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It's time to revise the role of positive D- penicillamine challenge test in diagnosis of Wilson disease

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ABSTRACT

Hepatic involvement in Wilson disease consists of isolated elevated liver enzyme, asymptomatic hepatomegaly, cirrhosis and acute liver failure. Here, we report three patients with unexplained elevated liver enzymes. By considering the level of urinary excretion of copper after penicillamine challenge test, we had some problems in the process of diagnosis. Therefore, we thought of cautiously applying the diagnostic cut-off in the mentioned challenge test.

INTRODUCTION

Wilson is an autosomal recessive disorder which is described by degenerative changes in brain, liver and Kayser Fleischer (KF) ring in cornea. The incidence of this disease is 1 in 30,000 to 1 in 50,000 live births [1, 2]. A defect in P1B-ATPase which is coded by ATP7B on chromosome 13 long arm, is found in many of the patients [1]. Hepatic involvement in Wilson disease consists of asymptomatic hepatomegaly, subacute or chronic hepatitis and acute liver failure (with or without hemolytic anemia). In any child or adolescent with a chronic or unexplained acute or chronic elevated liver enzymes, neurological manifestations (tremor, dysarthria, dystonia, chorea, parkinsonism, disorders of academic performance and behavioral change), acute hemolysis, psychiatric disease (depression, anxiety, psychosis), Fanconi syndrome, unexplained skeletal or muscular disease, it is important to consider Wilson disease. In this disease, Serum ceruloplasmin levels are less than 20 mg/dL, and the urinary copper excretion rate is greater than 100 mcg/day and mostly more than 1000 micro gram in 24 hours [2]. Due to unusual and uncommon manifestations in diagnosis of Wilson disease, using chelator challenging test is helpful [3]. With administration of 500 mg of D- Penicillamine every 12 hours, urinary excretion becomes more than 1600 micrograms per 24 hours. Detecting the KF ring and performing Liver biopsy to measure Hepatic copper concentration (> 250 micrograms) are helpful in diagnosis [4]. In this case series we want to present three patients with unexplained elevated liver enzyme (ELE) for more than one year whom their urinary excretion of copper after penicillamine challenge test (PCT) was misguiding.

CASE PRESENTATION

Case 1:

A 10-year-old obese male from Kashan (a city in Esfahan province in Iran) presented with chronic abdominal pain from 3 years ago that has ELE in the investigations since 1 year ago. Due to obesity and ELE, complete evaluations of auto immune and viral hepatitis, Wilson disease and anatomical abnormalities were performed (table 1). As far as the symptoms and signs were not relieved and the investigations were unremarkable, liver biopsy was performed and the pathology showed few points in favor of WD. Therefore, PCT was considered and it was in favor of WD (table 2). Afterwards, Penicillamine was prescribed for him as a standard treatment for WD (10-20 mg/

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kg/day). During the 1 year follow up there were no improvement in liver enzymes, therefore, genetic study for WD was considered after reevaluation of other probable reasons for ELE that was negative and WD was ruled out. The patient is now on treatment as a case of nonalcoholic steatohepatitis (NASH) and metabolic syndrome.

Case 2:

An 18-year-old male from Urmia (center of west Azerbaijan province in Iran) presented with chronic abdominal pain and headache from 4 years previous to visit which was intensified in the last year. The patients' mother has been suffering from Rheumatoid arthritis since 10 years ago. While evaluating the patient, isolated ELE was found. Further complementary evaluations (table 1) for viral, auto immune, infiltrative and metabolic liver involvement were done. As far as the symptoms and signs were not relieved and the investigations were unremarkable, liver biopsy was performed and the pathology showed few points in favor of WD. Therefore, PCT was considered and it was in favor of WD (table 2). Penicillamine was prescribed for the patient as a standard treatment for WD (10-20 mg/kg/day). During follow up there were no improvement in liver enzyme, so complete reevaluations including genetic study for WD were considered and mutations in ATP7B gene and other related genes to WD was negative. From 5 months ago the patient has showed arthralgia in both knees, considering the positive family history he was referred to a rheumatologist and all of the rheumatologic evaluations were normal. The patient is now on treatment as a case of NASH and under rheumatologic follow up.

Case 3:

An 18 years old male teenager from Tehran (capital of Iran) became a candidate for a hand orthopedic surgery due to a trauma. Thrombocytopenia was detected as an accidental finding in pre operation lab data. Due to this finding he was referred to an internist. The patient had no history of abdominal pain, nausea and vomiting, cutaneous lesions, constipation, ecchymosis, and icterus. In further evaluations, ELE and splenomegaly were detected (table 1). SoSo, he was referred to a hematologist and ,bone marrow aspiration and biopsy were normal.

In the visit by a gastroenterologist, it was revealed that he also has complaint from frontal headache with diffusion to left eye. A fine tremor with a progressive process has been established in the upper limbs since three months ago and mother of hishis mother reported anxiety disorder symptoms. According to moderate splenomegaly, normal hepatic and prehepatic vasculature and liver fibrosis in fibro scan in previous assessments, he was considered with hepatic disorders and reevaluation of hepatic function and related disorders were done, but nothing was found in favor of viral or autoimmune hepatitis and WD. Endoscopy findings were also normal. Brain MRI did not show any abnormality which could explain tremor. Percutaneous Liver biopsy was not possible because of the thrombocytopenia, so Penicillamine was prescribed due to positive PCT which was suggestive of WD (table 2). In further follow ups for up to 6 months, there were no improvement in platelet levels and liver enzymes. According to these findings Genetic workup

TABLE 1. Preliminary evaluations

	Case 1	Case 2	Case 3
WBC (cells/mcL)	9300	7500	2800
PMN (%)	54	59	58
Lymphocyte (%)	37	30	42
Hb (gm/dL)	13.4	14.8	12.7
Plt (cells/mcL)	359000	249000	30000
Bun (mg/dL)	11	13	26
Cr (mg/dL)	0.6	1	0.8
CPK (U/L)	103	101	333
LDH (U/L)	305	428	286
ESR (mm/hr)	7	6	11
CRP (mg/L)	Negative	Negative	Negative
AST (U/L)	185	47	23
ALT (U/L)	349	106	20
PT (sec)	12	12	15.2
PTT (sec)	26	28	41
INR	1	1	1.2
Total protein (g/dL)	7.5	7.7	7.2
Alb (g/dL)	4.8	5.4	4.3
Total Billirubin (mg/dL)	0.5	0.4	7.2
Direct Billirubin (mg/dL)	0.35	0.2	4.3
GGT (U/L)	24	31	25
AFP (ng/mL)	0.45	0.5	0.4
Virology	Negative	Negative	Negative
ASMA	<1/160	<1/160	<1/160
Anti LKM	<1/10	<1/10	<1/10
AMA (units)	<0.1	<0.1	<0.1
Free T4 (ng/dL)	11.4	9.1	10.2
TSH (milli-IU/L)	3.4	2.1	1.79
Protein electrophoresis	Normal	Normal	Normal
ANA	<1/40	<1/40	<1/40
C3 (mg/dL)	N/A	N/A	95
C4 (mg/dL)	N/A	N/A	12
Anti.ds DNA(IU/mL)	N/A	5.2	5.8
P-ANCA (AU/mL)	N/A	1	1.1
C- ANCA (AU/mL)	N/A	1.2	1.8
Lupus anticoagulant (MPL units)	N/A	Negative	Positive
Anti-Cardiolipin (MPL units)	N/A	1.7	1.9
ASCA (EU/mL)	N/A	1.5	1.9
CH50 (U/mL)	N/A	122	126
RF (U/mL)	N/A	Negative	Negative

TABLE 1. Preliminary evaluations

TABLE 1. Complementary evaluations for WD

	Case 1	Case 2	Case 3
Plasma ceruloplasmin (mg/dL)	41	23.4	15
Urine Copper excretion (µg/24 hr)	35	31	21
Urine copper (24 hr) post D- penicillamine challenge test (µg/24 hr)	452	572	1206
Hepatic Copper concentration (µg/g) dry weight	39.3	60	N/A
Kayser–Fleischer ring	Absent	Absent	Absent
mutations in ATP7B gene and other related genes to WD	Negative	Negative	Negative

for WD was performed and all of the common mutations were negative.

DISCUSSION

WD has a wide spectrum of clinical presentations, but the most common features are hepatic and neurologic ones [5]. Establishing the diagnosis of WD may be hard especially in children with liver disease [1, 5]. Neither the absence of KF rings nor normal values of ceruloplasmin can exclude WD. Ceruloplasmin has been shown to have sensitivity and specificity of 82.4% and 94.4%, respectively [5]. In the present case series, low serum ceruloplasmin was found in all 3 cases and none of our cases was presented with KF rings. KF rings may be absent in only 5% of cases with neurological presentation but it is usually absent in children presenting with liver disease [5]. A urinary copper excretion more than 100 µg/24 hr is helpful in diagnosing WD and if it is greater than 40 µg/24 hr, further investigations should be done to confirm WD diagnosis [1, 4]. Copper values are often normal in children with mild hepatic involvement [4]. All 3 cases in our study had Urine Copper excretion lower than 40 µg/24 hr. A positive PCT (>1600 µg/24 hr) is a confirming finding in patients with WD [1, 4, 5]. The PCT (i.e. 0.5 g D-penicillamine given at the beginning of the 24-hour urine collection and 12 hours later) is not enough to confirm the diagnosis in asymptomatic children with a sensitivity of 12% [1]. Decreasing the cut-off to 5 times the upper normal range of basal urinary copper excretion (200 mg/24 hr) increased the sensitivity to 88% but the specificity lowered to 24.1% [1, 3]. We have used this scale for suspecting WD for the three patients as their PCT was lower than 1600 µg/24 hr but 5 time greater than upper normal limit (UNL). The WD scoring system proposed by Ferenci et al. [8] maybe a reliable tool in this subset of patients if this limit is used for evaluating the 24-hour urinary copper excretion. In these patients PCT cannot help much for diagnosis [1, 2]. A genetic study is valuable in such patients [1, 2]. In our study, genetic assay showed no mutations in ATP7B gene and other related genes to WD. In the present case series, the PCT gave low values in all three WD suspected patients. Although our patients had a positive PCT of 5 times more than UNL as a diagnostic criteria by some studies whilst they were followed up on treatment, it was revealed that they were misdiagnosed as WD.

CONCLUSION

The manifestations of WD in children are very diverse. It is difficult to make a definitive diagnosis with minimum rare manifestations. A single positive or negative diagnostic test is not enough to confirm or ruleout WD. A positive PCT with a copper excretions 5 times more than UNL in the patients suspicious of WD is not enough to confirm the diagnosis. A positive PCT should be mentioned when urinary copper excretion is >1600 µg/24 hr to make the correct diagnosis. In the cases with equivocal PCT, positive mutation in ATP7B gene and other related genes to WD can be helpful to make a definite diagnosis.

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