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Case Report

Reversal of acute liver failure due to Wilson's disease in an adult without liver transplant: role of intravenous albumin and plasmapheresis

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Abstract.

Wilson's Disease is a recessively inherited autosomal disease related to mutations in the ATP7B gene caused by the accumulation of excess copper in the body, particularly in the liver, brain, and kidney. The clinical profile of hepatic manifestations may vary from asymptomatic biochemical abnormalities and steatosis to acute hepatitis, acute liver failure, chronic hepatitis, and cirrhosis. We present the case of a 20-year-old woman presented to the emergency room with a five-day history of right upper quadrant discomfort and weakness who was diagnosed with acute liver failure due to Wilson's Disease. We discuss the role of intravenous albumin and plasmapheresis on the reversal of acute liver failure due to Wilson's disease.

KEYWORDS: Wilson Disease; albumins; plasmapheresis; acute liver failure

Introduction

Wilson's Disease (WD) is a recessively inherited autosomal disease related to mutations in the ATP7B gene caused by the accumulation of excess copper in the body, particularly in the liver, brain, and kidney. It especially affects children and young adults, but it can occur before three and after 40 years of age[1]. The clinical profile of hepatic manifestations may vary from asymptomatic biochemical abnormalities and steatosis to acute hepatitis, acute liver failure, chronic hepatitis, and cirrhosis. Acute liver failure (ALF) is commonly associated with Coombs-negative hemolytic anemia, an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio greater than 2, normal or subnormal alkaline phosphatase (ALP) with an ALP to total bilirubin ratio typically less than 4, coagulopathy that is unresponsive to vitamin K, encephalopathy, and acute kidney injury[2]. Diagnosis is based on a combination of clinical and laboratory parameters, including the presence of Kayser-Fleischer rings, neurologic symptoms or magnetic resonance imaging findings, serum ceruloplasmin levels, 24-hour urinary copper, coombs-negative hemolytic anemia, total liver copper levels in liver histology, and the presence of genetic mutation[3]. Although clinical treatment can keep many patients stable and with the disease under control, severe cases of acute liver failure usually require liver transplantation[2].

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Case Report

A 20-year-old woman was presented to the emergency room with a five-day history of right upper quadrant discomfort and weakness. Two days prior to admission, she developed jaundice and coluria. She denied any prior comorbidities and reported drinking 1.5 L of beer fortnightly. She used levonorgestrel 0.15mg + ethinylestradiol 0.03mg as a contraceptive method and reported no family history of liver disease. Upon physical examination, she was jaundiced and pale; the abdomen was flat, painless upon palpation, and without visceromegaly or ascites. No signs of hepatic encephalopathy were initially present.

Laboratory tests upon admission showed a total bilirubin of 16.3 mg/dL; direct bilirubin 12.7 mg/dL; aspartate aminotransferase 198 U/l; alanine aminotransferase 34 U/l; gamma-glutamyltransferase 371 U/l; alkaline phosphatase 29 U/l; serum albumin 2.6 g/dL; international normalized ratio 2.12; creatinine 1.5 mg/dL; and serology for viral hepatitis, antinuclear antibodies, and anti-liver kidney microsome type 1 were negative. Smooth muscle antibody was positive at a low titer (1:40). Laboratory data also suggested a Coombs-negative hemolytic anemia, with a hemoglobin of 9.6 g/dL, a corrected reticulocyte count of 3.67%, high lactate dehydrogenase (732 U/l), and normal haptoglobin levels (<7.4 mg/dL). Doppler ultrasound of the abdomen of hepatic vessels was normal and an abdominal computed tomography revealed mild ascites, diffuse gallbladder wall thickening, and periportal edema. No signs of biliary obstruction or vascular liver disease were observed.

Additional specific investigations revealed a low ceruloplasmin level < 6.2 g/L (reference value 20-60 mg/dL); serum copper of 79.6 mcg/

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dL (reference value 80-155 pcg/dL); calculated serum free copper of 60.07 mcg/dL (normal up to 15); and urinary copper of 2533.5 micrograms/24h. Ophthalmological evaluation did not show Kayser-Fleischer rings. The diagnosis of acute WD was made based on the Leipzig diagnostic criteria of 5 (diagnosis established with values ≥ 4)[4] and on additional suggested features such as the presence of Coombs-negative hemolytic anemia, an ALP to total bilirubin ratio lower than 4, and the AST to ALT ratio higher than 2.2.

On the fourth day of hospitalization, the patient progressed to hypoglycemia, grade III hepatic encephalopathy, worsening of INR and bilirubin, oliguria, and stage 1 acute kidney injury (AKI), (creatinine of 1.99 mg/dL). At this point, the New Wilson's Index for predicting survival was 19 (values ≥ 11 indicate lower probability of survival)[3]. Due to the acute liver failure secondary to Wilson's disease, the patient was listed for liver transplantation. Albumin infusion was started at a dose of 1 mg/kg/day for the treatment of AKI and for its copper binding properties. Because of the renal impairment, D-penicillamine was not initially administered. After two days, the patient kept oscillating between grades 2 and 3 of hepatic encephalopathy, kidney function remained stable, and hemolysis parameters improved. Plasmapheresis was initiated and resulted in AKI reversion after two sessions. Given this initial improvement, treatment with D-penicillamine was started at 250 mg/day and the patient was removed from the transplant list. Over the following days, a significant improvement was seen in liver tests, hemolysis parameters, and mental status. After 10 days, plasmapheresis was discontinued and the D-penicillamine dose progressively increased. The patient was discharged after 35 days since admission and is currently undergoing follow-up treatment at our outpatient clinic without any signs of advanced liver disease, presenting normal liver tests and good tolerance to D-penicillamine 1000 mg/day.

Discussion

ALF, or fulminant hepatitis, is characterized by an acute liver injury that progresses to hepatic encephalopathy and prolonged prothrombin time. It is a condition associated with high mortality rates, even though the prognosis can be variable depending on the etiology of the liver injury. ALF may be the initial presentation of WD or occur in patients already diagnosed but who abandoned therapy, and it is more frequently seen in young females[3,5]. Although liver transplantation is typically considered the most effective treatment in ALF due to WD, case reports have shown that some strategies, such as albumin dialysis[6], plasmapheresis[7-12], and molecular adsorbent recirculating system therapy[12], can be used as an alternative or a bridge to transplantation. However, these therapies are complex and may not be readily available.

Copper is strongly bound to ceruloplasmin; circulating copper is also loosely bound and transported by albumin. This small blood pool constitutes the so-called free copper in healthy subjects and is greatly elevated in patients with fulminant Wilson disease. Kreymann et al.[6] hypothesised that this pool of free copper—the pathogenetic factor of fulminant Wilson disease—could be removed by albumin dialysis and that the detoxification function of the liver would be supported by the same method. They used this effective method of copper elimination as a bridge to liver transplantation. In our case, albumin infusion was attempted as a bridge to more effective therapy—plasmapheresis—and liver transplantation was avoided. The 5 – 10% of the total copper ions in the blood that is bound to serum albumin protein is generally considered as being the mode of transport of this metal. That is, its function is the delivery of copper ions to specific organs and tissues where the copper is incorporated into intracellular enzymes. After ingestion, copper—mainly in the form of copper-albumin—is rapidly transported via the portal bloodstream to the liver1[4]. A kinetically-inhibiting effect of albumin upon Cu uptake by liver cells in vitro has been noted1[5]. This albumin-copper fraction may be a storage form of the metal, as the large pool of albumin may work as a buffer to complex any increased metal levels[14], and this theory may justify the use of intravenous albumin as a bridging treatment in cases of acute liver failure.

Plasmapheresis removes ceruloplasmin, or albumin-bound copper, and may help prevent hemolysis and renal failure[16]. It also allows a large quantity of fresh frozen plasma to be transferred into the patient's body as a replacement fluid that can effectively restore the shortage of plasma albumin and coagulation factors. In contrast, this treatment requires a large quantity of fresh plasma and may lead to a possible although rare occurrence of allergic response, hypocalcemia, metabolic acidosis, and transfusion transmitted infection[8]. Although plasmapheresis is indicated as a Category I treatment for fulminant Wilson Disease by the American Society for Apheresis (ASFA) Issue 201, this recommendation is based on low-quality evidence (Grade 1C)[17]. There are only a few case reports describing the effect of plasmapheresis in patients with Wilson Disease and acute liver failure—mostly in children[7-11]. The chelating agents D-penicillamine and trientine have been used to promote renal copper excretion in stable Wilson's disease patients, as substantial copper removal is not achieved for at least one to three months; nonetheless the benefit for patients with acute liver failure is uncertain. D-penicillamine has been used in association with plasmapheresis in the acute setting with successful outcomes[11]. However, despite therapeutic efforts, the mortality rate in patients with ALF due to WD approaches 100% without emergent liver transplant[10]. In conclusion, prompt recognition of WD as the cause of ALF may permit the initiation of therapies that can serve as a bridge to—or even avoid—liver transplantation. We hypothesize that albumin infusion is a safe and widely available therapy that can be rapidly adopted to promote an initial stabilization, facilitating the employment of more effective strategies such as plasmapheresis and D-penicillamine. This stepwise approach may avoid liver transplantation or at least serve as a bridge, allowing the procedure to be performed under more favorable conditions.

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