Liver transplantation treats hepatic hereditary hemorrhagic telangiectasia in one case☆

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Abstract

BACKGROUND: Hepatic hereditary hemorrhagic telangiectasia (HHHT) is a rare disease, which can lead to life-threatening complications. Liver transplantation has been an only curative option; however, the therapeutic effect of liver transplantation in HHHT is rarely reported.

OBJECTIVE: To explore the therapeutic effect of liver transplantation in patients with HHHT.

METHODS: The clinical data of one 59-year-old female patient with HHHT, who had undergone orthotropic liver transplantation at the Institute of Liver Transplantation of General Hospital of Chinese People's Armed Police Forces, China was analyzed retrospectively. The period of follow-up was 8 months. Abdominal ultrasonography and liver function were observed after operation.

RESULTS AND CONCLUSION: This female patient had been in good health during 8-month follow-up after liver transplantation. She resumed family daily life. Liver transplantation can offer an effective therapy for patients with HHHT, and can provide satisfactory postoperative long-term results. Liver transplantation should be proposed earlier in the course of symptomatic HHHT presenting with life-threatening conditions. Palliative interventions, especially on the hepatic artery, should be avoided in view of their high (infectious) complication rate. However, the sample size was small with relatively short time follow-up. Thus, the long-term therapeutic effect still needs to be explored.

INTRODUCTION

Hepatic hereditary hemorrhagic telangiectasia (HHHT) is a rare, autosomal dominant disorder, which theoretically occurs in every organ and causes severe complications. Hepatic vascular malformations are described in about 73% of HHHT patients[1]. Only 5%–15% of cases are symptomatic. Liver transplantation in HHHT is not standardized. This study aims at a better definition of the value of liver transplantation for HHHT, based on a HHHT patient, in a broader attempt to provide a detailed review of the literatures on the controversial topic.

CASE REPORT

Case

A female patient aged 57 years.

Disease history

Repeated pains in right upper quadrant, debilitation, anorexia, progressive dyspnea were reported for recent 4 years. Melena and/or hematemesis were frequently visible, she had received blood transfusion often. The progressive symptoms prompted her to seek treatment in November 2010.

Physical examination

On admission, her general condition was poor. Physical examination revealed chronic sickly complexion, emaciation, cyanosis, mild jaundice, pleural effusion, telangiectasias on chest wall, and pitting edema in both lower extremities. Laboratory data revealed white blood cell count 3.0×10^9/L, hemoglobin 58 g/L, platelet 12×10^9/L, albumin 26.0 g/L, total bilirubin 59.3 μmol/L, direct bilirubuin 35.2 μmol/L, creatinine 77 μmol/L, blood ammonia 102 μmol/L, prothrombin time 13.2 seconds, prothrombin activity 67.7%, and international normalized ratio 1.18. Chest CT was normal, but abdominal CT scan revealed severe liver cirrhosis, hemangiomas of liver, intrahepatic vascular abnormality and displacement, multiple intrahepatic low-density nodes, embolus in initial segment of right portal vein branch, splenomegaly, varices, moderate ascites, dilation of hepatic artery, tumor-like dilation of vessel cluster in hepatic hilar region. Abdominal magnetic resonance imaging revealed intrahepatic hemangiomas and developmental anomaly in both shape and intrahepatic blood vessel. Chest X-photography showed enlarged heart shadow. Echocardiography noted a dilatation of ventricles, normal pulmonary arterial pressure and 62% ejection fraction. Ultrasound revealed enlargement of hepatic artery, and the hepatic resistive index was reduced. Gastroscopy revealed three severe varices extending to cardia of stomach with portal hypertensive

gastropathy. Visceral digital substraction angiography showed a bilateral diffusely hypervascular liver parenchyma in the capillary phase with early prominent hepatic venous filling. Hepatic function was classified as Child B in this patient.

Family pedigree analysis

There were eight HHHT patients in four generations: in the first generation, her grandmother died of upper gastrointestinal hemorrhage (UGIH) with HHHT at 59 years old; in the second generation, her mother and two uncles died of UGIH with HHHT at 59 years old, while her aunt was unaffected; in the third generation, her elder sister and elder brother died of UGIH under 60 years old, another elder brother was unaffected, elder sister died of cerebral hemorrhage with HHHT; in the fourth generation, the son of her elder sister's suffered from HHHT, both son and daughter of her elder brother's were not detected, her daughter was unaffected (Figure 1).

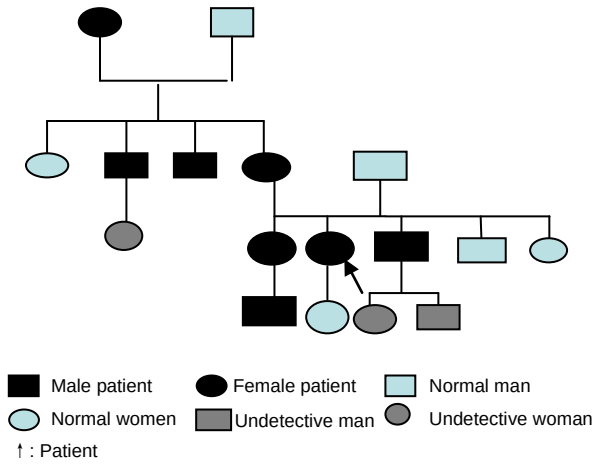

Figure 1 Family pedigree analysis

Orthotropic liver transplantation

Orthotropic liver transplantation was undertaken in this female patient with standard techniques without venovenous bypass on January 14th, 2011. There were about 100 mL ascites. The whole liver was obviously atrophic, but compensatory hyperplasia in the caudal lobe. The hepatic artery was dilated (diameter up to 0.9 cm). Splenomegaly and organized thrombus in portal vein were also found. Arterial anastomosis was fashioned in the recipient on the proper hepatic artery, on the origin of the common hepatic artery. The anastomoses of common bile duct and portal vein were done according to rule. The total operating time was 503 minutes, and the cold ischemic time was 362 minutes. Total blood loss was 2 000 mL during liver transplantation and blood transfusion of 17 U was necessary. The routinely immunosuppressive regimen after liver transplantation included tacrolimus, mycophenolate mofetil and methylprednisolone.

Pathological findings

The histopathological finding post-liver transplantation showed that, degenerative and necrotic hepatic cells can be observed. In portal area, there were mild inflammatory cells (mainly lymphocytes) infiltration and intraheapatic vascular hyperplasy that are short of endothelial cells (Figure 2). Immunohistochemical examination revealed negative hepatitis B surface antigen and hepatitis E surface antigen. The pathological diagnosis was HHHT.

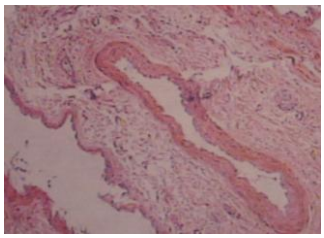

Figure 2 Histopathological findings of the patient post-liver transplantation (Hematoxylin-eosin staining, ×40)

DISCUSSION

So far liver transplantation regimen for treating HHHT has rarely been reported in China.

Etiology of HHHT

HHHT or Rendu-Osler-Weber disease is a genetic disease[2], has no racial and sex differences, and its estimated prevalence is one to two cases per 10 000[3]. The prevalence of HHHT increases with the age. The telangiectasia is the characteristic lesion in HHHT. HHHT is prone to pseudofibrosis[4], mainly leading to hepatic lesion and overloading in circulation system. With the wide application of ultrasound, CT and magnetic resonance imaging, intrahepatic vascular malformations have been described in up to 73% of patients[1], including hepatic arteriovenous shunt (type Ⅰ) and hepatic arterioportal shunt (type Ⅱ). Intrahepatic portovenous shunt (type Ⅲ) has more rarely been reported because it is more difficult to identify by CT scan. The intrahepatic shunt can induce portal hypertension, especially when the arteriovenous fistula. This hypertensive state can be further worsened by the remodeling of pseudocirrhosis due to ischemia-induced regenerative node-like formation and by the development of heart failure.

Clinical manifestations of HHHT

The clinical features of HHHT vary greatly with the number, type and site of vascular malformations. Garcia-Tsao *et al* [5] reported that symptom of HHHT appeared mainly in female patients and under 30 years

old. Most HHHT is asymptomatic and unspecific, but 8% of cases are symptomatic[4]. Three most common clinical features are high-output cardiac failure (HOCF), biliary ischemic disease, and portal hypertension[6]. HOCF is the most common clinical manifestation in HHHT, mainly in middle-aged female patient, characterized by dyspnea on exertion, orthopnea, ascites and edema. This female case had the symptom of HOCF. The paroxysmal HOCF occurred often. Portal hypertension is secondary to HOCF, mainly in 60-year-old patient, most resulting from intrahepatic shunt (type Ⅱ) or retrogressive and nodular hyperplasia, in which UGIH is more common. This patient had suffered from UGIH many times in the past. The symptoms of UGIH were more common when the hemoglobin level of this patient was more than 80 g/L. Biliary diseases are common in about 40-year-old female patient with HHHT, main symptom is abdominal pain. Recent research reported that dilation of intrahepatic and extrahepatic artery and increased blood flow rate are the main characteristics of HHHT. Ultrasonography in this female patient had the typical characteristics. CT revealed atrophy of the whole liver and compensative hyperplasia of caudal lobe in the case. CT angiography and digital subtraction angiography showed diffusive dilation of intrahepatic vessels. But arteriovenous fistula had not been found in the patient.

Diagnosis and differential diagnosis of HHHT

The diagnosis of HHHT is established according to the following criteria[7]: (1) spontaneous, recurrent epistaxis; (2) telangiectasia; (3) a positive family history; (4) visceral lesions. The diagnosis of HHHT is definite if three criteria are present, possible/suspected in the presence of two criteria, and unlikely if fewer than two criteria are recognized. Intrahepatic vascular malformations can lead to life-threatening complications, but they are often asymptomatic. Agiography is the gold standard of HHHT[4, 8], which can confirm the type of intrahepatic vascular malformations. It should be remembered that in patients with a suspected diagnosis of HHHT, liver biopsy should be avoided considering the high prevalence of liver vascular malformations because of probable intrahepatic vascular malformations. The differential diagnosis of HHHT includes (1) dilation of hepatic artery from liver cirrhosis and intrahepatic lump, in which the anatomic course of hepatic artery is normal; while HHHT, the dilation of hepatic artery is relatively slight; (2) portal vein cavernous transformation; (3) Budd-Chiari syndrome.

Treatment and prognosis of HHHT

Patients with asymptomatic HHHT should not receive any treatment[9], while the therapeutic options for symptomatic patients include treatment of the specific complication, symptomatic treatment and liver transplantation.

The symptomatic treatment aims directly at severe complications. HOCF is treated with conventional medical therapy. Bevacizumab in symptomatic HHHT patients is partially effective. Portal hypertension is managed according to present guidelines. Blood transfusions maintain a hemoglobin level of 80 g/L. Transjugular intrahepatic portosystemic shunt cannot effectively improve the symptom of UGIH because it can increase intrahepatic shunting volume and aggravate the hyperkinetic circulatory state. Cholangitis associated with biliary disease should be managed with antibiotics and analgesics; these patients should not undergo invasive imaging procedures which can trigger the development of ascending cholangitis. The placement of biliary bracket should be avoided in case of severe biliary complications.

According to the recent report, hepatic artery embolization and ligation had been successfully used to relieve the symptom of HOCF and portal hypertension with HHHT[10]. But its therapeutic efficacy is transient. So these two procedures are recommended to be performed as a preferred treatment while there are contraindications to liver transplantation[11]. But these two procedures should be avoided while severe cholangitis or cholecystitis occurred[12].

Liver transplantation is an only radically curative therapeutic tool. Although the optimal timing for listing HHHT patients is controversial, the main indications to liver transplantation should be the intractable HOCF, biliary necrosis after hepatic artery embolization or ligation, and portal hypertension not responding to conventional therapeutic procedures[13]. The model for end stage liver disease is currently used to manage the waiting list for liver transplantation[14]. It has recently been recommended that an additional score of 40 and 22 points in model for end stage liver disease, respectively, should be assigned to HHHT patients with acute biliary necrosis or intractable HOCF waiting for liver transplantation. With a high prevalence of pulmonary hypertension in HHHT, right heart characterization should always be performed in HHHT patients before liver transplantation; because of high perioperative mortality, liver transplantation should be performed in patients whose pulmonary vascular resistance less than 240 dynes s/cm^5 and who have no severe pulmonary hypertension[4]. Liver transplantation appeared to be somewhat technically challenging in HHHT patients, as exemplified by the elevated need for red blood cells during the operation or the prolonged hospital stay. With hepatic hypervascular characteristics, the surgical procedure of liver transplantation is very difficult. The perioperative mortality rate of liver transplantation varies from the complication of HHHT. The patients with HOCF benefit from liver transplantation greatly, with 7%

mortality rate. The second highest mortality in the patients with biliary ischemic disease is about 25%. The highest mortality rate is among the cases with portal hypertension. The mean follow-up period after liver transplantation was 69 months and seven patients (17.5%) died in the early post-operative period. Both cardiovascular function and Karnofski score are improved in the vast majority of cases[15]. For those patients with HHHT with pulmonary artery hypertension, liver transplantation should be undertaken conservatively because of high mortality rate (up to 50%). A reported a satisfactory survival rate (up to 90%) after liver transplantation[13]. Intra-abdominal hemorrhage, biliary leak and multiple organ failure are the common causes of death. It is notable that some reports have revealed a high recrudescence risk in HHHT through follow-up[16]. The hemodynamics of HHHT can be remarkably relieved after liver transplantation[17-18]. After 8-month follow-up of the female case in this study, her chemical examination and abdominal ultrasonography are satisfactory, and her symptom of pre-liver transplantation disappears completely.

With the application of non-invasive diagnostic techniques, the liver has been discovered to be the visceral target organ involved in HHHT[19]. Fortunately, most HHHT patients are asymptomatic. For symptomatic patient with HHHT, medication should be used at first, hepatic artery embolization or ligation is a secondary choice for these patients without severe biliary ischemic complications. Liver transplantation is strongly recommended to be performed especially before severe pulmonary artery hypertension.

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肝移植治疗肝脏遗传性出血性毛细血管扩张症 1 例☆

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文章亮点：

分析 1 例肝脏遗传性出血性毛细血管扩张症女性 59 岁患者行肝移植的临床资料，患者肝移植 8 个月后，身体状况良好，提示肝移植对肝脏遗传性出血性毛细血管扩张症的治疗有效。

摘要

背景：肝脏遗传性出血性毛细血管扩张症是一种少见病，可引起多种威胁生命的并发症。肝移植是惟一根治性选择，但有关肝移植治疗肝脏遗传性出血性毛细血管扩张症的疗效罕有报道。

目的：探讨肝移植对肝脏遗传性出血性毛细血管扩张症的疗效。

方法：回顾性分析了中国武警总医院肝移植研究所 1 例肝脏遗传性出血性毛细血管扩张症女性 59 岁患者行肝移植的临床资料，患者肝移植后共随访 8 个月，对肝移植后 8 个月内的肝功能和腹部超声进行严密观察。

结果与结论：患者肝移植后身体状况良好。肝移植对肝脏遗传性出血性毛细血管扩张症的治疗有效，对其长期生存效果满意，且应在该疾病出现威胁生命的症状前进行肝移植。尽量避免对肝脏遗传性出血性毛细血管扩张症进行姑息性介入治疗，尤其是对肝动脉的介入治疗措施，因为姑息性介入治疗可能增加其并发症发生率，但远期疗效有待于进一步评估。

关键词：遗传性出血性毛细血管扩张症；肝脏；肝移植；诊断；治疗；预后

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本文创新性：既往国内外有关肝脏遗传性出血性毛细血管扩张症的报告一般均为影像学报告，本文首次对其病理学检查结果进行分析，其本文还是国内首例利用肝移植治疗肝脏遗传性出血性毛细血管扩张症的报道。

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