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High efficacy of D-penicillamine in Wilson's disease: Contribution of noncompliance to the occurrence of d-penicillamine treatment "failure"

Author: Dan Han[1], Taotao Yan[1], Jingjing Sun[1], Wanhu Fan[1], Hongmei Chen[1]*, Guoliang Li[1]*,

[1]First Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China

[*]**Corresponding author:** Guoliang Li, First Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China. Email: liguoliang_med@163.com, Hongmei Chen, First Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China. Email: chenhongmei1107@126.com

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ABSTRACT

Wilson's disease (WD), a genetic disorder of copper metabolism due to the mutant ATP7B enzyme, is characterized by reduced excretion, disordered accumulation and abnormal deposits of copper causing toxic damage to various organs. D-penicillamine (D-PCA) is an effective oral chelation agent for WD. A WD patient with clinical manifestations was reversed by D-PCA. However, the patient thought that he was healthy enough to lead to the administration of penicillamine being terminated. The reoccurrence of many manifestations of Wilson's disease were reported but the regular fellow-up were also stopped. In addition, his liver function after drinking alcohol started to deteriorate with the findings of symptoms such as progressive jaundice (yellowing of the skin and eyes), dark urine, fatigue, nausea, vomiting, migraine headaches, lower extremity edema, diarrhea. There were no signs of alleviation of Wilson's disease after taking a few pairs of Chinese herbs. Approximately 4 months after the administration of D-PCA treatment, improvement in jaundice and dysphoria, reduced serum levels of alanine aminotransferase, and elevated ceruloplasmin, as well as stabilization in the radiographic of neurologic and hepatic examination, were observed. Our case provides major recommendations for improving the compliance of WD patients and it is a lifelong challenge in terms of the management of WD.

KEYWORDS: D-Penicillamine (D-PCA), Wilson's disease (WD), Noncompliance

INTRODUCTION

Wilson's disease (WD) is a genetic disorder of copper metabolism due to an autosomal recessive inheritance of ATP7B gene mutation. Increasingly advanced genetic techniques estimate that genetic prevalence of WD being142 per 1 000000. The prevalence of WD varies significantly, and the highest being 885 per 1 000000 in Romania within the mountainous region of Rucar [1, 2]. In affected individuals, there is a reduced excretion of copper in bile due to the mutant ATP7B enzyme, disordered accumulation of excess copper and abnormal deposits can be found in various tissues and organs by binding with protein, especially in liver, brain and cornea, leading to the toxic damage to those organs. WD can present clinically as liver disease, acute liver failure, chronic hepatitis and cirrhosis, hemolysis, neurologic disease, psychiatric symptoms and other manifestations [3]. Liver related clinical manifestations include persistently elevated serum aminotransferases, chronic hepatitis, cirrhosis (decompensated or compensated) and fulminant hepatic failure (+/-

haemolytic anaemia). Brain related clinical manifestations of WD are variable including a kinetic-rigid syndrome similar to Parkinson's disease; pseudosclerosis dominated bytremor; ataxia and dystonic syndrome. In many cases, neurological signs are very difficult to classify as patients can have more than one abnormality, each with different levels of severity. Ophthalmic manifestations of WD include K-F rings and sunflower cataracts. Psychiatric manifestations such as impulsiveness, labile mood, sexual exhibitionism, personality changes, paranoia, schizophrenia, depression, neuroses, psychosis, are common and some of them may precede neurologic or hepatic signs and symptoms for many years [3, 4].

WD is progressive and can invariably results in severe disability and even death if not treated. Therefore, earlier diagnosis is important to screen the individuals with WD and start adequate treatment for them. Advances in pathogenesis and clinical, biochemical, and genetic markers are increasingly available to confirm the clinical diagnosis of WD. The diagnostic criteria of Wilson's disease are as follows:

1. Clinical manifestations of liver damage or neurological symptoms;

2. Decrease of ceruloplasmin (<0.2g/L)

3. Adultly 24-hour urinary copper >100μg and

4. Visible corneal-pigmented ring (K-F ring) under the slit lamp [1, 5].

If discovered earlier, effective treatments will prevent or reverse many manifestations, and usually lead to better prognoses in the individuals with WD. Copper chelating agents, orally or intravenously, excrete copper out of the various WD tissues from liver to skin, by combining copper to form water-soluble copper complex, which can be excreted by the stool and urine. D-penicillamine (D-PCA), the first effective oral chelation agent, was initially made its appearance in 1956 by British neurologist John Walshe and its clinical benefit of penicillamine in WD is well documented. However, the side-effects of D-PCA were reported in 20–50% of patients with a neurological presentation and which in some cases cannot be reversed, about 20-32% of the patient's finally discontinued D-PCA treatments because of the serious adverse reactions [6, 7]. We here report a case of patient with WD, whose clinical manifestations were reversed by D-PCA for around 11 years; however, the patient thought that he was healthy enough to lead to the administration of penicillamine being terminated. Termination of D-PCA treatment leads to the reoccurrence of many manifestations of WD and predispose WD to liver failure.

CASE REPORT

A 28-year-old man presented with episodes of jaundice, as well as intermittent dysphoria. At the age of 14 years, he was reported dysarthria, movement abnormalities (tremor, involuntary movements), as well as mild dysphagia. Ophthalmic examination revealed that Kayser–Fleischer rings and sunflower cataracts. Neurologic examination revealed a postural tremor of the arms, lack of motor coordination, drooling, dysarthria, and headaches. Laboratory tests revealed persistently elevated serum levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, as well as low serum levels of ceruloplasmin of 0.12 g/L (normal laboratory range 0.2 to 0.6 g/L). Structural brain magnetic resonance imaging of the patient shown widespread signal lesions in the putamen, globus pallidus, caudate, thalamus, midbrain, pons, and cerebellum as well as cortical atrophy and white matter changes. Ferenci score of this patient was as least 6 indicating WD highly likely [8]. A primary diagnosis of WD was made though there was no evidence of genetic testing. The treatment of penicillamine, which acts as the copper-chelator and enhances urinary copper excretion, was started. The initial dose of penicillamine was 500 mg per day, increasing over four weeks to 1500 mg per day in three divided doses taken 1 h before food. Throughout the administration of penicillamine, blood routine, urine routine, 24-hour urine protein, liver function and kidney function were regularly monitored and no obvious adverse effects were reported. Approximately 11 years after the administration of penicillamine treatment, the Kayser–Fleischer rings had been reverse almost completely and there was stabilization in neurologic examination. However, around three years ago, the patient thought that he was healthy enough to lead to the administration of penicillamine being terminated. The reoccurrence of many manifestations of Wilson's disease were reported but the regular fellow-up were also stopped. Three weeks ago, the liver function after drinking alcohol started to deteriorate with the findings of symptoms such as progressive jaundice (yellowing of the skin and eyes), dark urine, fatigue, nausea, vomiting, migraine headaches, lower extremity edema, diarrhea. The patient was hospitalized in another hospital. The laboratory tests revealed alanine aminotransferase of 221.4U/L (normal laboratory range 15 to 40 U/L), aspartate aminotransferase of 201.7U/L (normal laboratory range 9 to 50 U/L), alkaline phosphatase of 264U/L, γ-glutamyltransferase of 104 U/L, total bilirubin of 346.5 μmol/L, direct bilirubin of 264.9 μmol/L, albumin 32.2g/L, total protein 64.2g/L There was no signs of alleviation of Wilson's disease after taking a few pairs of Chinese herbs.

After the patient presented in our hospital, the physical examination revealed dysarthria, movement abnormalities (tremor, involuntary movements), spider naive and jaundice. The computed tomography of the abdomen revealed cirrhosis, portal hypertension, the mesenteric lymph node edema (Figure. 1).

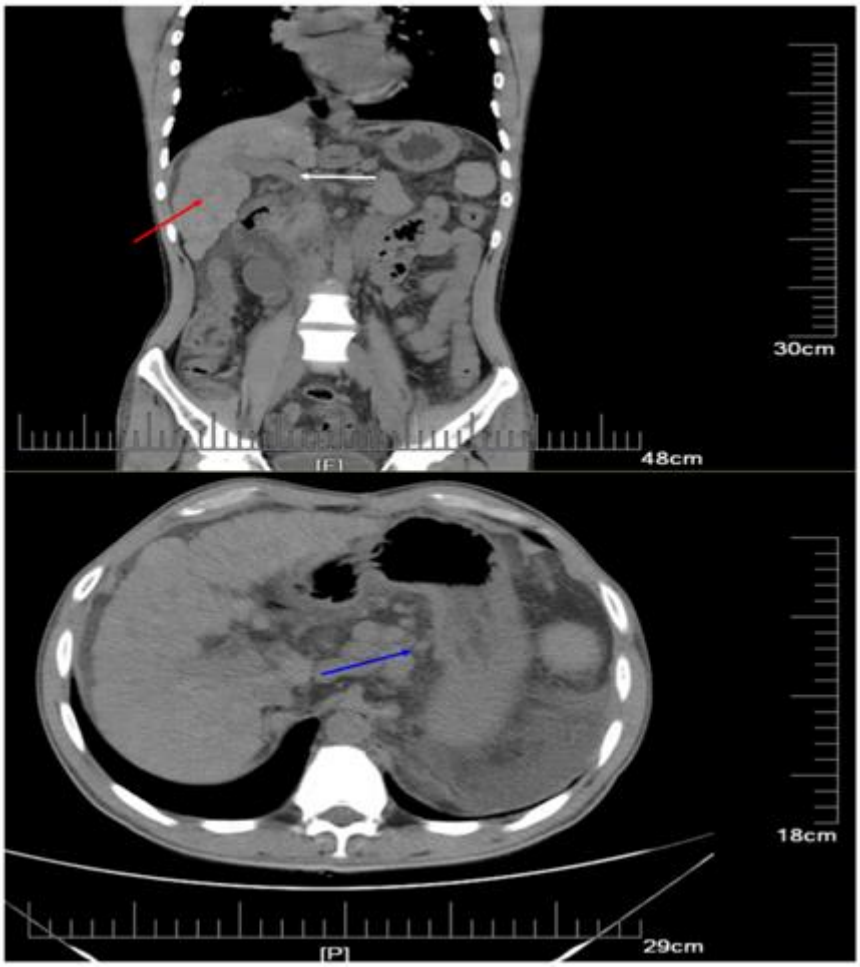

Figure1: The computed tomography of the abdomen revealed cirrhosis (red arrow), portal hypertension (white arrow), and the mesenteric lymph node edema (blue arrow).

The laboratory tests revealed alanine aminotransferase of 261 U/L (normal laboratory range 15 to 40 U/L), aspartate aminotransferase of 326 U/L (normal laboratory range 9 to 50 U/L), alkaline phosphatase of 329 U/L, γ-glutamyltransferase of 114 U/L, total bilirubin of 350.8 μmol/L, direct bilirubin of 402.0 μmol/L, indirect bilirubin of 73.4μmol/L, albumin 27.9 g/L (normal laboratory range 40 to 45 g/L), total protein 64.2g/L (normal laboratory range 65 to 85 g/L), serum creatinine 56μmol/L, blood ammonia 108μmol/L (normal laboratory range 9 to 47 g/L), ceruloplasmin of 0.08 g/L (normal laboratory range 0.2 to 0.6 g/L).The levels of copper in the blood and the amount of copper excreted in urine during a 24-hour period are not available. The patient received a diagnosis of the acute-on-chronic liver failure based on the data (symptoms, signs, and laboratory tests), which showed the rapidly deteriorating condition of Wilson's disease. We only provided symptomatic treatment rather than chelating agents for medical therapy to promote copper excretion from the body. The main problem is that the supplier of the copper-chelator penicillamine has stopped producing it in China and other alternative agents are unable to get access.

The most recent follow-up was conducted 3 months after discharge by telephone contact with the relatives. They finally got D-PCA from another hospital in Hefei province of China. Approximately 4 months after the administration of D-PCA treatment, improvement in jaundice and dysphoria, reduced serum levels of alanine aminotransferase, and elevated ceruloplasmin, as well as stabilization in the radiographic of neurologic and hepatic examination, were observed.

DISCUSSION

The case provides major recommendations for improving the compliance of WD patients. WD is one of the medicable or nearly curable genetic diseases by the drugs, early diagnosis with early and lifelong treatment lead to better prognoses. In this case report of WD, the data clearly show there is a confidence in the use of D-PCA for the chelation therapy of neurological and hepatic disease. Termination of D-PCA treatment was the main cause of the reoccurrence of many manifestations of WD, alcohol and Chinese herbs were deemed as the contributory factors of deterioration. Independent of the chosen therapeutic strategies, non-adherence or discontinuation of medical therapy due to poor-compliance is associated with the risk of intractable hepatic decompensation [1]. Many reviews emphasized the severity of noncompliance in WD, reported that noncompliance is a major problem in the treatment during maintenance therapy. EASL guidelines of WD also stressed that prognosis for survival depends on the severityof liver and neurological disease and compliance with drug treatment. Maselbas reported that persistence with treatment resulted in significantly better results of self-assessment (total improvement in 39.7% vs. 7.7% in the non-persistent group, $p = 0.003$; partial improvement in 53.8% vs. 30.8%, respectively, $p = 0.045$; and deterioration: none in the persistent group vs. 42.3% in the non-persistent group, $p < 0.0001$) [3, 9, 10]. Therefore, if the reoccurrence of neurological and hepatic manifestations appear in WD patients, clinicians should firstly question noncompliance and confirm and correct these risk behaviors before recommending alternative therapy if possible. In addition, the potential of costs, complications associated therapy on compliances should be further analyzed. Secondly, clinicians should evaluate the relationships between noncompliance and recurrent symptom, because some other factors contributing to the recurrence of WD are sometimes overlooked.

Education is the primary tool to improve copper-excreting drugs and the avoidance of risk behaviors inducing hepatotoxicity or liver damage. The concerns about taking copper-excreting drugs included nephrotoxicity, hematological abnormalities, and elastosis perforans serpiginosa. In addition, some patients on treatment remain or become asymptomatic, which may generate the false impression of a “cure”, and a cavalier attitude may result in the frequent skipping or stopping of medication. To counter these possibilities, lifelong follow-up by physicians to monitor the treatment compliance and clinical progress (symptoms, signs, and laboratory tests) to be alert to the side effects of drugs play an important part among the WD patients. In addition, once-daily medication regimens work best for improving compliance. Moreover, the risk of noncompliance should be discussed regularly between clinicians, patients, and families.

To sum up, it is a lifelong challenge in terms of the management of WD, because physicians face with a lifelong need to encourage compliance to therapy. On the other hand, patients face with a lifelong need for medication. These are the two main challenges [1].

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