A Case of Fulminant Wilson's Disease Complicated with Citrate Toxicity

Mey Talip Petmezci[1], Hasan Serdar Kıhtır[1], Osman Yeşilbaş[1], Elida Yüksel[2], Seda Balkaya[1], Zerrin Önal[2], Esra Şevketoğlu[1]

[1]Pediatric Intensive Care Unit, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey
[2]Clinic of Pediatric, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

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Abstract

When Wilson's disease is accompanied with severe acute liver failure, it is named as fulminant Wilson's disease, which is a life-threatening condition. With the widespread use of rapid diagnostic facilities and therapeutic plasma exchange for preperation to transplantation as well as the appropriate use of similar bridge treatments, mortality rate can be lowered. A 14-year-old female patient presented with hemolytic anemia. Based on the preliminary diagnosis, her indirect hyperbilirubinemia was treated with plasmapheresis until she was definitely diagnosed with Wilson's disease; she soon died due to severe hemorrhagic complications. We are presenting our case to highlight that bridge therapies may be unsuccessful because of rapidly developing clinical manifestations despite plasmapheresis;and as well to remind that transfusions may cause citrate toxicity as in this patient.

Key words: Wilson's disease, acute liver failure, plasma exchange, hemolytic anemia
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Introduction

Wilson's disease (WD) is an autosomal recessive genetic disorder that courses with copper accumulation in the liver, brain, and other organs. Although the clinical picture is variable, liver disease and cirrhosis, neuropsychiatric disorders, Kayser-Fleischer Ring in the cornea, and acute hemolytic anemia frequently associated with acute liver failure (ALF) are the important characteristics of WD (1). Cases with acute liver failure are called fulminant Wilson's disease (FWD) and have high mortality. Although plasma exchange and chelation treatments can provide temporary recovery, curative therapy is the liver transplantation (LT) (2). Citrate is used as a preservative for anticoagulation in blood products. It is known that toxicity may develop due to citrate metabolism disorder in liver failure. In this article, we present a 14-year-old female patient with FWD who was followed up with ALF in our pediatric intensive care unit (PICU) due to with a fatal course developing citrate toxicity (CT) despite the therapeutic plasma exchange (TPE) treatment.

Case Report

A 14-year-old female patient was admitted to the pediatric emergency department with the complaints of intermittent abdominal pain for the last 20 days, vomiting for three days, yellow discolouration of the body and darkening of the urine color which had started the day before. In the first evaluation of the patient, she was conscious, her general condition was weak, and her vital signs were within the normal ranges according to her age [body temperature axillary 37°C, heart rate (HR): 80/min, blood pressure (BP):115/70 mmHg, SpO_2: 98%]. The patient was admitted to the pediatric ward for further examination upon determining anemia (Hb:8.7 g/dL), elevated liver enzymes [aspartate aminotransferase (AST)] 124 U/L, alanine aminotransferase (ALT) 35 IU/L, gamma glutamyl transferase (GGT) 313 U/L, bilirubin (total/direct bilirubin 16.4/12.5 mg/dL), lactate dehydrogenase (LDH) (444 U/L), and prolonged prothrombin time (PT:20 sec) and international normalized ratio (INR:1.67), and normal activated partial thromboplastin time (aPTT:35 sec) in the laboratory examinations. She had general weakness and paleness within 24 hours following the admission and the control laboratory tests revealed; severe anemia (Hb:5.8 g/dl), significant increase in bilirubin (Total/direct bilirubin 34/25 mg/dL), prolongation of PT and INR (22.4 sec INR:1,84) unresponsive to fresh frozen plasma (FFP) and the administration of vitamin K, so the patient was admitted to PICU with the initial diagnosis of ALF and hemolytic anemia. The patient had a poor general condition, was pale and icteric, conscious, and the Glasgow coma score (GCS) was determined to be 13. In the evaluation of peripheral blood smear, findings consistent with extravascular hemolysis was observed with no blasts. While the liver size and contours were observed to be normal and its echogenicity was observed to be heterogeneous in the abdominal ultrasonography, no abnormality was observed in the intra- and extrahepatic biliary tract. Minimal fluid was present around the gallbladder as well as a large number of lymphadenopathies up

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Address for Correspondence: Dr. Mey Talip Petmezci, e.mail: meytalip@gmail.com
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to two-centimeter (cm) in diameter around the liver-pancreas-aorta. WD was suspected due to Coombs negative hemolytic anemia with a high level of bilirubin, prolonged PT, and low alkaline phosphatase level and the copper level in 24-hour urine was sent. The Kayser-Fleischer ring was not observed in the patient's eye examination. Despite the fresh frozen plasma infusions and vitamin K replacement it was decided to perform TPE with FFP to the patient considering the persistent prolongation of PT (24 sec) and INR (2.1) and rapidly progressing clinical course. The single-volume plasma dose (2000 cc) required for the therapeutic plasma exchange was calculated with the formula of 0.065 x weight x (1-hematocrit). On the first day, the TPE procedure was applied with 1.5 volume and on the other days with one volume. No anticoagulation was used during the procedure, and the procedure was completed within 4 hours (Prismaflex®, TPE 2000 filter, Gambro Lundia AB, Sweden). While no significant improvement was observed in the clinical findings and laboratory results of the patient to whom therapeutic plasma exchange was applied, the platelet count which was normal (173x103/mm^3) at the time of hospitalization decreased within days. The thoracic and abdominal computed tomography examinations were performed upon observing blunted sinuses on the chest x-ray of the patient developing tenderness and defense in the abdomen along with respiratory distress on the third day of the hospitalization. Hemorrhage was suspected in the patient when fluid in the pleural and peritoneal spaces were detected, because of the thrombocytopenia (37x103/mm^3) and PT and INR values (25 sec/2) that did not normalize despite TPE. Defibrinated blood was aspirated from the patient who underwent diagnostic thoracentesis and paracentesis. The patient, whose general condition worsened and respiratory distress increased, was intubated and followed under the mechanical ventilation.

The patient, whose abdominal distension increased remarkably and Hb level decreased to 5.6 g/dL, was transfused erythrocyte suspensions (6 units) aiming an Hb level above 7 gr/dL and TPE was performed with FFP (9 units).

Citrate toxicity (CT) and lactic acidos were considered in the patient due to frequent erythrocyte transfusions and TPE with FFP with the development of deep metabolic acidosis with high anion gap (pH:6,96 HCO_3:5.4 meq / L), increased lactate 16 mmol/L, low ionized calcium level (0.6 mmol/L) and high total calcium (10.9 mg/dL).Therefore TPD treatment was not repeated from the fourth day. Fresh frozen plasma infusions were continued at standard doses.

Continuous venovenous hemodiafiltration (CVVHDF) was initiated in the patient, who was observed to have renal dysfunction (urine output <0.5 mL/kg/hour) along with deep metabolic acidosis and CT and was receiving inotropic support (adrenaline 1 mcg/kg/min, noradrenaline 0.5 mcg/kg/min, dopamine 10 mcg/kg/min) due to hypotension (BP:76/34 mmHg, HR:100/min). On the fifth day of the hospitalization, the patient died after a cardiac arrest despite the improvement in metabolic acidosis (pH:7.12 HCO_3:10) and regression in CT findings (ionized calcium:1.0 mmol/L, total calcium:9.8 mg/dL). Antinuclear antibody (ANA) positivity ceruloplasmin:9.11 mg/dL (20.9-46.2 mg/dL), haptoglobin:<7.44 mg/dL (30-200 mg/dL), serum copper:126 ug/dL (normal: 70-150 ug/dL), and 24-hour urine copper:2387 ug (normal:0-40) were determined in the examinations after the loss of the patient. Other tests for hepatitis serology were negative. The patient was accepted to have WD, and the family members were directed to the genetic and gastroenterology outpatient clinics. The patient's consent could not be obtained because our case report was written retrospectively and the patient was lost.

Discussion

Wilson's disease is a rare genetic disorder that causes copper accumulation and toxicity in the organs due to an enzyme disorder in the biliary tract where copper is excreted. Fulminant hepatic failure develops in only 5% of the cases (3). It has been reported in the literature that Wilson's disease-related fulminant hepatic failure can be accompanied by acute renal failure and severe hemolytic anemia with rapid clinical deterioration (4). Although our patient presented with ALF and hemolytic anemia, renal failure was subsequently added to the clinical picture.

If WD is suspected in acute liver failure, the diagnosis must be quickly confirmed because of poor prognosis. The presence of low serum ceruloplasmin (<0.1 g/L) together with the Kayser-Fleischer ring is considered to be sufficient for the diagnosis. The Kayser-Fleischer ring may not be observed when Wilson's disease occurs with the involvement of the liver, and it is known that low ceruloplasmin level is not significant for the diagnosis, and ceruloplasmin level can also be determined to be low in cases such as autoimmune hepatitis, severe liver failure, celiac disease, and genetic aceruloplasminemia (5). The examinations of our patient sent for WD resulted after the loss of the patient, and the Kayser-Fleischer ring was not observed during the eye examination. However, the rapid progression of hemolytic anemia and ALF, low ALP/total bilirubin ratio, and high AST/ALT ratio in the case followed up with the pre-diagnosis of hepatitis caused us to think that WD was in the forefront. The liver biopsy could not be performed because of the coagulation disorder that could not be corrected and thrombocytopenia.

The plasma exchange cleans the plasma from large molecule weighted matters such as autoantibodies, immunoglobulins, immunocomplexes, and at the same time, anticoagulation with heparin or citrate is required to be used to achieve extravascular fluidity of the blood. Although allergic reactions, hypotension, electrolyte abnormalities, and catheter-associated complications are common, CT rates are very low in the studies (6).

Citrate solutions are used for anticoagulation in blood bank products. The most commonly used formulation is Acid-Citrate-Dextrose A (ACD-A). The citrate contents of commercial solutions are variable, and ACD-A contains 3% citrate (citrate 112 mmol/L or 21.3 mg/mL). Upon examining the blood products, the citrate content of FFP is two to three times higher than that of erythrocyte suspension (7). The citrate content of FFP is approximately 20 mmol/L (8).

The most common side effect due to citrate is hypocalcemia. Ionized calcium deficiency can lead to neurological symptoms, myocardial dysfunction, and life-threatening conditions such as hypotension and arrhythmia. In the apheresis procedure,the ST risk rises due to the use of plasma as a replacement fluid and continue on repeated days (7).

While it is known that citrate metabolism may be insufficient in patients with hepatic failure, citrate toxicity is not reported frequently except in cases with severe hepatic failure (9). It is known that in liver failure cases, CT can develop even with citrate-containing plasma solutions used in the TPE procedure; however, in our case, metabolic acidosis with the increased anion gap was not observed in follow-up after TPE. On the third day of hospitalization, severe metabolic acidosis with the increased anion gap, ionized calcium deficiency, and total calcium elevation, which developed after erythrocyte suspensions and FFP transfusions performed for anemia, clearly demonstrate CT. Since infection markers were negative, hypotension and lactate elevation suggested us myocardial dysfunction. In our case, after the

standard FFP and erythrocyte suspensions transfusions performed following the deterioration on the third day of hospitalization, the total calcium was determined to be 10.6 mg/dL (2.6 mmol/L), and ionized calcium was determined to be 0.56 mmol/L. CVVHDF was preferred in our patient with the high total/ionized calcium ratio and metabolic acidosis with the increased anion gap (85 mmol/L), and an improvement was observed in acidosis (pH from 6.8 to 7.25) and anion gap (24.4 mmol/L) within 24 hours after the treatment. The plasma citrate concentration depends on the infusion rate, citrate metabolism, and urinary excretion. There is literature stating that CT may develop in patients with renal insufficiency due to the rapid infusion of FFP even if citrate is not used as anticoagulation (10). Although we have not used citrate anticoagulation in our patient, we think that the CT development has occurred due to the rapid transfusion of multiple blood products, TPE, and underlying liver failure.

Liver transplantation (LT) is the ultimate treatment of FWD, and it takes time to find suitable donors. The aim of chelation, TPE, and hemodialysis treatments is to support the deteriorated liver functions and lead to rapid reduction of elevated serum copper. Thus, the direct toxicity of free copper to erythrocytes is prevented, hemolysis is reduced, coagulation failure is fixed, and time is gained for the preparation for LT (4). The diagnostic laboratory tests for WD are not routinely performed in many centers in our country, so samples must be sent to other hospitals. This can cause critically ill patients not to be given priority and result in delays in diagnosis. Our patient's 24-hour urine copper and ceruloplasmin levels were studied at a different center, and the results could only be obtained after the loss of the patient although communication was established with the laboratory regarding the patient's urgency. For these reasons, it is necessary to communicate with the related centers to prioritise the results of the patients with suspected FWD.

When a patient is diagnosed with WD, the evaluation of family members is also required (11). Thus, in asymptomatic patients, treatment can be started with early diagnosis. In the family scan of our patient, WD diagnosis was confirmed in the patient's 16-year-old brother, and the chelation therapy was started.

Conclusion

In cases where TPE is used for ALF regardless of the reason, the citrate load should be closely monitored, and the renal replacement therapy should be started without delay when needed. Considering that the clinic may progress very rapidly in cases suspected of Wilson's disease, we believe that laboratory examinations should be organized quickly and early and that preparations for LT should be initiated in the earliest period.

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