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CASE REPORT

Life Saving Plasmapheresis for the Management of Hemolytic Crisis and Acute Liver Failure in Wilson's Disease

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Wilson's disease, caused by a deficient cellular copper export system, is transmitted as an autosomal recessive inherited disorder and results in copper accumulation in liver and other organs, particularly in brain. Acute hepatic failure and severe Coombs' negative hemolysis may occur in the course of the disease which has a poor prognosis and most patients do not survive the crisis. Only liver transplantation has been recommended as an effective medical intervention. Herein, we presented a 25-year-old woman with impaired consciousness, acute hepatic failure and hemolysis who was treated with plasmapheresis and albumin replacement. Beside improvement in medical condition, serum copper and hemolysis decreased significantly and renal function was preserved. We concluded that plasmapheresis may be a life saving intervention during fulminant hepatic failure of Wilson's disease.

Keywords: **Wilson's disease, Plasmapheresis, Acute Hepatic Failure, Hemolysis**

Introduction

Wilson's disease, an autosomal recessive disorder due to mutation in ATP7B, results in copper accumulation in liver and subsequent liver injury which is attributable to copper oxidizing effect [(1)]. Most clinical manifestations are caused by toxic effects of copper in various organs, particularly in brain and liver [(2)].

Acute hepatic failure scarcely happens and gives rise to necrosis and copper release into the serum [(3)]. Acute renal failure and severe hemolysis as the consequences of hypercupremia are seen during the course of acute hepatic failure [(4)]. The prognosis is poor and most of the patients die of the condition despite an intensive medical care. The only potential approach for saving such patients is liver transplantation [(5, 6)], but, it is usually not readily accessible in such situations.

Though seeking medical interventions to provide sufficient time until finding an appropriate liver donor, seems logical, recently, extraction of circulating copper by plasmapheresis has been suggested to play a role in establishing a better prognosis. Herein, we presented a female patient

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with Wilson's disease with acute liver failure and hemolysis, who was treated successfully with plasmapheresis.

Case report

A 25-year-old married female was admitted to the emergency room due to impaired consciousness in January 2009. The diagnosis of Wilson's disease had been made at the age of nine, according to the laboratory studies and liver biopsy during the workup for jaundice. At that time, treatment with penicillamin (1 g/day) had been initiated for a period of two years after which time the patient withdrawn drug consumption without any consultation to her physician. Up to five months before, she was relatively well. Then, she gradually became aggressive and depressed which finally resulted in committing suicide. At that point, penicillamin was reinitiated. After two months of drug consumption, she developed pancytopenia. Administration of penicillamin was therefore stopped and bone marrow aspiration and biopsy were performed which revealed erythroid hyperplasia.

About three to four days before, her aggression and agitation turned out to be more severe and gradually her level of consciousness dropped. At the time of admission to the emergency room, her orientation to time, place and person was impaired and other signs such as dysarthria and incontinency were evident. Kayser-Fleischer ring rimming the cornea was visible with naked eye (Fig. 1). Furthermore, she had an icteric sclera, nasal speech, resting tremor, rigidity, spasticity and palpable spleen three cm below the costal margin. She had no signs of petechia, purpura, ascitis, abdominal distension, tenderness or muscle weakness. Laboratory findings revealed Coombs' negative hemolytic anemia, hepatic dysfunction and slightly elevated liver enzymes, a serum copper level of 185 (normal range:70–140) g/dL and a serum ceruloplasmin level of 12 (normal range: 25–63) mg/dL. Table 1 demonstrates the results of the initial laboratory studies.

Considering the high serum copper, low ceruloplasmin, presence of Kayser-Fleischer ring and previous records of the patient, the diagnosis of Wilson's disease was established and the patient was transferred to the intensive care unit. Due to unavailability of rapid liver transplantation, plasmapheresis was initiated to decline the excessive copper load and prevent hemolytic anemia. A total of five plasmapheresis courses were carried out each with 2.5 liters of fresh frozen plasma to retain coagulation factors and albumin replacement (20 g in each course). During the five-day period of plasmapheresis, no adverse reactions were observed. Thereafter, serum copper and liver enzymes levels declined markedly (Fig. 2). Moreover, the serum LDH and total bilirubin were also decreased after the treatment (Table 2); the hemoglobin level was maintained at about 8.0 g/dL with no need to further transfusions during the hospitalization.

Thirty-six hours after the initiation of plasmapheresis, encephalopathy recovered gradually and no renal failure occurred in the course of her disease. Due to severe hepatic failure and cirrhosis, the patient was then introduced for urgent liver transplantation.

Discussion

Acute or fulminant liver failure can be the first manifestation of Wilson's disease or may occur later in the course of the illness. Most cases of Wilson fulminant hepatitis are seen among children and young adolescents and are accompanied with hemolytic anemia as a result of circulatory free copper ions. This condition, which is usually manifested by hemoglobinuria and renal failure, accounts as one of the indications for urgent liver transplantation [7]. The final outcome in patients who received transplantation has been shown to be acceptable with

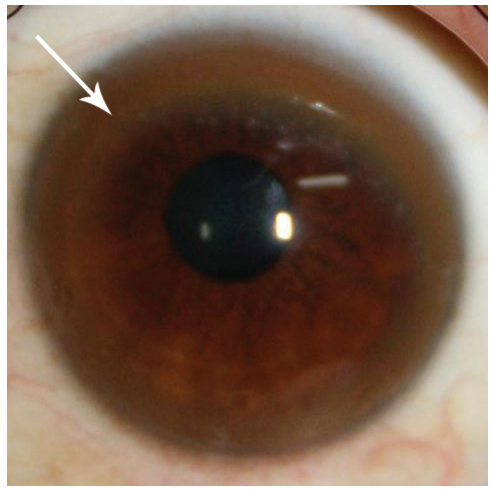

Figure 1. Kayser-Fleischer ring. During physical examination, Kayser-Fleischer ring rimming the cornea was visible with naked eye (the white arrow). This finding was confirmed by an ophthalmologist after the patient was discharged from the hospital.

a one-year-survival of about 79% [8] but appropriate donor is barely accessible and efforts should have been made in order to save the patients until receiving the transplant because of fatal nature of the crisis and ineffectiveness of medical therapy [5, 6].

Aminotransferase enzymes are usually slightly elevated in Wilson's disease with higher AST levels compared to ALT and these changes exhibit weak correlation with the extent of hepatic damage [5, 9]. The same pattern was seen in our patient with trivial elevation of the enzymes (AST>ALT). In more than 35% of patients, neuropsychiatric manifestations are present [10]; those include a wide range such as resting tremor, rigidity, nasal speech, and dysphasia which are mostly found in patients with H1069Q mutation in ATP7B gene [10]. Personality alteration, paranoia and depression have also been reported in 10% of the patients [11, 12]. As mentioned above, dysphasia, rigidity, nasal speech and agitative depression were found in our patient resulting in severe social and familial troubles.

Copper toxicity on erythrocytes is not well understood but changes that caused by copper in enzymatic pathways of red blood cells and its oxidative effect are possible explanations [13]. Anemia, elevated LDH and indirect hyperbilirubinemia in this patient were suggesting hemolytic anemia but low reticulocyte count (1.7%) was not in agreement with the diagnosis. Nonetheless, in those with iron and folate deficiency and bone marrow suppression, hemolysis can be seen in the absence of sufficient bone marrow response, though this discrepancy might be explained with previous history of pancytopenia and bone marrow suppression possibly due to consumption of penicillamin.

Treatment of fulminant Wilson hepatitis by plasma exchange, has been reported with diverse outcomes. Most studies could not express any relationship between copper ion removal from circulation and any clinical outcome [14, 15]. In 1998, plasmapheresis was reported to be effective for rapid reduction of elevated serum copper levels in two patients. More recently, plasmapheresis has been shown to be markedly effective in some cases. Although it is not of established efficacy, and in some cases it did not result in better outcome [14], there are reports that plasmapheresis, when initiated in case of severe hemolytic anemia and acute decompensation of hepatic failure, may change the final outcome and save patient's life [16-18]. In these reports, plasmapheresis, when initiated early in the phase of hemolytic anemia and fulminant hepatitis, reduced circulatory copper, bilirubin, liver enzymes and further hemolysis. These changes in addition to

Table 1. Initial laboratory survey performed after admission to the emergency room.

Lab Data	Admission day	Normal Range
White blood cells	6500	3.54-9.06 × 10^3/mm^3
Hemoglobin	12.6	12.0-15.8 g/dL
Platelets	87000	165-415 × 10^3/mm^3
Hematocrit	36.5%	35.4%-44.4%
Mean corpuscular volume (MCV)	69	79-93.3 fL
Partial thromboplastin time (PTT)	40	26.3-39.4 s
Prothrombin time (PT)	22	12.7-15.4 s
International normalized ratio (INR)	2.5	
BUN	24	7-20 mg/dL
Creatinine	0.8	0.5-1.9 mg/dL
Aspartate transaminase (AST)	92	12-38 U/L
Alanine transaminase (ALT)	39	7-41 U/L
Alkaline phosphatase (ALP)	222	33-96 U/L
Total bilirubin	9	0.3-1.3 mg/dL
Direct bilirubin	1.1	0.1-0.4 mg/dL
Lactate dehydrogenase (LDH)	1001	115-221 U/L
Creatin phosphokinase (CPK)	143	39-238 U/L
Total serum protein	2.5	6.7-8.6 g/dL
Albumin	2	4.0-5.0 g/L
Calcium	7.1	8.7-10.2 mg/dL
Phosphorus	3.7	2.5-4.3 mg/dL
Na	133	136-146 meq/L
K	3.9	3.5-5.0 meq/L
Direct Coombs test	Negative	
Indirect Coombs test	Negative	
Reticulocyte count	1.7%	
Arterial blood gas		
pH	7.45	7.36-7.44
PCO_2	34.4	32-45 mmHg
[HCO_3-]	24.5	24 ±2 mEq/L
PO_2	75	72-104 mmHg
O_2 Saturation	94	94-100%

PTT: partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; LDH: lactate dehydrogenase; CPK: creatin phosphokinase.

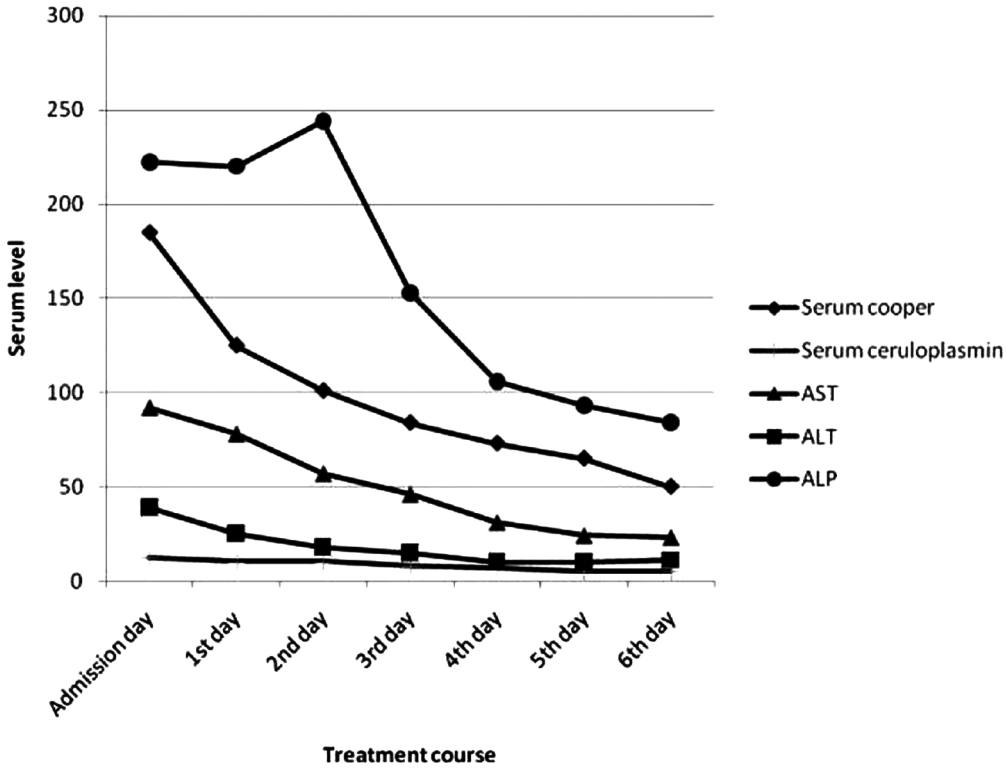

Figure 2. Serum copper, ceruloplasmin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) before and during plasmapheresis. All measures decreased markedly after five courses of plasma exchange with fresh frozen plasma.

Table 2. Changes in laboratory data in response to plasmapheresis in the course of treatment.

Lab Data	Admission day	1st day	2nd day	3rd day	4th day	5th day	6th day
White blood cells	6500	7400	7500	3600	2300	2700	2800
Hemoglobin	10.6	9.4	8.2	8	8.4	8.6	8.5
Platelets	87000	97000	90000	69000	69000	55000	72000
Hematocrit	30.5	27.5	24.9	24.2	25.5	26.1	25.9
PTT	40	31	25	30	34	32	34
PT	22	15.5	29.5	16.5	25.7	24	25.7
INR	2.5	3.1	4.2	3.5	3.3	3.1	3.3
Urea	24	34	35	29	26	28	27
Creatinine	0.8	1	1.1	1	0.9	0.8	0.8
Total bilirubin	9	-	5.9	-	3.4	-	-
Direct bilirubin	1.1	-	1	-	1	-	-
LDH	1001	-	824	-	406	-	-
CPK	143	-	103	-	52	-	-

improvement of clinical picture were thought to be related to rapid plasma exchange. Other than plasmapheresis, single pass albumin dialysis has been used for rapid copper removal in some cases [19]. But, this has been followed by extra plasmapheresis sessions for a complete response. Conclusively, it seems that copper removal is a critical and common point in all these reports despite of possible differences. Likewise, in the our patient, the plasmapheresis obviously improved the patient's clinical manifestation so that within only 36 hours after initiation of plasma exchange, patient's orientation was restored completely. Additionally, renal function due to sufficient hydration and urine alkalization along with rapid plasma exchange was preserved and there was no need for dialysis. These results may provide the sufficient ethical explanation to perform a study about the role of plasmapheresis in patients with end-stage Wilson's disease with acute decompensation of hepatic failure and hemolytic crisis for whom liver transplantation is not available.

Conclusions

The current report points toward a possible role for rapid plasma exchange in fulminant hepatitis in order to remove excessive free circulatory copper in patients with Wilson's disease and may provide sufficient time to plan for an appropriate liver transplantation.

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