

Late onset fulminant Wilson's disease: A case report and review of the literature

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Abstract

Wilson's disease (WD) is an autosomal recessive inherited disorder of hepatic copper metabolism. WD can be present in different clinical conditions, with the most common ones being liver disease and neuropsychiatric disturbances. Most cases present symptoms at < 40 years of age. However, few reports exist in the literature on patients in whom the disease presented beyond this age. In this report, we present a case of late onset fulminant WD in a 58-year-old patient in whom the diagnosis was established clinically, by genetic analysis of the *ATP7B* gene disclosing rare mutations (G1099S and c.1707+3insT) as well as by high hepatic copper content. We also reviewed the relevant literature. The diagnosis of WD with late onset presentation is easily overlooked. The diagnostic features and the genetic

background in patients with late onset WD are not different from those in patients with early onset WD, except for the age. Effective treatments for this disorder that can be fatal are available and will prevent or reverse many manifestations if the disease is discovered early.

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Key words: Wilson's disease; Late onset; Fulminant; *ATP7B* gene mutations; Copper

Core tip: There are few reports in the literature on patients in whom Wilson's disease presented well beyond the age of 40 years and much less when the presentation is fulminant. We present a 58-year-old patient with late onset fulminant Wilson's disease and very rare mutations in the *ATP7B* gene. In addition, we review the relevant literature on late onset fulminant Wilson's disease.

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INTRODUCTION

Wilson's disease (WD) is an autosomal recessive inherited disorder of hepatic copper metabolism caused by mutation of an intracellular copper transporter ATPase, *ATP7B*, that is mainly expressed in hepatocytes. Loss of *ATP7B* function results in reduced hepatic biliary copper excretion, reduced incorporation of copper into ceruloplasmin^[1] and the accumulation of copper in many organs and tissues. WD can be present in different clinical

cal conditions, with liver disease and neuropsychiatric disturbances being the most common ones. The diagnosis of WD relies on detection of Kayser-Fleischer rings, low ceruloplasmin, elevated urine and hepatic copper level, signs of liver and/or neurologic disease and associated histologic changes in the liver^[1]. If untreated, WD results invariably in severe disability and death^[1]. Available medical therapies and liver transplantation can be offered to patients with this fatal disorder. The early detection of the disease and prompt initiation of treatment to prevent disease progression and reverse pathologic findings if present are warranted^[2]. The disease is common in children and young adults, and presents in most cases between the age of 3 and 40 years. However, there are few reports in the literature in whom the disease presented beyond this age^[3-14], with some of them in the form of case reports^[3-10]. Three case series included also older patients^[11-13], and one large study by Ferenci *et al*^[14] included 46 patients who became symptomatic at > 40 years of age. Thus, more attention is needed to identify older patients with WD. In this report, we present a case of late onset fulminant WD in a 58-year-old patient and reviewed the relevant literature.

CASE REPORT

A 58-year-old morbid obese patient complained of fatigue and poor appetite for one year. In her physical examination she had leg edema and newly diagnosed ascites. She denied alcohol consumption and regular or under-the-counter-medication use. Ultrasound investigation revealed a hyperechoic fatty liver, enlarged spleen and a moderate amount of ascitic fluid. Doppler examination revealed patent portal and hepatic veins. Laboratory data included: total bilirubin (Bil), 4 mg/dL (direct, 2.5 mg/dL); alkaline phosphatase (ALP), 194 U/L (normal, 115 U/L); aspartate aminotransferase (AST), 112 U/L (normal, < 40 U/L); alanine transaminase (ALT), 175 U/L (normal, < 42 U/L); albumin, 2.8 g/L, international normalized ratio (INR), 1.7; hemoglobin, 12.1 g/L; white blood cell count, $5.5 \times 10^9/L$; and platelet count, $112 \times 10^9/L$. Blood sugar, urea, and creatinine were normal. Serological screening revealed that the patients tested negative for hepatitis B surface antigen, hepatitis B core antigen, and hepatitis C virus. Serum titers of smooth muscle antibodies and nuclear and mitochondrial antibodies were negative. The patient was diagnosed as having cirrhosis due to nonalcoholic fatty liver disease (NAFLD) and was discharged with diuretic therapy. Several weeks later she was re-admitted with increasing fatigue, weakness and jaundice. Repeated blood tests demonstrated severe impairment in liver synthetic function: INR, 3.1; albumin, 2.5 g/L; and Bil, 6.7 mg/dL (direct, 4.5 mg/dL). Her hemoglobin was 12.8 g/L, white blood cell count $10.0 \times 10^9/L$, and platelet count $10^6 \times 10^9/L$. The condition of the patient deteriorated rapidly and her liver function tests were aggravated: AST, 91 U/L; ALT, 42 U/L; ALP, 21 U/L; Bil, 52 mg/dL; and INR, 6.5 (Figure 1). She developed

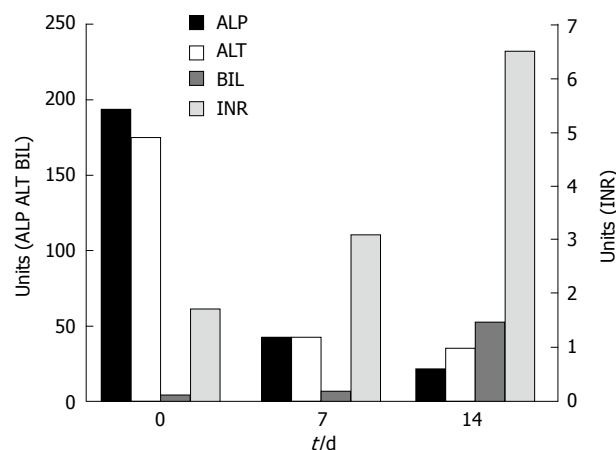


Figure 1 Biochemical parameters and international normalized ratio. Serum ALP and ALT decreased while bilirubin level increased. The INR level increased dramatically, indicating the fulminant course of the disease. ALP: Alkaline phosphatase; ALT: Alanine transaminase; Bil: Bilirubin; INR: International normalized ratio.

renal failure (creatinine, 2.93 mg/dL) and grade 3 hepatic encephalopathy (ammonia, 180 micgr/dL) and was transferred to our intensive care unit. A tentative diagnosis of fulminant late onset WD was made and a transjugular liver biopsy was performed. Histological examination of liver tissue displayed acute hepatitis with bridging necrosis and advanced fibrosis, macro- and micro-vesicular steatosis (Figure 2A) and accumulation of copper binding proteins (Figure 2B). Hepatic copper content was 986 mcg/g dry weight (normal < 50 mcg/g dry weight). Serum ceruloplasmin level was 12 mg/dL. There was no evidence for the presence of a Kayser-Fleischer ring. To confirm the diagnosis of WD, we performed DNA sequence analysis of the *ATP7B* gene, which disclosed rare mutations: G1099S and c.1707+3insT. These findings were compatible with the definite diagnosis of WD with a fulminant course. The patient was transferred to a liver transplant center where molecular absorbent recycling system and plasmapheresis were performed and was urgently listed for status 1 liver transplantation. However, the patient died several days later as no liver donor was available.

DISCUSSION

The diagnosis of fulminant late onset WD was established in our case mainly by the low ceruloplasmin level, the high hepatic copper content and the genetic analysis. However, the diagnosis of fulminant WD was deferred in our patient due to her age and the morbid obesity leading to the wrong assumption that her primary liver disease was related to NAFLD. Without urgent liver transplantation, acute liver failure (ALF) due to WD is invariably fatal^[1]. Thus, rapid diagnosis of fulminant WD should prompt transplant listing. Korman *et al*^[15] reported that utilizing conventional WD testing such as serum ceruloplasmin and/or serum copper levels are less sensitive and specific in identifying patients with ALF-WD than

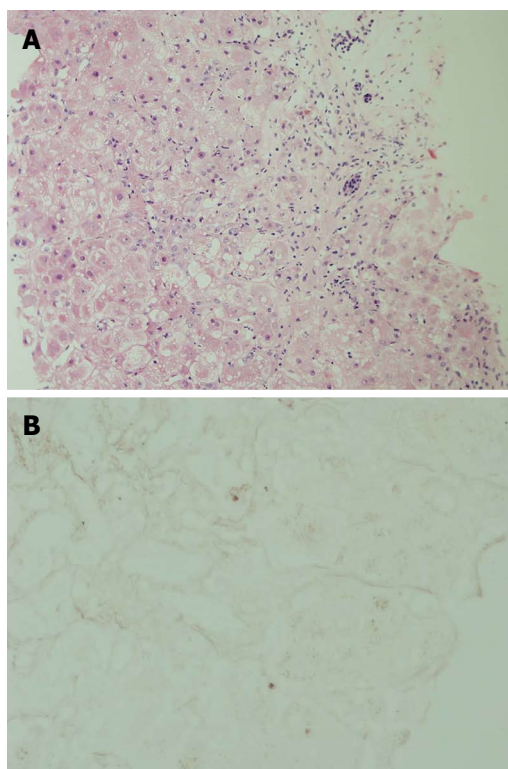


Figure 2 Histological evaluation of liver tissue (hematoxylin-eosin staining, $\times 20$). A: Histological examination of liver tissue displayed acute hepatitis with bridging necrosis and advanced fibrosis, macro- and micro-vesicular steatosis; B: Using orcein (copper binding protein stain), accumulation of copper binding protein was revealed.

other available tests. It was suggested in that study that laboratory tests including alkaline phosphatase, bilirubin and serum aminotransferases provide the most rapid and accurate method for diagnosis of ALF due to WD. An AST:ALT ratio > 2.2 yielded a sensitivity of 94%, and a specificity of 86% and an ALP to total bilirubin ratio < 4 yielded a sensitivity of 94%, and a specificity of 96% for diagnosing fulminant WD^[15]. Our patient fulfilled these criteria as her ALP to total bilirubin ratio was 0.4 and her AST/ALT ratio was 2.2, and the diagnosis of ALF-WD could be established using these simple criteria. The main reason that WD has been overlooked in our patient at the beginning was the morbid obesity and the NAFLD (detected by ultrasound and liver histology) that our patient suffered from. However, the most frequently observed hepatic histological lesion in WD is hepatic macro-steatosis and glycogenated nuclei^[16], which are features that can be seen also in nonalcoholic steatohepatitis. In a recently published study^[17], the hepatic steatosis in WD was not induced by metabolic comorbidities but by the accumulation of copper in the liver tissue. However, metabolic alterations could be co-factors in the pathogenesis of steatosis in these patients. Thus, the presence of fatty liver should not exclude the diagnosis of WD.

WD may become symptomatic at any age and should be considered in any patient presenting with unclear hepatic or neurologic disease. Medical therapy includes several chelating agents and zinc salts^[1,2]. In the largest study

published so far^[14], the diagnostic features and the genetic background in patients with late onset WD were not different from the overall cohort of 1223 patients with WD, except for age. Reviewing the literature on late onset WD, we have detected 70 reported cases (including our case): 8 case reports^[3-10], 3 case series^[11-13] and 1 large study^[14] (Table 1). The definite diagnosis of WD was not achieved in all of the reported cases. A large variability was noted in the clinical presentation of WD (ranging from limited hepatic chronic or fulminant disease or central nervous system disease to disease that involves both organs), in the serum level of ceruloplasmin (ranging from normal to low serum level) and in the presence of a Kayser-Fleischer ring (Table 1). In all the reported cases that the liver copper content was measured, it was $> 250 \mu\text{g/g}$ dry weight. The H1069Q mutation was the most frequently detected (Table 1). We have detected 6 cases (including our patient) that presented with a fulminant course. DNA sequence analysis of the *ATP7B* gene was not performed in these patients. However, in our patient we have detected rare mutations: the G1099S and the c.1707+3insT. These mutations have been reported so far only in the Greek population and at a frequency of 1% each^[18]. This huge variability in the clinical presentation of WD reflects our limited knowledge on the natural history of WD. The phenotype is required to be defined as accurately as possible in genetic associated studies^[19]. There are several explanations for the misdiagnosis of WD in older subjects. First, our diagnostic criteria that rely on the neurological symptoms, the presence of a Kayser-Fleischer ring, and a low ceruloplasmin concentration^[1,2,20] are sometimes inaccurate to detect the disease. Plasma ceruloplasmin is often within the normal range and in some studies up to 50% of affected individuals with severe decompensated liver disease have normal ceruloplasmin level^[2]. Kayser-Fleischer ring is absent at least in one-third of patients, and neurologic symptoms are absent in most^[1,2,20]. Relying only on the diagnostic criteria can lead to misdiagnosis of WD at any age and not just in late onset. Additional laboratory data are helpful to establish the diagnosis, such as the increase in urinary copper excretion and the increased hepatic copper content, but these tests still have limitations^[1,2]. Copper concentrations that are falsely low can be detected in hepatic specimens with extensive fibrosis and few parenchymal cells. In addition, greatly increased hepatic copper concentrations can be seen in long-term cholestasis^[2]. Genetic testing is also now a diagnostic tool, but its application in the clinical routine is limited by the lack of general availability (cost) and the huge number of mutations^[1,2,20]. Even in the largest study by Ferenci *et al.*^[14], based on clinical symptoms and laboratory findings, diagnosis was certain only in 39 (84.7%) of their patients. Other explanations for overlooking WD in older subjects are: WD may have a slowly progressing course as reported in 3 cases, of whom two presented at the age of 70 and 72 years (siblings)^[8] and one presented at the age of 84 years^[10]. A longer time delay from onset of symptoms until definitive diagnosis (3 years) is typically detected in

Table 1 Baseline characteristics at diagnosis of late onset Wilson's disease - literature review

Ref.	n	Mean age (yr)	Diagnosis	Fulminant	Hepatic	Neurologic	Ceruloplasmin (mg/dL)	Kayser Fleischer ring	Mutation	Copper (μ g) per gram liver dry weight
Fitzgerald <i>et al</i> ^[3]	1	55	Possible	No	Yes	No	NA	NA	NA	NA
Czlonkowska <i>et al</i> ^[4]	1	46	NA	No	NA	Yes	NA	NA	NA	NA
Ross <i>et al</i> ^[5]	1	57	Definite	No	No	Yes	14	No	NA	400
Hefter <i>et al</i> ^[6]	1	60	Possible	No	No	Yes	13	No	NA	356
Dib <i>et al</i> ^[7]	1	57	Possible	No	No	No	7	No	NA	1300
Ala <i>et al</i> ^[8]	2	70-72	Definite	No	Yes	Yes	37	Yes	E1064A and H1069Q	671
Perri <i>et al</i> ^[9]	1	60	Definite	No	Yes	No	Normal	No	H1069Q and E1064A	1021
Czlonkowska <i>et al</i> ^[10]	1	84	Definite	No	Yes	No	33.4	Yes	H1069Q	NA
Danks <i>et al</i> ^[11]	4	43-58	Definite in 3 patients	Yes in 2 patients	Yes	No	12-normal	No	NA	717-1199
Gow <i>et al</i> ^[12]	5	44-58	Definite	Yes in 2 patients	Yes	No	14-37	Yes in 2 patients	NA	516-1526
Pilloni <i>et al</i> ^[13]	5	40-57	NA	NA	yes	NA	NA	NA	NA	NA
Ferenci <i>et al</i> ^[14]	46	40-57	39 diagnosed on clinical grounds; 33 diagnosed by mutation, 5 patients diagnosis possible	Yes in 1 patient	Yes in 15 patients	Yes in 31 patients	< 20 mg/dL in 41 patients	Yes in 32 patients	H1069Q/H1069Q in 13, H1069Q/R969Q in 3, H1069Q/other in 4 patients	Liver copper > 250 in 13 of 17 biopsied patients
Current case	1	58	Definite	Yes	Yes	No	12	No	G1099S and c.1707+3insT	986

Reviewing the literature on late onset Wilson's disease (WD), we have detected 70 reported cases (including our case): 8 case reports^[3-10], 3 case series^[11-13] and one large study^[14]. NA: Not applicable.

patients with WD and neuropsychiatric symptoms than in patients with hepatic symptoms^[21].

In conclusion, the diagnosis of WD with late onset presentation is easily overlooked. There is considerable phenotypic variation in WD. Except for the age, the diagnostic features and the genetic background in patients with late onset WD are not different from those with early onset WD. Effective treatments are available that will prevent or reverse many manifestations of this disorder if the disease is discovered early.

COMMENTS

Case characteristics

A 58-year-old female with a 1-year history of fatigue and poor appetite presented with newly diagnosed ascites.

Clinical diagnosis

Morbid obese, with leg edema and ascites.

Differential diagnosis

Decompensated cirrhosis due to nonalcoholic fatty liver disease.

Laboratory diagnosis

Total bilirubin, 4 mg/dL (direct, 2.5 mg/dL); alkaline phosphatase, 194 U/L (normal, 115 U/L); aspartate aminotransferase, 112 U/L (normal, < 40 U/L); alanine transaminase, 175 U/L (normal, < 42 U/L); albumin, 2.8 g/L, international normalized ratio, 1.7; hemoglobin, 12.1 g/L; white blood cell count, $5.5 \times 10^9/L$; platelet count, $112 \times 10^9/L$. Serum ceruloplasmin level, 12 mg/dL.

Imaging diagnosis

Ultrasound investigation revealed a hyperechoic fatty liver, enlarged spleen and a moderate amount of ascitic fluid. Doppler examination revealed patent portal and hepatic veins.

Pathological diagnosis

Severe acute hepatitis with bridging necrosis and advanced fibrosis, macro-

and micro-vesicular steatosis and accumulation of copper binding proteins. Hepatic copper content was 986 mcg/g dry weight (normal, < 50 mcg/g dry weight).

Treatment

The patient was transferred to a liver transplant center where molecular absorber recycling system and plasmapheresis were performed and was urgently listed for status 1 liver transplantation. However, as no liver donor was available, the patient died.

Experiences and lessons

Wilson's disease (WD) can have a late onset presentation. Without emergency liver transplantation, acute liver failure due to WD is invariably fatal. Therefore, rapid diagnosis of WD should aid prompt transplant listing.

Peer review

The diagnostic features and the genetic background in patients with late onset WD are not different from those with early onset WD, except for the age. If discovered early, effective treatments are available that will prevent or reverse many manifestations of this disorder that is fatal.

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