

[CASE REPORT]

Late-onset Wilson Disease in a Patient Followed-up for Nonalcoholic Fatty Liver Disease

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Abstract:

A 73-year-old woman was referred to our hospital for persistent liver dysfunction. When the patient was 45 years old, her youngest sister had been diagnosed with Wilson disease (WD). The patient therefore underwent several family screening tests, all of which were unremarkable. She had an annual medical checkup and was diagnosed with liver dysfunction and fatty liver at 68 years old. A liver biopsy and genetic testing were performed, and she was diagnosed with WD; chelation therapy was then initiated. In patients with hepatic disorders and a family history of WD, multiple medical examinations should be conducted, as the development of WD is possible regardless of age.

Key words: Wilson disease, late-onset, nonalcoholic fatty liver disease, ATP7B gene

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Introduction

Wilson disease (WD) is an autosomal recessive inherited disorder of hepatic copper metabolism, the causative gene for which is the ATP7B gene. In patients with WD, the ATP7B protein is defective or impaired, resulting in the accumulation of copper in hepatocytes instead of its excretion from the liver into bile. When copper stored in hepatocytes reaches the storage threshold, copper ions and free radicals, such as hydroxyl radicals, accumulate and cause cytotoxicity. In addition, copper is deposited in the liver and other organs, including the basal ganglia, cornea, and kidneys, causing organ injury.

The incidence of WD is estimated to be 1 in 30,000 worldwide (1), with some ethnic or geographic variations; however, due to advancements in genetic analyses, reports have revealed that it is now more common than previously considered (2, 3). In Japan, the peak age of the onset of WD is 6-10 years old, and the average age of the onset is 10 years and 5 months old (4).

The development of symptoms and the diagnosis in patients with WD most likely occurs between 3 and 40 years old; however, a large multinational study reported that approximately 4% of patients present with symptoms beyond 40 years old (5). Older cases of WD are often diagnosed with a brother as the proband, because if a brother has WD, there is a 25% chance of a patient having the disease (6). If the patient is left undiagnosed and untreated, even after the peak age of the onset, disease progression is expected, and there is an increased risk of developing liver cirrhosis or liver cancer. Late-onset WD at an early stage is difficult to diagnose because there are no symptoms specific to WD, and various imaging findings are present.

Although the characteristics of WD in older patients remain unclear, we herein report a case of WD diagnosed at 73 years old after liver damage was noted at 68 years old and followed up as nonalcoholic fatty liver disease (NAFLD).

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Table. Laboratory Data.

WBC	5,680 / μ L	HBs-Ag	Negative
Hb	12.1 g/dL	HBc-Ab	Negative
Platelet	11 \times 10 ⁴ / μ L	HCV-Ab	Negative
PT%	62.3 %	Antinuclear Ab	Negative
PT-INR	1.25	Antimitochondrial M2 Ab	Negative
Albumin	3 g/dL	Ferritin	199 ng/mL
TB	0.4 mg/dL	Type IV collagen 7S	12 ng/mL
AST	78 U/L	Serum copper	30 μ g/dL
ALT	63 U/L	Ceruloplasmin	8 mg/dL
LDH	202 U/L	FIB4 index	6.52
ALP	736 U/L		
γ -GTP	269 U/L	Urinary copper excretion	166 μ g/day
Glucose	90 mg/dL		
Insulin	4.6 μ U/mL	Copper content in liver tissue	1,452 μ g/dry-g
BUN	12 mg/dL		
Cr	0.5 mg/dL	ATP7B gene analysis	Mutations c.2868delC1 (p.Pro957ProfsX9) c.4007T>C (p.Ile1336Thr)

ATP7B gene revealed a complex heterozygote of c.2868delC1 (p.Pro957ProfsX9) and c.4007T>C (p.Ile1336Thr).

PT-INR: prothrombin time-international normalized ratio, TB: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ -GTP: γ -glutamyltranspeptidase, BUN: blood urea nitrogen, Cr: creatinine, HB: hepatitis B, HCV: hepatitis C virus, Ag: antigen, Ab: antibody

Case Report

A 73-year-old woman was referred to our hospital due to persistent liver dysfunction. She had two siblings. When the patient was 45 years old, her youngest sister had died of liver failure due to WD. Thereafter, the patient had been subjected to several family screening tests at another university hospital. She was referred to the Department of Internal Medicine, Neurology, and Ophthalmology; however, the findings were unremarkable. Her second sister had no liver damage and did not develop WD. Her parents were not consanguineous. Thereafter, she underwent medical checkups annually, and liver function tests were unremarkable. However, at 68 years old, she developed mild liver dysfunction with aspartate aminotransferase (AST) 51 U/L, alanine aminotransferase (ALT) 36 U/L, and γ -glutamyl transpeptidase (γ -GTP) 58 U/L. She consulted with her family doctor, and fatty liver was noted, for which she underwent regular follow-up. She was referred to our hospital at 73 years old for progression of liver dysfunction.

Regarding her personal and social history, she was a non-smoker and nonalcoholic beverage drinker. She was 153 cm tall and weighed 55.5 kg, with a body mass index of 23.7. Physical findings showed no obvious neurological abnormalities. An ophthalmological examination did not reveal a Kayser-Fleischer ring, but corneal copper deposition was suspected. Laboratory data showed elevated hepatobiliary enzymes and decreased levels of albumin and platelets. She

was negative for hepatitis C virus (HCV) antibody, hepatitis B (HB) s antigen, and HBc antibody as well as for antinuclear antibody and anti-mitochondrial M2 antibody. Her fibrosis 4 (FIB4) index was high at 6.52. Ferritin 199 ng/mL and fasting blood insulin 4.6 μ U/mL were normal, but type IV collagen 7S was high at 12 ng/mL, and her NAFIC score was 1 point. Furthermore, her serum copper (30 μ g/dL) and serum ceruloplasmin (8 mg/dL) levels were decreased, and her urinary copper excretion was increased (166 μ g/day) (Table).

Abdominal ultrasonography (US) revealed multiple intrahepatic diffuse small nodules (Fig. 1). Abdominal contrast-enhanced computed tomography showed chronic liver damage and splenomegaly. Magnetic resonance imaging of the head showed no basal ganglia abnormalities.

A percutaneous liver biopsy was conducted, and the biopsy specimen showed liver steatosis, cell loss due to inflammation, and precirrhotic fibrosis (Fig. 2). Rhodanine staining was positive, and the degree of copper deposition varied depending on the site. The copper content in liver tissue was as high as 1,452 μ g/dry-g. Genetic testing was performed by direct sequencing of all exons and exon-intron junctions (7). A genetic analysis of exons 1 to 21 of the ATP7B gene revealed her to be a complex heterozygote of c.2868delC1 (p.Pro957ProfsX9) and c.4007T>C (p.Ile1336Thr). Both mutations had been reported in Japanese patients with WD and had a high incidence among Japanese patients. Based on these findings, she was diagnosed with WD, and treatment with D-penicillamine, a cop-

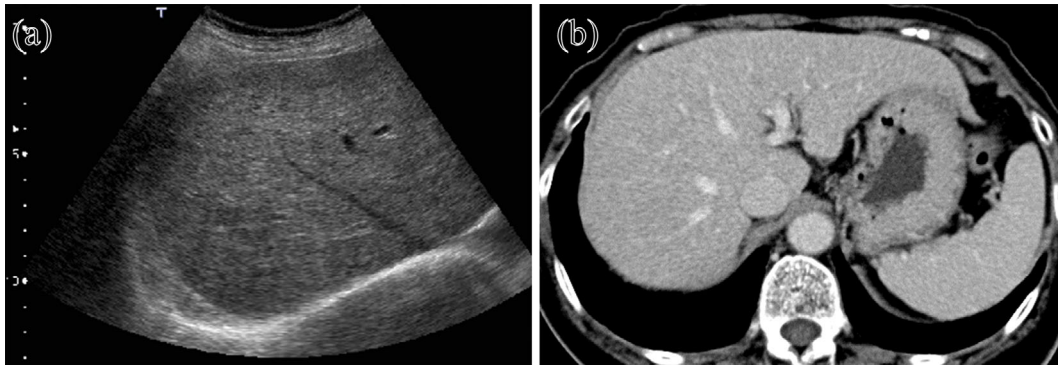


Figure 1. (a) Abdominal ultrasonography revealed an irregular liver surface, coarse liver parenchyma, and multiple intrahepatic diffuse small nodules. (b) Abdominal contrast-enhanced computed tomography showed chronic liver damage, mild left hepatic lobe swelling, and splenomegaly.

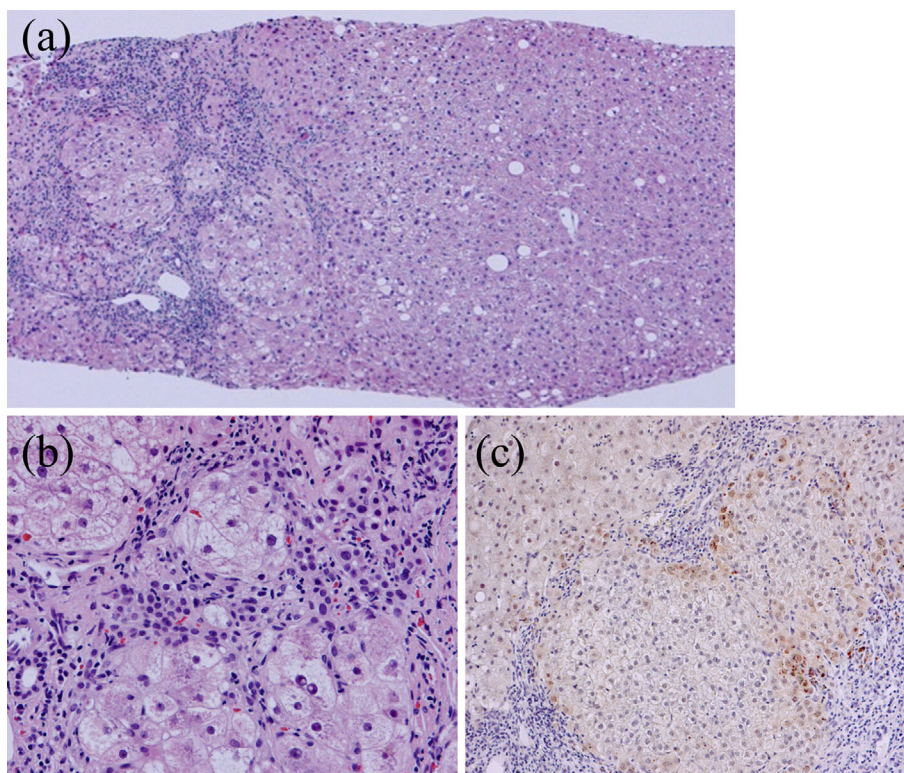


Figure 2. (a) Hematoxylin and Eosin (H&E) staining (×40) showed liver steatosis and pre-cirrhotic liver fibrosis. (b) H&E staining (×400) showed hepatocyte loss with inflammatory cell infiltration, hepatocyte ballooning, and Mallory-Denk body. (c) Rhodanine staining (×100) showed copper deposition in hepatocytes; the degree varied depending on the site.

per chelator, was initiated.

One month after administration of D-penicillamine, her liver function had improved from AST 78 to 68 U/L (13% decrease), ALT 63 to 32 U/L (49% decrease), and γ -GTP 269 to 146 U/L (45% decrease).

Discussion

The patient was diagnosed with fatty liver by US performed by a local family physician and was followed up. Although a histopathological examination was suggestive of

fatty liver, WD occasionally presents with variegations in liver imaging. Furthermore, in WD, there are no imaging findings specific to the liver, but abdominal US often reveals clusters of nodule-like echoes and fatty liver in the early stages (8).

The present patient had no neurological symptoms, and ophthalmologic findings were unclear. Therefore, differentiating pre-cirrhotic liver injury due to WD from NAFLD is difficult based on general examinations alone. The pathological findings of WD are diverse, with many nonspecific findings noted, often mimicking NAFLD. Because of the va-

riety of WD symptoms, a diagnosis is often delayed, with 1 report showing an average of 2 years from the symptom onset to the diagnosis and treatment (9). The initial diagnoses of patients with liver injury have included jaundice, portal hypertension, cirrhosis, infective hepatitis, and chronic liver disease. An early diagnosis and treatment can contribute to a good prognosis for WD patients. Since the number of patients with fatty liver disease has been increasing in recent years with the rise of obesity and lifestyle-related diseases, it is important for physicians to identify and suspect WD even among elderly patients.

Hepatic damage in WD is noted as early as approximately three years old (10). Neurologic manifestations usually begin after school age. Adult-onset WD is often accompanied by neurological symptoms. Late-onset WD has been reported in the 70- to 80-year-old population (6, 11, 12). The diagnostic features and frequency of late-onset WD gene mutations are no different from those in early disease-onset patients (5). Late-onset WD is a frequently overlooked condition, and WD should be considered in patients of all ages (13). Because of the broad clinical spectrum of WD, age alone should not be used as a basis for ruling it out.

The WD diagnosis is established by evaluating the typical symptoms, serum ceruloplasmin level, 24-hour urinary excretion of copper, and hepatic parenchymal copper levels as well as by conducting a mutation analysis of the ATP7B gene. Several diagnostic algorithms have been proposed (13, 14). Genetic testing for the ATP7B mutation is useful for confirming the WD diagnosis when biochemical tests are inconclusive. In addition, genetic testing is also useful for screening first-degree relatives of the index case as a measure to prevent the onset of cirrhosis and neurological symptoms through the prompt initiation of treatment while asymptomatic. Genetic variations in WD are diverse, and the association between genetic variation and an older onset age remains unclear. Although the genetic analysis of ATP7B does not predict the disease course, in Chinese patients, p.P992 L or p.N1270S was associated with presentation before 12 years old, and p.I1148T occurred almost exclusively in patients presenting from 12 years old (15). There are no firm genotype-phenotype correlations of WD (16). Aside from ATP7B mutations, epigenetic factors, environmental factors, global DNA hypomethylation, and the dietary intake of copper may also influence the etiology and clinical manifestations of WD (17, 18).

Treatment of WD consists of an initial treatment that induces the active excretion of the copper accumulated in the body and a maintenance treatment. The initial treatment should be selected according to the clinical symptoms and severity of WD at the time of the diagnosis, including a low-copper diet. Although there is no stringent consensus on how dietary copper should be strictly limited in WD, WD cannot be treated exclusively by dietary interventions (19). The recommended initial treatment of symptomatic or asymptomatic patients with active disease is the use of chelating agents, although zinc may be adequate for some

cases (20, 21). Its early detection and diagnosis are extremely important for ensuring a good prognosis.

Conclusion

We encountered a case of WD that was diagnosed at 73 years old after liver damage was discovered at 68 years old. It is important to obtain a family history in patients with NAFLD, especially those with hepatic disorders who have a family history of WD. These patients should undergo multiple medical examinations due the risk of WD development, regardless of their age.

The authors state that they have no Conflict of Interest (COI).

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