ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

# Dysregulation of Copper Metabolism in a Patient With Acute-on-Chronic Liver Failure Worked up for Fulminant Wilson Disease

Ethan Diamond, MD[1], Jacob Newman, DO[1], Reid Schalet, DO[1], Coen J. Lap, MD, PhD[1], and Ameer O. Abutaleb, MD, MS[1,2]

[1]*The George Washington University School of Medicine, Washington, DC*
[2]*The George Washington Transplant Institute, The George Washington University MFA, Washington, DC*

## ABSTRACT

Wilson disease (WD) is estimated present in 6%–12% of patients younger than 40 years hospitalized with acute liver failure (ALF). Fulminant WD carries a poor prognosis without treatment. A 36-year-old man with HIV, chronic hepatitis B virus, and alcohol use had ceruloplasmin 6.4 mg/dL and 24-hour urine copper 180 μg/L. WD workup was otherwise negative, including ophthalmic examination, hepatic copper quantification, ATP7B sequencing, and brain MRI. ALF commonly features copper dysregulation. Few studies on WD biomarkers have included fulminant WD. Our patient with WD biomarkers and other causes of liver failure highlights the need to study copper dysregulation in ALF.

**KEYWORDS:** acute-on-chronic liver failure; copper; Wilson disease

## INTRODUCTION

Wilson disease (WD) is due to a mutation in the *ATP7B* gene that prevents the biliary excretion of copper. This results in systemic copper deposition, commonly affecting the liver.[1,2] WD occurs in 1 in 30,000 individuals but is estimated present in 6%–12% of patients younger than 40 years hospitalized with acute liver failure (ALF).[1,3] Although patients may have cirrhosis at the onset of fulminant WD (FWD), FWD is classified as ALF.[4] FWD can quickly progress to hepatic and renal failure and carries 95% mortality if left untreated.[5,6]

WD should be considered in young patients in ALF or acute-on-chronic liver failure (ACLF). However, ALF/ACLF may cause aberrations in copper metabolism, complicating the diagnosis of FWD.[7] We present a patient with ALF from non-WD liver disease and evidence of copper dysregulation that met criteria for the diagnosis of WD by some guidelines but not others. His case highlights the need to study copper dysregulation in ALF and standardize criteria specific to diagnosing FWD.

## CASE REPORT

A 36-year-old man with a history of seizures, HIV (viral load undetectable), chronic hepatitis B virus, and alcohol use suffered a seizure and was brought by ambulance to an outside hospital. At the outside hospital, imaging showed gallbladder distension with wall thickening, hepatosplenomegaly, mild reversal of blood flow in the hepatic portal vein, and ascites. He was transferred to our hospital in a postictal state and intubated for airway protection. Vitals were pulse 101, blood pressure 136/87, respiratory rate 16 on 80% FiO2, and maximum temperature 36.5°C. Physical examination was notable for jaundice, hepatomegaly, and abdominal distension. Home medications were amlodipine, levetiracetam, bictegravir, emtricitabine, and tenofovir alafenamide. There was no surgical history. The patient's mother denied a family history of tremors, psychosis, or liver disease. His social history was significant for heavy alcohol use, documented on multiple encounters with emergency medical services, and marijuana use.

*ACG Case Rep J* 2023;10:e01084. doi:10.14309/crj.0000000000001084. Published online: July 7, 2023

**Correspondence:** Ethan Diamond, MD (ediamond@mfa.gwu.edu).

In the intensive care unit, the patient received 2 units of red blood cells for hemoglobin 6.4 g/dL and a heparin infusion for possible portal vein thrombosis. He was managed for ACLF (CLIF-C 56) and acute kidney injury (Cr 7.7 mg/dL), receiving N-acetylcysteine, lactulose, rifaximin, and octreotide and undergoing an extensive laboratory workup (Table 1). He never required dialysis. Ceruloplasmin (Cp) 6 mg/dL prompted a workup for FWD (Table 2). Ophthalmic examination was negative for Kayser-Fleischer rings and sunflower cataracts. Two 24-hour urine copper collections were >2× the upper limit of normal, and serum-bound copper was low. He underwent a transjugular liver biopsy on hospitalization day (HOD) 17. Portosystemic gradient was 15 mm Hg. Biopsy was negative for copper on rhodamine stain and showed patchy hepatocyte dropout with ballooned hepatocytes containing Mallory bodies. There was some bridging fibrosis but no definite cirrhosis. Quantitative hepatic copper was 18 mcg/g (Ref <50). Brain MRI showed an increased T1 signal within the bilateral globus pallidi, suggestive of chronic liver disease, but classic findings of WD were absent. Whole-exome sequencing was negative for pathogenic ATP7B variants.

**Table 1. ALF workup**

| | |
|---|---|
| Toxic | |
| Salicylates | <1.0 mg/dL |
| Acetaminophen | <10 mg/dL |
| Phosphatidylethanol (ref <250 ng/mL) | 45 μg/L |
| Infectious | |
| Anti-HAV, IgM | Nonreactive |
| HBeAg | Reactive |
| Anti-HBe | Nonreactive |
| HBV DNA quantification | <10 IU/mL |
| Anti-HCV | Nonreactive |
| HCV RNA quantification | Not detected |
| HDV RNA quantification | Not detected |
| HEV RNA quantification | Not detected |
| HIV viral load | 44 copies/mL |
| CD4 count | 568 cells/μL |
| EBV PCR | Not detected |
| CMV PCR | 371 IU/mL |
| HSV-1/2 PCR | Not detected |
| Parvovirus B19 PCR | Not detected |
| Leptospirosis Ab, IgM/IgG | Nonreactive |
| *Cryptococcus* serum antigen | Not detected |
| Autoimmune | |
| Antinuclear antibody | Not detected |
| Antimitochondrial antibody | Not detected |
| Anti–smooth muscle antibody | Not detected |
| IgG4 | 20 mg/dL |
| Genetic | |
| Alpha-1 antitrypsin | 171 mg/dL |
| Ferritin | 754 ng/mL |
| HFE gene | No pathogenic variants detected |
| Vascular | |
| Doppler US | No thrombotic venous disease |
| Neoplastic | |
| AFP | 2.31 IU/mL |
| Liver MRI | No focal abnormalities |

Ab, antibody; AFP, alpha fetoprotein; ALF, acute liver failure; CMV PCR, cytomegalovirus polymerase chain reaction; EBV PCR, Epstein-Barr virus polymerase chain reaction; HBeAg, hepatitis B envelope antigen; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HFE, hemachromatosis; IgM, immunoglobulin M; IgG, immunoglobulin G.

The patient was transferred to the floor on HOD 7 for decreasing oxygen requirement and improving mentation. His hospital course was complicated by acute pancreatitis and acalculous cholecystitis requiring a percutaneous cholecystostomy tube on HOD 13 (note: urine copper was obtained after percutaneous cholecystostomy). On HOD 28, the patient was deemed medically and psychosocially not suitable for transplantation. The patient's family decided to pursue home hospice care, and he died 2 months later.

## DISCUSSION

There are no standard guidelines for diagnosing FWD. The European Association for the Study of the Liver endorses Leipzig scoring for diagnosing WD, which considers family history, clinical features, and laboratory abnormalities.[1] Our patient's score, 3, suggested that WD was possible but could not be ruled in. At the time of our patient's presentation, the American Association for the Study of Liver Diseases (AASLD) diagnostic algorithm ruled out WD due to hepatic copper <50 μg/g.[8] By contrast, an algorithm inspired by both the AASLD and the European Association for the Study of the Liver criteria ruled our patient in by Cp and 24-hour urine copper excretion.[9] This algorithm resembled the latest AASLD recommendations for diagnosing WD, which were published after our patient's discharge.[10] By AASLD's current algorithm, we could have misdiagnosed WD without obtaining biopsy or ATP7B sequencing, although it is not validated for diagnosing FWD.[9,10] Ultimately, we feel that alcohol-related hepatitis is a more probable diagnosis given biopsy findings and AT7B sequencing.

Dysregulation of copper metabolism can occur in ALF or ACLF. The mechanism is likely due to the release of stored copper from necrotic hepatocytes and impaired liver synthetic activity.[11] Patients with ALF have trends of decreased Cp, elevated 24-hour urinary copper, and low or normal serum-bound copper.[12] Although there is no current diagnostic role of urinary copper levels in undifferentiated ALF, 3 small case series were notable for statistically significant increased 24-hour urine copper levels in patients with FWD compared with other ALF cases.[11–13]

Patients with ALF or ACLF may not be included in studies on WD biomarkers. A recent Cochrane meta-analysis on

**Table 2. Pertinent WD workup**

| | |
|---|---|
| Bilirubin | |
| Total | 21.2 mg/dL |
| Direct | 13.5 mg/dL |
| INR | 1.93 |
| AST | 175 U/L |
| ALT | 39 U/L |
| Alkaline phosphatase | 286 U/L |
| Ceruloplasmin (ref >20 mg/dL) | 6.4 mg/dL |
| Serum-bound copper (ref 69-132 mcg/dL) | 30 mcg/dL |
| Urine studies | |
| Urine copper, 24 h | 140, 192 μg/L |
| Cu/Cr ratio, 24 h | 181, 245 |
| Liver biopsy, rhodamine | Copper not detected |
| Liver biopsy, copper dry weight (ref <50 μg/g) | 18 μg/g |
| *ATP7B* gene whole-exome sequencing | No pathogenic variants detected |
| Ophthalmic examination | Negative for Kayser-Fleischer rings and sunflower cataracts |
| Brain MRI | Classical findings for WD were not observed |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio; WD, Wilson disease.

biomarkers of WD excluded studies including patients with FWD.[14] Research on the utility of directly measuring ATP7B peptides to diagnose WD is promising; however, to date, it has not specifically been studied in FWD and is limited by small sample sizes and predominantly White populations.[15] The ratio of serum exchangeable copper to total copper, relative exchangeable copper, set a threshold of relative exchangeable copper >18.5% is 100% sensitive for differentiating WD from asymptomatic patients and heterozygotes and WD from non-Wilsonian chronic liver disease.[16,17] However, neither study included patients with FWD or ALF. Blood copper isotope composition, the ratio of copper isotopes in blood, is altered in end-stage liver disease, early nonalcoholic fatty liver disease, and hepatocellular carcinoma.[7,18,19] It has been studied to prognosticate WD but not in FWD or ALF.[20]

Our case highlights the need for further research on copper dysregulation in ALF and ACLF. Although early treatment is vital for a good prognosis in FWD and FWD is relatively common in young patients with ALF/ACLF, little research on copper biomarkers in this setting hinders accurate diagnosis and prompt treatment.

## DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. E. Diamond is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received February 16, 2023; Accepted May 29, 2023

## REFERENCES


1. European Association for the Study of the Liver. EASL clinical practice guidelines: Wilson's disease. *J Hepatol.* 2012;56(3):671–85.
2. Ferenci P. Wilson's disease. *Clin Liver Dis.* 1998;2(1):31–49.
3. Sandahl TD, Laursen TL, Munk DE, Vilstrup H, Weiss KH, Ott P. The prevalence of Wilson's disease: An update. *Hepatology.* 2020;71(2):722–32.
4. European Association for the Study of the Liver. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. *J Hepatol.* 2017;66(5):1047–81.
5. Pan JJ, Fontana RJ. CAQ Corner: Acute liver failure management and liver transplantation. *Liver Transpl.* 2022;28(10):1664–73.
6. Schilsky ML. Liver transplantation for Wilson's disease. *Ann N Y Acad Sci.* 2014;1315(1):45–9.
7. Van Campenhout S, Hastuti AAMB, Lefere S, et al. Lighter serum copper isotopic composition in patients with early non-alcoholic fatty liver disease. *BMC Res Notes.* 2020;13(1):225.
8. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. *Hepatology.* 2008;47(6):2089–111.
9. Schilsky ML. Wilson disease: Treatment and prognosis. UpToDate, 2016. Disponível em (http://www. uptodate. com/home). Accessed October 26, 2022.
10. Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: Executive summary of the 2022 practice guidance on Wilson disease from the American Association for the Study of Liver Diseases. *Hepatology.* 2022;77(4):1428–55.
11. Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. *World J Gastroenterol.* 2007;13(11):1711–4.
12. McCullough AJ, Fleming CR, Thistle JL, et al. Diagnosis of Wilson's disease presenting as fulminant hepatic failure. *Gastroenterology.* 1983;84(1):161–7.
13. Sallie R, Katsiyiannakis L, Baldwin D, et al. Failure of simple biochemical indexes to reliably differentiate fulminant Wilson's disease from other causes of fulminant liver failure. *Hepatology.* 1992;16(5):1206–11.
14. Ryan A, Nevitt SJ, Tuohy O, Cook P. Biomarkers for diagnosis of Wilson's disease. *Cochrane Database Syst Rev.* 2019;2019(11):CD012267.
15. Collins CJ, Yi F, Dayuha R, et al. Direct measurement of ATP7B peptides is highly effective in the diagnosis of Wilson disease. *Gastroenterology.* 2021;160(7):2367–82.e1.
16. El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: A new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. *Clin Chim Acta.* 2011;412(23-24):2254–60.
17. Guillaud O, Brunet AS, Mallet I, et al. Relative exchangeable copper: A valuable tool for the diagnosis of Wilson disease. *Liver Int.* 2018;38(2):350–7.
18. Lauwens S, Costas-Rodríguez M, Van Vlierberghe H, Vanhaecke F. Cu isotopic signature in blood serum of liver transplant patients: A follow-up study. *Sci Rep.* 2016;6(1):30683.
19. Telouk P, Plissonnier M-L, Merle P, et al. Copper isotope evidence of oxidative stress–induced hepatic breakdown and the transition to hepatocellular carcinoma. *Gastro Hep Adv.* 2022;1(3):480–6; ISSN 2772-5723.
20. Lamboux A, Couchonnal-Bedoya E, Guillaud O, et al. The blood copper isotopic composition is a prognostic indicator of the hepatic injury in Wilson disease. *Metallomics.* 2020;12(11):1781–90.