

Review Article

Osler-Weber-Rendu and Liver Transplant

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ABSTRACT

Introduction: Osler-Weber-Rendu (OWR) or Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant disease characterized by angiodysplastic lesions that may affect many organs. Hepatic involvement in HHT is observed in 8-31% of cases and can lead to arteriovenous shunts within the liver causing high output cardiac failure. Liver transplantation may provide cure for patient with severe hepatic involvement, cholangitis and / or perturbed hemodynamics causing high output cardiac failure. The aim of this article is to review reported cases in the literature, the indication for liver transplantation and the outcomes.

Material and Methods: A MEDLINE search was performed (1970-present) for all case reports and case series of HHT requiring liver transplantation.

Results: A total of 22 cases were reported in the literature. 95.4% were females. Indications for transplantation included decompensated liver disease, congestive heart failure and biliary sepsis. Nine patients (41%) required transplantation for more than one indication. The overall survival was 90.9% ranging from one month to 7.5 years of follow up period.

Conclusion: Liver transplant is a viable option for patients suffering from HHT with complications related to liver involvement.

KEY WORDS: hereditary hemorrhagic telangiectasia, liver, liver transplantation, Osler-Weber-Rendu

INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT) is a systemic autosomal dominant disease that occurs in all races with equal gender distribution. It is characterized by multiorgan involvement with angiodysplastic lesions of the skin, lungs, gastrointestinal tract, and the brain. The classic clinical triad includes recurrent epistaxis and muco-cutaneous telangiectasia in the setting of hereditary transmission^[1-8]. The estimated frequency of HHT is 1-2/100,000 in European populations with a penetrance of 97%^[3,8,9]. In retrospective studies, the reported prevalence of hepatic involvement in patients with HHT has ranged from 8 to 31% and out of these, 30-50 % are asymptomatic^[1,2,10-12].

Synthetic function is generally well preserved, but liver failure caused by significant replacement of hepatic parenchyma with or without hepatocellular carcinoma has been reported^[1,2,5,13-15]. When symptoms are present, clinical features vary but the most common presentation is right upper quadrant abdominal pain. Recurrent encephalopathy can occur, especially after gastrointestinal bleeding despite normal hepatocellular function^[2,13,15]. Patients often present with significant right-sided congestive

heart failure secondary to left to right intrahepatic shunts correlating with the size of the arteriovenous fistula. Portal hypertension and variceal formation can result from increased sinusoidal blood flow leading to increased deposition of fibrous tissue and nodularity. Conversely, hypoperfusion of the peribiliary plexus may result in ischemic necrosis of the extrahepatic or intrahepatic biliary tree leading to biliary stricture, bilomas and biliary sepsis^[1,5,11,16-24].

Treatment for liver involvement in HHT is generally conservative unless complications occur. Medical therapy is of marginal value in high cardiac output failure. Two invasive techniques for reduction of left-to-right intrahepatic shunting have been described: embolization; and ligation of hepatic artery. The results of these techniques are controversial^[5,8,17,21-26]. Liver transplantation may provide a cure for patient with severe hepatic involvement in the form of cholangitis or portal hypertension and / or perturbed hemodynamics causing high output cardiac failure. There have been many case reports and several small series regarding the utility of orthotopic liver transplantation (OLT) for HHT with symptomatic liver involvement^[5,7-9,12,20,22,23,27-30] (Table 1).

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Table 1: Case reports and case series of HHT requiring liver transplantation

Author	Age	Gender	Cardiac output (pre and post OLT)	Reason for OLT	Period of F/U / post OLT complications
Amaris J <i>et al.</i> ^[20]	48	F	Pre OLT :18L/min	High cardiac output failure and infectious cholangitis	- / None
Bauer <i>et al.</i> ^[9]	33	F	Pre OLT :12 L/min	High cardiac output failure and liver failure due to biliary necrosis and sepsis	24 months /None
Neuman <i>et al.</i> ^[22]	45	F	Pre OLT : 8.8 L/min	High cardiac output failure treated with hepatic artery ligation Decompensated liver cirrhosis (variceal bleeding)	- / None
Le Corre <i>et al.</i> ^[28]	40	F	Pre OLT: 12.5 L/min Post OLT: 8.0 L/min	Developed recurrent bile duct necrosis post hepatic artery ligation High cardiac output failure	1 month / None
McInory <i>et al.</i> ^[18]		F	ND	Spontaneous progressive biliary necrosis after pregnancy	- / None
Hillert <i>et al.</i> ^[12]	39	F	ND	RUQ pain during pregnancy. Hemobilia treated with hepatic artery embolization complicated by progressive cholestasis & therapy resistant biliary sepsis followed by liver failure	1 yr / None
Saxena R <i>et al.</i> ^[8]	43	F	ND	End stage liver disease and fibropolycystic liver disease Rec. biliary strictures post surgical dearterialization	- / Severe bleeding during OLT
Odorico <i>et al.</i> ^[27]	48	F	ND	Embolization of hepatic artery for mesenteric ischemia followed by biliary sepsis and liver failure	12 months /Splenic rupture
	47	F			9 months /Delayed closure
Boillot <i>et al.</i> ^[5]	36	F	Pre OLT: 9.5 L/min Post OLT:5.5 L/min	RUQ pain during pregnancy developed CHF necessitating premature delivery followed by biliary sepsis and liver failure	65 months /None
	50	F	Pre OLT: 11.3 L/min Post OLT: 4.1 L/min	Refractory ascites. Portal HTN	53 months /None
	42	F	Pre OLT: 10.8 L/min Post OLT: 4.8 L/min	Right sided heart failure; ascites	29 months / None
Pfitzman <i>et al.</i> ^[23,29]	45	F	Pre OLT : 8.0-13.3L/min Post OLT : 4.5-6.3L/min	Right sided heart failure; dyspnea	12-65 months / None
	69	F		Right sided heart failure; dyspnea; ascites; biliary ischemia; ventricular arrhythmia	2 Patients died : Day 2 ** Day 11*** 4 Patients are alive: 3-7.5yrs /None
	54	F		Right sided heart failure; ascites; pulmonary HTN	
	55	F		Right sided heart failure ; arrhythmias	
Azoulay <i>et al.</i> ^[30]	38-66	5 F 1 M	Pre OLT: 9.2+/-3.0 L/min Post OLT : 5.7+/- 0.5 L/min	3 Cases: recurrent cholangitis with or without hepatic abscesses 2 Cases: Severe portal HTN, intractable ascites, and recurrent variceal bleeding 1 Case: High cardiac output failure with cholangitis	

● ** Secondary to intracerebral hemorrhage

● *** Secondary to massive gastric bleeding due to large AVM

● F = Female, M = Male, OLT = Orthotopic Liver Transplantation, HTN = Hypertension, ND = Not Done, F/U = Follow up, RUQ = Right Upper Quadrant

The aim of this article is to review the reported cases in the literature, indication for liver transplantation, and the outcomes.

MATERIAL AND METHODS

A Medline search of English language literature from 1970 to July 2004 was performed using the key words: hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu, liver and liver transplantation. Articles were considered by review of their titles and abstracts when available. From this initial body of literature, we identified additional articles using the bibliographies of the original set. A total of 35 articles dating back to 1978 were thoroughly examined. Of these, 12 articles were found to

specifically address liver transplantation in patients with HHT. The remainders addressed the epidemiology, clinical manifestation, natural history, diagnosis and other forms of treatment for patients with HHT and hepatic involvement other than liver transplantation. The results are presented in Table 1.

RESULTS

In the 12 articles reviewed for patients with HHT requiring liver transplantation, a total of 22 cases were identified (Table 1). Seven of these were case reports and the rest were small case series, ranging from 2-6 cases, transplanted between year 1992 and 2001.

The age range was between 33 and 69 years. Although the disease is autosomal dominant with equal gender distribution, 95.4% (21/22) of transplanted patients were women and out of these three were either diagnosed or decompensated during pregnancy.

The indications for liver transplantation included: decompensated liver cirrhosis (portal hypertension, ascites, variceal bleeding) in seven patients (31.8%), congestive heart failure in 11 patients (50%) and recurrent cholangitis and biliary sepsis secondary to biliary ischemia either spontaneous or post hepatic artery ligation or following massive gastrointestinal bleeding in 11 patients (50%). Nine patients (40.9%) required liver transplantation for more than one indication.

Most authors did not report pre-transplant details of liver synthetic function. Neuman *et al* reported only elevated bilirubin; and Pfitzman *et al* documented Child-Pugh score preoperatively. Furthermore, liver pathology has been documented only by Le Corre *et al* as absence of cirrhosis whereas Saxena *et al* confirmed the presence of portal fibrosis in the explant.

The survival rate was 90.9% (20/22) and ranged from one month to 7.5 years of follow up period with two deaths occurring on day two and 11 post transplant secondary to intracerebral hemorrhage and massive gastric bleeding due to large AVM respectively.

Liver transplantation was associated with a reduction of cardiac output and improvement of hemodynamic circulation, the median pre-transplant and post-transplant cardiac output was 11.1 l/min and 6.7 l/min respectively.

The cited period of follow up following transplant varied from one month to 7.5 years. The patients remained asymptomatic during the cited period of follow up.

DISCUSSION

The treatment of HHT with liver involvement is generally conservative unless complications occur. Beta-blockade is attempted to reduce the hyperkinetic syndrome and hepatic blood flow, but their use is limited by their cardio-depressive effects^[5]. Digitalis and diuretics are used for heart failure but medical therapy is of marginal value in high cardiac output failure.

Transjugular intrahepatic portosystemic shunts (TIPS) failed to palliate the symptoms of two patients with HHT and liver cirrhosis presenting with refractory gastrointestinal bleeding from telangiectasia, portal hypertension and ascites as reported by Lee^[31].

Devascularization of feeding arteries has been attempted for reduction of left-to-right intrahepatic

shunting by ligation or embolization. Serious and fatal complications have resulted from the procedures in up to 42% of cases. These measures are particularly dangerous in these patients with compromised portal venous systems^[1,2,5, 8,17,21-26,32]. Hepatic and biliary necroses are the most significant complications, with development of recurrent cholangitis and biliary sepsis. If ligation or embolization is successful, revascularization of the AVM usually occurs within months with recurrence of symptoms. Embolization and hepatic ligation are therefore, not viable options^[1,2,17,22,25-27,32].

Liver failure after arterial ligation or embolization required rescue OLT. Neuman *et al* reported a 45-year-old woman having HHT with multiple intrahepatic arteriovenous fistulas and high cardiac output failure treated initially with hepatic artery ligation. Fourteen months later the patient presented with elevated levels of bilirubin, alkaline phosphatase reflecting bile duct necroses; and recurrent bleeding episodes from esophageal varices for which the patient underwent successful OLT with excellent recovery^[22].

Liver transplantation can be considered as a successful curative treatment for patients with HHT and liver involvement having high output cardiac failure and / or biliary sepsis as reported by Bauer T *et al*, Amaris J and Le Corre *et al*^[9,20,28].

The clinical manifestations of liver involvement may fluctuate overtime with spontaneous exacerbations and remissions. Development of heart failure may present at around 24 weeks of pregnancy necessitating aggressive therapy^[5,11,12,33-34]. McNory *et al* treated a woman who presented during pregnancy with abdominal pain and spontaneous progressive biliary necrosis^[18]. The case reported by Hillert *et al* had a much more complicated course. A 39-year-old woman presented in her second pregnancy with right upper quadrant pain and massive hemorrhage from gastric ulcer, necessitating surgical therapy (Billroth-I). Persistent bleeding from the biliary tree was treated with hepatic artery embolization. Progressive cholestasis and biliary sepsis ensued, followed by liver failure requiring OLT. The patient was followed for one year with uncomplicated course^[12].

It has been postulated that deterioration during pregnancy maybe due to increase in the level of sex hormones particularly in view of progression of arteriovenous malformations during pregnancy. However, combined estrogen-progesterone treatment at high doses has been reported as being beneficial for recurrent epistaxis. The exact mode of action of sex hormones is therefore, far from clear and their place in management of severe visceral vascular malformations uncertain. Receptors for progesterone have been detected in the mucosa of patients

suffering from HHT, but their significance needs to be defined^[17,32-35].

Several case series of patients undergoing OLT for HHT have been reported. The first case series by Odorico *et al* reported two women with hepatic AVMs that caused mesenteric angina-like symptoms that were treated with hepatic artery embolization (pancreatico-duodenal artery in one and hepatic artery in the other); however, within two weeks and two months respectively, they developed parenchymal and bile duct necrosis, intrahepatic bilomas, and refractory biliary sepsis, subsequently leading to liver failure. This was treated successfully by liver transplantation^[27]. Boillot *et al* reported three women with right sided congestive heart failure and/or liver failure which were treated successfully by liver transplantation. The follow up periods of 29, 53 and 65 months after transplantation for these three patients were uneventful^[51].

Pfitzmann *et al* reported four women with HHT and liver involvement requiring liver transplant between 1995 and 1999 with a follow up time of 12 to 65 months. All patients had normal graft function and good cardiopulmonary status^[23,29].

In the largest series, Azoulay *et al* reported six cases (five women and one man) analyzing the technical and hemodynamic aspects pre and post liver transplantation for patients with HHT and liver involvement. Two patients died at day two and 11 secondary to intracranial hemorrhage and massive gastric bleeding due to large arteriovenous malformations respectively. The remaining patients were alive 3 - 7.5 years (median = 4 years and 9 months) after transplantation with normal liver function and without any cardiac symptoms^[30].

CONCLUSION

Liver transplantation appears to offer a viable therapeutic option for the treatment of end organ disease in HHT. It can restore cardiac function and normalize arterial and venous hepatic blood flow.

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