

Wilson's disease in an adult asymptomatic patient: a potential role for modifying factors of copper metabolism

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Abstract

Diagnosis of Wilson's disease (WD) still remains a challenge since no single test has an accuracy of 100%. Molecular testing for *ATP7B* gene mutations can help reach the diagnosis when routine testing is equivocal. We herein report an asymptomatic WD patient diagnosed accidentally by genetic analysis. This case suggests that WD is a challenge even in particular contexts such as family screening. Genetic testing of *ATP7B* gene should be recommended in the family members of WD patients with minimal alterations of specific tests such as ceruloplasmin, and presence of steatosis or increased body mass index.

Keywords Wilson's disease, asymptomatic, diagnosis, *ATP7B* mutation

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Introduction

Wilson's disease (WD), an autosomal recessive disorder of copper transport with a broad range of genotypic and phenotypic characteristics, results from mutations in the *ATP7B* gene [1]. Diagnosis WD still remains a challenge since no single test has an accuracy of 100% [1]. Molecular testing for *ATP7B* mutations is an important criterion when routine testing is equivocal for WD [1]. Because of its transmission mode, WD occurs in siblings more often than in consecutive generations, and has been reported only in offspring. We herein report a case of an asymptomatic adult patient with WD detected only by genetic analysis.

Case report

A 4-year-old girl of Sardinian origin investigated for hypertransaminasemia of unknown origin was diagnosed with WD during the work-up to determine the cause of recurrent infections. WD diagnosis was based on low ceruloplasmin and serum copper levels, and increased 24-h urine copper and liver copper content (Table 1).

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Genetic analysis was carried out using the sequencing method as described previously [2] that revealed the presence of compound heterozygous state for c.-441_427del/p.V1146M mutations [3]. The c.-441_427del was passed on by the father while p.V1146M was passed on by the mother. Her 3-year-old sister had not acquired either mutation. All family members were apparently healthy. Subsequently, haplotype analysis was performed in the family, on *ATP7B* gene polymorphisms by sequencing method [2] during which the 45-year-old father was found to carry another mutation c.19_20delCA on the other chromosome, resulting in a compound heterozygote for c.-441_427del/c.19_20delCA. This mutation, already described in a WD patient of Czech origin, was detected in heterozygosity in the sister [4]. Given the genotype, the father underwent thorough investigation (Table 1). He denied being an alcoholic. He had a body mass index (BMI) of 30, without hepatomegaly. Blood glucose levels and liver chemistry showed normal values. Lipid profile analysis showed slight increases of total cholesterol, triglycerides, and high-density lipoprotein, with normal low-density lipoprotein. Copper metabolism assessment only showed a slight ceruloplasmin decrease, while serum copper, 24-h urine copper and liver copper content were within normal range. Slit-lamp examination showed no Kayser-Fleischer (KF) rings. Abdominal ultrasound showed diffused fine hyperechogenicity in the liver, suggesting the presence of steatosis, further confirmed by liver biopsy. Magnetic resonance imaging (MRI) of the brain detected no abnormalities. RNA studies of the c.19_20delCA mutation showed no alternative splicing (data not shown). Based on these findings, he was considered an asymptomatic WD patient with a very mild clinical picture and Zinc therapy was proposed but declined. Since diagnosis in 2009, the patient has been examined annually without substantial alteration in the clinical picture (Table 1). Informed consent was obtained for the publication of this case report and so was the approval of the Hospital and University Ethics Committee.

Table 1 Clinical and laboratory data of the family reported in this paper

Family under investigation	Patient's data at diagnosis	Patient's data after 4 years	Daughter's data at diagnosis
Year of study	2009	2013	2003
Sex	M	M	F
Symptoms	A	A	A
Kayser-Fleischer rings	-	-	-
AST (5-45 U/L)	22	22	73
ALT (5-43U/L)	28	23	159
Ceruloplasmin (25-62 mg/dL)	20	17	3.2
Serum copper (50-150 µg/dL)	67	49	10
Urine copper basal (<50 µg/24h)	10	44	55
Penicillamine challenge (µg/24h)	600	NP	NP
MRI	Normal	Normal	NP
Liver histology	Steatosis	-	Steatosis
Liver copper content (<50 µg/g dry tissue)	110	ND	1075
Genotype	c. 441_427del/c. 19_20delCA		c. 441_427del/p.V1146M
Leipzig scoring without mutations	2		5
Leipzig scoring with mutations	6		9

M, male; A, asymptomatic; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NP, not performed; MRI, magnetic resonance imaging

Discussion

The patient reported herein is a rare case of WD with minimal clinical and biochemical alterations, no symptoms, and normal enzymes values. Liver ultrasonography and histology revealed steatosis, and patient's lipid profile was altered, confounded by his increased BMI. In this context, steatosis could not be attributed to WD because it could be due to only alteration of lipid metabolism or to both alteration of lipid metabolism and WD. Copper metabolism assessment only showed slight ceruloplasmin decrease, while serum copper, 24-h urine copper and liver copper content were within normal range [1]. Applying the Leipzig scoring system evaluation, we obtained a score of 2 not considering mutation analysis and 6 after including genetic testing [5]. There are a few reported cases of adult asymptomatic patients detected with familial screening after a family member was diagnosed for WD [6-8]. In all cases, besides the genetic results, some alterations were also present. In a 43-year-old asymptomatic patient of Armenian origin, compound heterozygous for p.G691R/p.I1230V, the presence of KF was found and copper biochemical tests were also altered [6]. In another paper, 2 cases of asymptomatic twins of WD patients were reported [7]. The first case was diagnosed at 39 years by genetic analysis revealing compound heterozygosity for p.H1069Q/c.1211_1212insA mutations. She only showed low ceruloplasmin and copper serum levels, while clinical and biochemical assessment resulted in the normal range. 24-h urine test, copper liver biopsy and liver copper content were not evaluated in this case. In another case report, a Polish woman was diagnosed at 54 years by family screening [8]. Her physical examination, hepatic work-up and brain MRI were normal, KF were positive,

ceruloplasmin and serum copper were normal, and 24-h urine copper was slightly increased. She refused treatment and remained asymptomatic until 84 years. Our case is particular since he was diagnosed accidentally during a genetic analysis research study. Biochemical and copper metabolism analysis in the context of a family screening would not have allowed the diagnosis since he was completely asymptomatic with only steatosis and a slight decrease in ceruloplasmin that could be present in any overweight WD carrier. Penicillamine challenge test showed 600 µg/24h urinary copper excretion, but, since the test has not been standardized in adults, it is not recommended for WD diagnosis. This raises questions on the penetrance of *ATP7B* mutations. The c.-441_427del is the most common Sardinian mutation and is detected in approximately 65% of Sardinian WD patients, thus indicating its pathogenicity. The c.19_20delCA mutation creates a frameshift and a STOP codon in a position 20, resulting in a truncated functionless protein. Alternatively, this mild phenotype could be explained by the intervention of modifier genes regulating copper metabolism in the presence of defective *ATP7B* protein function, leading to the normal copper metabolism parameters observed in the patient. Such modifier proteins for liver function are *CTR1*, *ATOX1*, *MURR1* but their roles in WD have not yet been demonstrated [9]. The explanation of their significance could change the therapy of WD.

In conclusion, this case adds more information about the natural history of WD and suggests that WD is a challenge even in particular contexts such as family screening. This is particularly true in asymptomatic patients including the pediatric age group and in adults with asymptomatic increase in liver tests. In these patients, the presence of normal values of some of the copper metabolism tests decreases the accuracy

of the Leipzig score. Thus, the use of genetic testing becomes imperative in the diagnosis of WD [10]. Genetic testing of the entire *ATP7B* gene should be conducted in cases of relatives of WD patients with minimal alterations of copper metabolism in tests such as ceruloplasmin and signs such as steatosis, even in overweight patients.

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