed after 22 months end of follow-up. (Table)

Table 1

BIOCHEMICAL PROFILE OF THE PATIENT AT DIAGNOSIS AND DURING THE FOLLOW UP

Laboratory analysis (normal values)	At diagnosis	After 4 months from start of Zn acetate therapy	After 15 months from start of Zn acetate therapy	After 22 months from start of Zn acetate therapy
Total bilirubin (<1 mg/dL)	1.22	0.71	0.51	0.8
Hb (11.5-16.5 g/dL)	13.8	13.6	12.9	14.3
PLT(150-400000/mm ³)	112000	114000	156000	154000
Albumin (4.02-4.76 g/dL)	3.33	n.d.	4.29	4.6
Total protein (6-8 g/dL)	6.02	n.d.	7.01	7.5
PT ratio (0.82-1.19)	1.63	1.22	1.06	n.d.
PTT ratio (0.80-1.21)	1.44	1.38	1.33	n.d.
AST (<35 U/L)	105	49	33	27
ALT (<35 U/L)	60	55	48	39
PCE (3000-8000 U/L)	1779	2804	n.d.	n.d.

n.d.: not determined

Discussion

The onset of Wilson disease includes occasionally haemolytic anaemia^{1,12,13,14}, which is mainly due to oxidative damage of the red cell membrane caused by excess copper released by damaged hepatocytes.¹⁵ In our patient, the suspicion of Wilson disease was confirmed as highly probable, with score 6 by the diagnostic scoring system based on clinical and laboratory parameters developed by Ferenci et al.¹⁶

In our view, this case is deserving of interest given the good response achieved with zinc acetate monotherapy in a severe form of disease. The therapy of Wilson disease is aimed at reducing circulating copper and/or at decreasing copper accumulation in tissues.¹

The penicillamine represents the gold standard for therapy and the most widespread used in Europe. While it is indeed effective at reducing copper levels (thanks to its copper-binding properties and elimination through urine), its use can be hampered by some major side effects: kidney and liver toxicity, bone marrow suppression¹ and, at the start of treatment, a potential irreversible worsening of neurological symptoms.⁹ Brewer et al also documented a 26% incidence of neurologic worsening in patients treated with trientine.¹⁷ Although chelating agents are recommended for initial therapy in Wilson disease³, a valid alternative therapy seems to be zinc¹⁸: it induces the production of metallothionein, which selectively binds to copper in the cells of intestinal mucosa, prevents copper absorption and favours its faecal elimination within 7 to 8 days.¹⁹ Moreover, zinc plays an important role in limiting copper hepatotoxicity by increasing the sequestration of free copper through binding with metallothionein.²⁰ In presymptomatic patients long-term studies have shown that zinc monotherapy can induce a negative copper balance and can normalise transaminase values.²¹

The zinc monotherapy approach may be adopted in patients with exclusively hepatic or combined presentation, on the condition that liver disease is not advanced.²²

In symptomatic patients Zinc administered exclusively as monotherapy is controversial: current recommendations call for its use after a period of chelating therapy.³ Nevertheless, there are reports in the literature on its immediate use as monotherapy in these patients.^{7,10,11} Recently, Linn et al.²² described their experience with long-term zinc monotherapy (median follow-up of 14 years) in 17 patients with Wilson disease, presentation of which was only hepatic in seven subjects, only neurologic in five, and combined in five. The authors concluded that zinc monotherapy is the therapy of choice in patients with exclusively neurological presentation considering the significant potential for neurologic deterioration with chelating agents.

In our patient, the decision to not use for treatment chelating agent was prompt by the possibility of appearance of neurological compromise in patient with severe and symptomatic disease showing a very bilateral complete KF King.

The choice of zinc acetate monotherapy as first treatment has thus far achieved good results. After 22 months of follow-up we have observed a clinical improvement and the recovery of hepatic synthesis parameters.

The traditional therapy with Zinc is based on zinc sulphate; zinc acetate retains the pharmacological properties of zinc sulphate, but is more agreeable and induces fewer gastrointestinal side effects. Zinc acetate was approved for use in the United States by the FDA and in Europe by the EMEA.

The optimal compliance and the good clinical response to treatment with zinc acetate monotherapy in our case might lend to consider the use of zinc monotherapy as initial therapy under close clinical observation, also in symptomatic patients with Wilson disease with risk of toxicity by chelating agents.

Clinical trials are needed to provide evidence for use of zinc monotherapy as first-line therapy in symptomatic patients with Wilson disease.^{23,24}

References

- 1 Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. *Lancet* 2007;369:397-408.
- 2 Medici V, Rossaro L, Sturniolo GC. Wilson disease - a practical approach to diagnosis, treatment and follow-up. *Dig Liver Dis* 2007;39:601-609.
- 3 Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update; American Association for Study of Liver Diseases (AASLD). *Hepatology* 2008;47:2089-2111.
- 4 Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487-495.
- 5 Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. *Lancet* 1982;1:643-647.
- 6 Brewer GJ, Dick RD, Yuzbasiyan-Gurkin V, Tankanow R, Young AB, Kluin KJ. Initial therapy of patients with Wilson's disease with tetrathiomolybdate. *Arch Neurol* 1991;48:42-47.
- 7 Brewer GJ, Hill GM, Prasad AS, Cossack ZT, Rabbani P. Oral zinc therapy for Wilson Disease. *Ann Int Med* 1983;99:314-320.
- 8 Hill GM, Brewer GJ, Prasad AS, Hydrick CR, Hartmann DE. Treatment of Wilson's disease with zinc. I. Oral zinc therapy regimens. *Hepatology* 1987;7:522-528.
- 9 Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. *Arch Neurol* 1987;44:490-493.
- 10 Hoogenraad TU, Van Hattum J, Van den Hamer CJA. Management of Wilson's disease with zinc sulfate: experience in a series of 27 patients. *J Neurol Sci* 1987;77:137-146.
- 11 Medici V, Trevisan CP, D'Inca` R, et al. Diagnosis and management of Wilson's disease: results of a single center experience. *J Clin Gastroenterol* 2006;40: 936-41.
- 12 Prella M, Baccalà R, Horisberger JD, Belin D, Di Raimondo F, Invernizzi R, Garozzo R, Schapira M. Haemolytic onset of Wilson disease in a patient with homozygous truncation of ATP7B at Arg1319. *Br J Haematol* 2001;114:230-232.
- 13 Balkema S, Hamaker ME, Visser HB, Heine GD, Beuers U. Haemolytic anaemia as a first sign of Wilson's disease. *Neth J Med* 2008;66:344-347.
- 14 El Khattabi A, Seddik H, Fatih J, Salaheddine H, Badaoui M, Améziane T, Mahassine F, Ohayon V. Acute recurrent haemolytic anemia as the first manifestation of Wilson's disease: Report of a case. *Transfus Clin Biol* 2009;16:39-42.

- ¹⁵ Forman SJ, Kumar KS, Redeker AG, Hochstein P. Hemolytic anaemia in Wilson disease. Clinical Findings and biochemical mechanism. *Am J Hematol* 1980;9:269-275.
- ¹⁶ Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. *Liver Int* 2003;23:139-142.
- ¹⁷ Brewer GJ, Askari F, Lorincz MT, Carlson M, Schilsky M, Kluin KJ, Hedera P, Moretti P, Fink JK, Tankanow R, Dick RB, Sitterly J. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol* 2006;63:521-527.
- ¹⁸ Hoogenraad TU. Paradigm shift in treatment of Wilson's disease: zinc therapy now treatment of choice. *Brain Dev* 2006;28:141-146.
- ¹⁹ Yuzbasiyan-Gurkan V, Grider A, Nostrant T, Cousins RJ, Brewer GJ. Treatment of Wilson's disease with zinc, X: intestinal metallothionein induction. *J Lab Clin Med* 1992;120:380-386.
- ²⁰ Brewer GJ, Askari FK. Wilson's disease: clinical management and therapy. *J Hepatol* 2005;42(Suppl 1):S13-21.
- ²¹ Marcellini M, Di Ciommo V, Callea F, Devito R, Comparcola D, Sartorelli MR, Carelli G, Nobili V. 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;145:139-143.
- ²² Linn FH, Houwen RH, van Hattum J, van der Kleij S, van Erpecum KJ. Long-term exclusive zinc monotherapy in symptomatic Wilson disease: experience in 17 patients. *Hepatology* 2009;50:1442-1452.
- ²³ Schilsky M. Zinc treatment for symptomatic Wilson disease: moving forward by looking back. *Hepatology* 2009;50:1341-1343.
- ²⁴ Wiggelinkhuizen M, Tilanus ME, Bollen CW, Houwen RH. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. *Aliment Pharmacol Ther* 2009;29:947-958.