Diagnosis and management of fulminant Wilson's disease: a single center's experience

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Background: **Medical therapy is rarely effective in patients with fulminant Wilson's disease (FWD). Liver transplantation is limited by the lack of donor liver in most patients with FWD at the time of diagnosis. New Wilson's index, model for end-stage liver disease (MELD) and Child-Pugh score are useful tools for decision-making of liver transplantation; however, none of them is an independent decisive tool. It is worthwhile to explore a more effective and practical therapeutic strategy and reevaluate the prediction systems for patients with FWD.**

Methods: **Nine patients with FWD associated with hemolytic crisis and fulminant hepatic failure (FHF) were investigated. The clinical presentation, prognostic score and medical therapies of the patients were analyzed.**

Results: **In 7 of the 9 patients with FWD who received the comprehensive therapy of corticosteroid, copper-chelating agent (dimercaptopropansulfonate sodium) and therapeutic plasma exchange (TPE), 6 patients recovered from FHF. The remaining one had been improved through the comprehensive therapy but died of septicemia 51 days later. Two patients with spontaneous bacterial peritonitis (SBP) died from liver failure in three or five hospital days without plasma exchange or chelating therapy. All of the 9 patients with FWD presented with acute hepatic failure, severe jaundice and mild to severe hemolytic anemia. No marked difference in the incidence of severe hemolytic anemia was detected between the survival and deceased groups. However, the incidence and the degree of hepatic encephalopathy (HE) in the non-survival group were higher than those in the survival group. Unlike the deceased group, the survival group had no complications induced by bacterial infection. Compared to new Wilson's index, Child-Pugh score and MELD score, the variation of prothrombin activity (PTA) between the survival and deceased groups was more evident.**

Conclusions: **For patients with FWD, the episode of severe hepatic encephalopathy or/and spontaneous bacterial peritonitis indicates worse prognosis, and PTA is a recommendable predictor. An emergent liver transplantation should be considered for patients whose PTA is below 20%, or for those with severe HE or/and SBP. The comprehensive therapy of corticosteroid, copper-chelating agent and TPE is effective for patients without SBP and whose PTA is higher than 20%.**

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Original article

Introduction

Wilson's disease (WD) is an inherited metabolic disorder caused by mutations in the copper transporting enzyme P-type ATPase gene.[1-3] WD is characterized by the accumulation of copper in the liver, brain, kidney and corneas, leading to hepatic or neurologic manifestations in the majority of patients.[2] A minority of patients develop fulminant hepatic failure (FHF) accompanied by a hemolytic crisis,[1,3] resulting in death within 1 or 2 weeks if a liver transplantation is not performed.[4] It has been reported that orthotopic liver transplantation is essential for a favorable outcome in patients with fulminant Wilson's disease (FWD).[5-8] However, it is limited by the lack of donor liver and an emergency liver transplantation cannot be performed in most cases at the time of diagnosis. Rapid and exact diagnosis by means of clinical, biochemical and genetic analysis and the immediate use of drug therapy with copper chelators are important for a favorable outcome in patients with FWD. However, medical therapy is rarely effective in patients presenting with acute liver

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failure resulted from WD, mainly due to the time required to remove toxic copper from the patients. It is worthwhile to explore a more effective therapeutic strategy for these patients.

Several prediction systems for FWD and liver transplantation decision-making have been developed. New Wilson's index,[9] Child-Pugh score and model for end-stage liver disease (MELD) score are useful tools for liver transplantation decision-making. A score of new Wilson's index greater than 11 is always fatal without liver transplantation.[10] Patients with a Child-Pugh score of ≥7, which places the patients in Child-Pugh class B or C, should be on the liver transplant waiting list. Cirrhotic patients who have experienced gastrointestinal bleeding caused by portal hypertension or a single episode of spontaneous bacterial peritonitis (SBP) would meet the minimal liver transplant criteria irrespective of their Child-Pugh score. Furthermore, patients with fulminant hepatic failure regardless of etiology of the onset of stage 2 hepatic encephalopathy meet the minimal criteria for liver transplant.[11] Patients with a higher MELD and higher Child-Pugh score are at greater risk of death without liver transplantation.[12,13]

In this study, an optimized comprehensive treatment including corticosteroid, copper-chelating agent (dimercaptopropansulfonate sodium, DMPS) administration and therapeutic plasma exchange (TPE) exerted positive effects on some patients with FWD whose prognosis had been unfavorably judged by the prediction systems for FWD and liver transplantation decision-making. It is reasonable to reevaluate the prediction systems and the therapeutic strategy for patients with FWD, especially in the case of donor liver shortage and an emergency liver transplantation cannot be performed.

Methods

The 9 patients with FWD who had been treated at the Second Xiangya Hospital of Central South University, Changsha between 2006 and 2013 were analyzed retrospectively. The diagnosis of WD was based on varied combinations of clinical and laboratory evidence of liver disease, presence of Kayser-Fleisher rings, low serum ceruloplasmin levels and elevated 24-hour urinary copper excretion. None of the patients presented with any neurologic symptoms. Diagnosed with FWD, all patients were subjected to negative serological analysis for hepatitis A-E (except for 1 patient with concurrent infection of hepatitis E), cytomegalovirus, herpes simplex virus, varizella zoster virus, Ebstein-Barr virus, and screening for autoantibodies and ferritin.

Results

The 9 patients with FWD were divided into two groups, a survival group and a deceased group, according to the outcome of treatment. The age of the survival group (3 males and 3 females) varied from 7 to 22 years, and that of the deceased group (1 male and 2 females) ranged from 11 to 21 years. None of the survival group was associated with bacterial infection. All the patients in the deceased group were associated with SBP. Moreover, one of them died from *Escherichia coli* septicemia. The incidence and degree of hepatic encephalopathy and ascites in the deceased group were higher than those of the survival group. The prothrombin activity (PTA) of the survival group was higher than 20%, whereas that of the deceased group was below 20%. New Wilson's index, Child-Pugh score and MELD score of the survival group varied from 10 to 15, 9 to 13, 26.9 to 31.1, respectively, whereas those of the deceased group ranged from 15 to 16, 14 to 15 and 27.8 to 53.5, respectively (Table 1). The difference of new Wilson's index and Child-Pugh score between the two groups was statistically different (*P* value=0.042, 0.003, respectively), but not very significant. However,

Table 1. Clinical presentation, prognostic score and outcome of patients with FWD

Case	Sex	Age	Ascites	HE	K-F ring	PTA (%)	New WI	Child-Pugh score	MELD score	Outcome	Follow up time (mon)
1*	M	7	Mild	I	+	41.8	13	11	27.1	Recovery	54
2	M	8	Moderate	I	+	32.4	15	13	30.6	Recovery	34
3	F	13	None	None	+	46.3	12	9	28.7	Recovery	44
4	F	16	None	None	+	25.8	11	11	31.1	Recovery	18
5	F	17	None	II	+	33.3	14	10	28.2	Recovery	6
6†	M	22	None	None	+	63.6	10	9	26.9	Recovery	18
7	M	11	Severe	IV	+	19.4	16	15	27.8	Died from liver failure	
8	F	15	Severe	II	+	18.4	15	14	34.5	Died from E. coli septicemia	
9‡	F	21	Severe	IV	+	12.2	15	15	53.5	Died from liver failure	

FWD: fulminant Wilson's disease; HE: hepatic encephalopathy; New WI: new Wilson's index; K-F ring: Kayser-Fleischer ring; PTA: prothrombin activity; MELD: model for end-stage liver disease; M: male; F: female; E. coli: *Escherichia coli*. *: liver biopsy was performed on case 1 when his liver function improved; †: case 6 combined with the infection of hepatitis E; ‡: necropsy was performed on case 9 two days after her death; +: positive.

there was no significant difference in MELD score between the two groups (Table 2). The 9 patients were associated with mild to severe hemolytic anemia. There was no marked difference in the incidence of severe hemolytic anemia between the two groups. To improve their anemia, concentrated red blood cells were infused to the patients with a hemoglobin level below 80 g/L (4 patients in the survival group and 3 in the deceased group). The basal urinary copper excretion of the two groups elevated similarly and the urinary copper excretion after decoppering treatment with DMPS increased markedly (Table 3). There was no significant difference in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) and total bilirubin (TBIL) between the two groups (Table 4). However, the patient co-infected by hepatitis E had a more elevated serum ALT level (patient 6).

Seven patients underwent the driving copper treatment (DMPS from 500 mg to 750 mg, infused intravenously, once per day for 5 days as a course of treatment followed by an interval of 2 days, 4-6 courses totally) combined with plasma exchange and a short-term methylprednisolone (40 mg infused intravenously once per day for 3-5 days)/dexamethasone (10 mg infused intravenously once per day for 3-5 days) administration. Adverse reaction of DMPS including fever and allergic dermatitis occurred in two patients (patients 6 and 8). D-penicillamine was used in these patients alternatively. At the first hospitalization, patient 8 was subjected to 5-day methylprednisolone administration and 2 times of plasma exchanges. Her total bilirubin level decreased from 521.7 to 277.6 μmol/L. However, her prothrombin time (PT) increased from 38.9 to 56.2 seconds. This patient was admitted

Table 2. Comparative analysis of prognostic score between the survival group and deceased group (Student's *t* test)

Group	Age	PTA	New Wilson's index	Child-Pugh score	MELD score
Survival	13.8±5.7	40.5±13.4	12.5±1.9	10.5±1.5	28.8±1.8
Non-survival	15.7±5.0	16.7±3.9	15.3±0.6	14.7±0.6	38.6±13.3
P-value	0.653	0.022	0.042	0.003	0.329

PTA: prothrombin activity; MELD: model for end-stage liver disease.

Table 3. Routine analysis of blood and parameters of copper metabolism of patients with FWD

Case	WBC ($\times10^9$/L)	Hb (g/L)	PLT ($\times10^9$/L)	CER (mg/L)	Basal UCE (μg/d)	UCE following DMPS (μg/d)
1	15.8	64	237	62.5	2787	6126
2	13.5	36	216	68.7	8549	15 362
3	12.5	49	176	97.2	1760	5216
4	6.0	91	57	141.0	2726	5908
5	14.6	63	151	128.0	3803	12 020
6	5.6	86	110	195.0	1777	4132
7	21.0	64	51	122.0	3438	13 585
8	12.8	67	87	153.0	3124	9831
9	29.3	71	32	20.6	2101	6074
RR	4-10	110-165	100-300	210-530	0-100	0-1500

FWD: fulminant Wilson's disease; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; CER: ceruloplasmin; UCE: urinary copper excretion; DMPS: dimercaptopropansulfonate sodium; RR: reference range.

Table 4. Biochemical tests of patients with FWD

Case	ALT (U/L)	AST (U/L)	AST/ ALT	ALB (g/L)	TBIL (μmol/L)	DBIL (μmol/L)	TBA (mmol/L)	TBA/ TBIL	ALP (U/L)	GGT (U/L)	BUN (mmol/L)	CRE (μmol/L)	PT (sec)	INR
1	28.8	95.5	3.3	32.2	883.4	584.4	64.0	0.072	46.1	74.4	5.4	66.6	21.8	2.13
2	16.7	234.2	14.0	29.6	610.0	423.9	46.7	0.077	19.8	87.8	15.7	81.3	25.7	2.79
3	13.8	124.0	9.0	27.3	865.9	582.5	64.0	0.074	6.3	173.7	24.3	105.0	20.5	1.68
4	55.0	112.5	2.1	27.9	533.4	399.0	144.2	0.270	54.8	104.1	2.8	84.4	30.1	2.95
5	42.0	161.0	3.8	30.5	829.4	658.1	101.8	0.123	2.0	104.0	3.1	82.8	25.2	1.99
6	158.3	217.6	1.4	29.4	944.5	634.8	96.1	0.102	55.4	66.8	4.2	103.3	17.2	1.41
7	22.4	154.9	6.9	25.7	610.7	299.0	64.1	0.105	19.4	38.6	3.1	50.6	37.2	3.25
8	21.2	114.5	5.4	21.9	521.7	344.1	131.0	0.251	13.2	110.9	2.0	84.0	38.9	4.04
9	24.5	140.9	5.8	28.9	1247.7	681.4	71.2	0.057	45.1	72.3	40.1	348.5	54.3	4.87

FWD: fulminant Wilson's disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; TBA: total bile acid; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; BUN: blood urea nitrogen; CRE: creatinine; PT: prothrombin time; INR: international normalized ratio.

to our hospital again 48 days later, complaining of fever and severe jaundice. Physical examination of the patient showed confusion and signs of peritonitis. She died from *Escherichia coli* septicemia 3 days later. The other 6 patients received the comprehensive therapy of corticosteroid, copper-chelating agent and therapeutic plasma exchange and they had improvement of FHF. Combined therapy of oral penicillamine and zinc was prescribed after their hospitalization. A follow-up for 6 to 54 months showed that they recovered from FHF. Hepatic function test revealed a mild increase of serum enzymology and the normal levels of serum albumin, total bilirubin and PT. Two patients associated with SBP and died from liver failure in 3 or 5 hospital days respectively without plasma exchange or DMSP administration (patient 7 and 9). Autopsy performed for patient 9 with informed consent from her parents 2 days after her death showed cirrhosis of the liver. Liver biopsy for patient 1 when his liver function improved showed cirrhosis too. Computed tomography scan of a patient with FWD revealed the liver with diffused nodules and splenomegaly, which indicated cirrhosis (patient 5).

Discussion

Most patients with FWD present with acute or subacute hepatic failure at the time of liver cirrhosis. It has been recommended that cirrhotic patients who experienced a single episode of SBP or the onset of stage 2 hepatic encephalopathy meet the minimal criteria for liver transplant.[11] In our study, the complications of hepatic encephalopathy and ascites were more serious in the deceased group than in the survival group. The abdominal bacterial infection of the decreased group was considered as the major cause for their massive asites and to be responsible for their progressive deterioration of liver function and worse outcomes. However, none of the patients in the survival group experienced bacterial infection. Obviously, the bacterial infection played a crucial role in the prognosis of the patients with FWD. The patients with severe hepatic encephalopathy and SBP had an aggressive clinical course and displayed a poor response to the medical treatment in the present study. The severe encephalopathy and occurrence of SBP might be taken as the predictors of ominous outcome of FWD. It was also recommended that more attention should be paid to the preventive and therapeutic measures of bacterial infection in such patients.

In the fulminant stage of FWD, damaged hepatocytes spill free copper into the circulation. The free copper inhibits red blood cell glycolytic enzymes, thus leading to oxidative stress and damage to erythrocyte membranes.[14] Red blood cell destruction results in a direct hemolytic anemia, which may progress to acute renal failure if the patient is left untreated.[15,16] Some patients with FWD presented with hemolytic anemia and renal insufficiency. The two groups experienced severe hemolysis, which suggested that their prognosis was irrelevant to hemolysis. Partly owing to the jaundice caused by hemolysis, the patients with FWD presented with a lower total bile acid/TBIL ratio than the patients with severe viral hepatitis or post-hepatitic cirrhosis.[17] Low serum alkaline phosphatase (ALP) and ALT levels are frequently observed in patients with FWD. All of the patients with FWD presented with a normal ALP level in the present study. Interestingly, only one patient who had been infected by hepatitis E presented with an elevated ALT level, whereas the remaining patients were associated with a normal ALT level and presented with an AST/ALT ratio higher than 2.0. No significant difference was noted in serum ALT, ALB, TBIL levels or in the amount of urinary copper between the deceased and survival groups. However, the PTA of the deceased group was markedly lower than that of the survival group, whereas the difference in new Wilson's index, Child-Pugh score and MELD score was not so significant between the two groups, indicating that PTA might be a good prognostic factor for those patients with FWD and severe jaundice.

WD presenting with fulminant hepatitis type is a life-threatening condition, for which liver transplantation is the ultimate treatment.[18,19] Liver transplantation seems to be one of the best therapies for FWD.[20] However, donor organs for liver transplantation are not always readily available. It has been reported that plasma exchange, continuous hemodiafiltration, the molecular adsorbents recirculating system, single pass albumin dialysis and prometheus system are effective for patients in the period up to liver transplantation or for patients where a transplant is impossible.[21-27] Treatment for patients with FWD requires a rapid decrease in serum copper levels, otherwise excess copper causes direct toxic injury to red blood cells. In addition, it is known that renal insufficiency is combined with WD. Kiss et al[28] reported that copper was removed effectively from two patients with FWD after the therapy of plasma exchange. The net copper removal of the treatment was proportional to the serum level. Matsumura et al[29] also reported that 2300 μg of copper was removed by the first plasma exchange in patients with FWD. DMPS is a water-soluble chelating agent that can be given orally or systemically and has been used to treat metal intoxication. DMPS can effectively mobilize copper to urine and decrease the copper concentrations of the kidneys,

liver and brain. DMPS and its disulfide metabolites are eliminated primarily by the kidneys. The copper displacement efficiency of intravenous DMPS was higher than that of oral penicillamine for patients with WD.[30] In our patients, the amount of copper removed by DMPS administration was about 1.8 to 4 folds of the patients' basal urinary copper excretion, ranging from 4132 μg/day to 15 362 μg/day. Efficiently removing serum copper could decrease hemolysis, prevent progression of renal failure,[1,10] and provide clinical stabilization. TPE could correct coagulopathy in patients with FHF and remove hepatotoxins or cytokines. This improvement was transient but could be used as a bridge until an organ was identified for liver transplantation or the liver itself regenerated.[31] The rapid removal of copper and the improvement of liver failure were achieved after the therapy of plasma exchange and DMPS administration. It was observed that, for those patients with microscopic hematury, the amount of erythrocytes in urine decreased when methylprednisolone was prescribed. Moreover, serum TBIL and lactate dehydrogenase levels decreased in these patients during TPE and administration of methylprednisolone and DMPS. These findings indicated that the comprehensive therapy could prevent further damage of copper to the liver and kidney as well as red blood cells in patients with FWD.

In conclusion, we reported 9 patients with FWD complicated with hemolytic anemia, who displayed different outcome mainly due to the variable degree of liver failure and complications. TPE, decoppering treatment with DMPS, and a short-term corticosteroid administration were performed in 7 patients. Copper was effectively removed and liver failure was improved by this therapy and an emergency liver transplantation was avoided in 6 patients. This therapy is safe and effective for patients with FWD whose PTA is higher than 20%. The need for liver transplantation for these patients should be evaluated carefully as their prognosis is not necessarily fatal.[32] However, patients with FWD whose PTA is below 20% and/or who are accompanied with bacterial infection and sever hepatic encephalopathy present with ominous outcomes. Early recognition of these with dismal prognosis may permit timely use of liver replacement/supportive therapies. An emergent liver transplantation should be considered for this kind of patients to improve their prognosis.[11,33] Nevertheless, our study is somewhat limited by the small number of patients and by the very small group of patients who died of FWD. Further clinical studies are needed to explore the therapeutic strategy for patients with FHF secondary to WD.

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References

1 Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology 2008;47:2089-2111.
2 Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet 2007;369:397-408.
3 Schilsky ML. Wilson disease: genetic basis of copper toxicity and natural history. Semin Liver Dis 1996;16:83-95.
4 Markiewicz-Kijewska M, Szymczak M, Ismail H, Prokurat S, Teisseyre J, Socha P, et al. Liver transplantation for fulminant Wilson's disease in children. Ann Transplant 2008;13:28-31.
5 Sutcliffe RP, Maguire DD, Muiesan P, Dhawan A, Mieli-Vergani G, O'Grady JG, et al. Liver transplantation for Wilson's disease: long-term results and quality-of-life assessment. Transplantation 2003;75:1003-1006.
6 Medici V, Mirante VG, Fassati LR, Pompili M, Forti D, Del Gaudio M, et al. Liver transplantation for Wilson's disease: the burden of neurological and psychiatric disorders. Liver Transpl 2005;11:1056-1063.
7 Sevmis S, Karakayali H, Aliosmanoglu I, Yilmaz U, Ozcay F, Torgay A, et al. Liver transplantation for Wilson's disease. Transplant Proc 2008;40:228-230.
8 Ohya Y, Okajima H, Honda M, Hayashida S, Suda H, Matsumoto S, et al. Re-evaluation of the indications for liver transplantation in Wilson's disease based on the outcomes of patients referred to a transplant center. Pediatr Transplant 2013;17:369-373.
9 Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl 2005;11:441-448.
10 European Association for Study of Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol 2012;56:671-685.
11 Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg 1997;3:628-637.
12 Yamashiki N, Sugawara Y, Tamura S, Kaneko J, Nojiri K, Aoki T, et al. Model for end-stage liver disease and model for end-stage liver disease-Na scores predict both before-listing and wait-list mortality. Transplant Proc 2012;44:389-392.
13 Sharpton SR, Feng S, Hameed B, Yao F, Lai JC. Combined effects of recipient age and model for end-stage liver disease score on livertransplantation outcomes. Transplantation 2014;98:557-562.
14 Boulard M, Blume KG, Beutler E. The effect of copper on red cell enzyme activities. J Clin Invest 1972;51:459-461.
15 Forman SJ, Kumar KS, Redeker AG, Hochstein P. Hemolytic anemia in Wilson disease: clinical findings and biochemical

mechanisms. Am J Hematol 1980;9:269-275.
16 Hamlyn AN, Gollan JL, Douglas AP, Sherlock S. Fulminant Wilson's disease with haemolysis and renal failure: copper studies and assessment of dialysis regimens. Br Med J 1977;2:660-663.
17 Shlomai A, Halfon P, Goldiner I, Zelber-Sagi S, Halpern Z, Oren R, et al. Serum bile acid levels as a predictor for the severity of liver fibrosis in patients with chronic hepatitis C. J Viral Hepat 2013;20:95-102.
18 Cheng F, Li GQ, Zhang F, Li XC, Sun BC, Kong LB, et al. Outcomes of living-related liver transplantation for Wilson's disease: a single-center experience in China. Transplantation 2009;87:751-757.
19 Narumi S, Umehara M, Toyoki Y, Ishido K, Kudo D, Kimura N, et al. Liver transplantation for Wilson's disease in pediatric patients: decision making and timing. Transplant Proc 2012;44:478-480.
20 Bellary S, Hassanein T, Van Thiel DH. Liver transplantation for Wilson's disease. J Hepatol 1995;23:373-381.
21 Jhang JS, Schilsky ML, Lefkowitch JH, Schwartz J. Therapeutic plasmapheresis as a bridge to liver transplantation in fulminant Wilson disease. J Clin Apher 2007;22:10-14.
22 Chiu A, Tsoi NS, Fan ST. Use of the molecular adsorbents recirculating system as a treatment for acute decompensated Wilson disease. Liver Transpl 2008;14:1512-1516.
23 Collins KL, Roberts EA, Adeli K, Bohn D, Harvey EA. Single pass albumin dialysis (SPAD) in fulminant Wilsonian liver failure: a case report. Pediatr Nephrol 2008;23:1013-1016.
24 Rodríguez Fariña E, Tremosa Llurba G, Xiol Quingles X, Lores Obradors A, Castellote Alonso J, Gornals Soler JB, et al. D-penicillamine and plasmapheresis in acute liver failure secondary to Wilson's disease. Rev Esp Enferm Dig 2003;95:60-62, 63-65.
25 Nagata Y, Uto H, Hasuike S, Ido A, Hayashi K, Eto T, et al. Bridging use of plasma exchange and continuous hemodiafiltration before living donor liver transplantation in fulminant Wilson's disease. Intern Med 2003;42:967-970.
26 Morgan SM, Zantek ND. Therapeutic plasma exchange for fulminant hepatic failure secondary to Wilson's disease. J Clin Apher 2012;27:282-286.
27 Asfaha S, Almansori M, Qarni U, Gutfreund KS. Plasmapheresis for hemolytic crisis and impending acute liver failure in Wilson disease. J Clin Apher 2007;22:295-298.
28 Kiss JE, Berman D, Van Thiel D. Effective removal of copper by plasma exchange in fulminant Wilson's disease. Transfusion 1998;38:327-331.
29 Matsumura A, Hiraishi H, Terano A. Plasma exchange for hemolytic crisis in Wilson disease. Ann Intern Med 1999;131:866.
30 Xu SQ, Li XF, Zhu HY, Liu Y, Fang F, Chen L. Clinical efficacy and safety of chelation treatment with typical penicillamine in cross combinationwith DMPS repeatedly for Wilson's disease. J Huazhong Univ Sci Technolog Med Sci 2013;33:743-747.
31 Akdogan M, Camci C, Gurakar A, Gilcher R, Alamian S, Wright H, et al. The effect of total plasma exchange on fulminant hepatic failure. J Clin Apher 2006;21:96-99.
32 Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. World J Gastroenterol 2007;13:1711-1714.
33 Kasahara M, Sakamoto S, Horikawa R, Koji U, Mizuta K, Shinkai M, et al. Living donor liver transplantation for pediatric patients with metabolic disorders: the Japanese multicenter registry. Pediatr Transplant 2014;18:6-15.

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