

LIVER DISEASE IN PATIENTS WITH HEREDITARY HEMORRHAGIC  
TELANGIECTASIA

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**ABSTRACT**

**Background** Hereditary hemorrhagic telangiectasia, or Rendu–Osler–Weber disease, is an autosomal dominant disorder characterized by angiodysplastic lesions (telangiectases and arteriovenous malformations) that affect many organs. Liver involvement in patients with this disease has not been fully characterized.

**Methods** We studied the clinical findings and results of hemodynamic, angiographic, and imaging studies in 19 patients with hereditary hemorrhagic telangiectasia and symptomatic liver involvement.

**Results** We evaluated 14 women and 5 men who ranged in age from 34 to 74 years. All but one of the patients had a hyperdynamic circulation (cardiac index, 4.2 to 7.3 liters per minute per square meter of body-surface area). In eight patients, the clinical findings were consistent with the presence of high-output heart failure. The cardiac index and pulmonary-capillary wedge pressure were elevated in the six patients in whom these measurements were performed. After a median period of 24 months, the condition of three of the eight patients had improved, four were in stable condition with medical therapy, and one had died. Six patients had manifestations of portal hypertension such as ascites or variceal bleeding. The hepatic sinusoidal pressure was elevated in the four patients in whom it was measured. After a median period of 19 months, the condition of two of the six patients had improved, and the other four had died. Five patients had manifestations of biliary disease, such as an elevated alkaline phosphatase level and abnormalities on bile duct imaging. After a median period of 30 months, the condition of two of the five had improved, the condition of one was unchanged, heart failure had developed in one, and one had died after an unsuccessful attempt at liver transplantation.

**Conclusions** In patients with hereditary hemorrhagic telangiectasia and symptomatic liver involvement, the typical clinical presentations include high-output heart failure, portal hypertension, and biliary disease. (N Engl J Med 2000;343:931-6.)

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**H**EREDITARY hemorrhagic telangiectasia, or Rendu–Osler–Weber disease, is an autosomal dominant disease characterized by angiodysplastic lesions (telangiectases and arteriovenous malformations) that affect many organs, including the skin, lungs, gastrointestinal tract, and brain.<sup>1</sup>

The prevalence of hepatic involvement in patients

with hereditary hemorrhagic telangiectasia has ranged from 8 to 31 percent in retrospective studies.<sup>2,3</sup> In a prospective study of a large family with 40 members who had hereditary hemorrhagic telangiectasia,<sup>4</sup> hepatic vascular malformations were detected in 13 of the 40 members; in only 2 were they symptomatic. Case reports of hereditary hemorrhagic telangiectasia with liver involvement describe disseminated intrahepatic telangiectases. The clinical presentations, however, vary considerably. We studied 19 patients with hereditary hemorrhagic telangiectasia and liver disease, and we report on their clinical features.

**METHODS****Patients**

From 1994 to 1998, we evaluated 19 patients with hereditary hemorrhagic telangiectasia for liver involvement because they had heart failure, ascites, pain in the right upper quadrant, a liver bruit, abnormal results of liver tests, or a combination of these findings. During this time, approximately 700 patients with this disease were referred to our center for genetic counseling and treatment of epistaxis and pulmonary, cerebral, or gastrointestinal arteriovenous malformations. Potential liver involvement was not assessed routinely.

**Confirmation of Liver Involvement**

In all 19 patients with hereditary hemorrhagic telangiectasia, liver involvement was confirmed by the presence of disseminated intrahepatic telangiectases, arteriovenous malformations, or both on angiograms or computed tomographic (CT) scans. In addition to hepatic involvement, at least two of the following criteria had to be met to establish the diagnosis of hereditary hemorrhagic telangiectasia: epistaxis, mucocutaneous telangiectases, a family history of hereditary hemorrhagic telangiectasia, and visceral involvement other than of the liver. These findings are in accordance with recently established diagnostic criteria.<sup>5</sup> Concomitant liver disease was ruled out by the absence of risk factors for chronic liver disease, such as alcoholism, intravenous drug use, and inflammatory bowel disease, and by negative results of tests for hepatitis B and C viral markers and antinuclear and antimitochondrial antibodies.

**Hemodynamic and Angiographic Studies**

Fifteen patients underwent hemodynamic or angiographic studies, or both. Right-heart catheterization was performed, with measurements of right atrial, pulmonary-artery, and pulmonary-capillary wedge pressures, and cardiac output was calculated with the use of thermodilution. A cardiac index higher than 4.0 liters per minute per square meter of body-surface area was considered abnormal.

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Portal pressure was measured indirectly on the basis of the hepatic venous pressure gradient, which was calculated by subtracting the pressure in the inferior vena cava from the wedged hepatic venous pressure. A hepatic venous pressure gradient greater than 5 mm Hg was considered abnormal. Digital-subtraction angiography of the abdominal aorta, hepatic artery, and superior mesenteric artery was used to confirm the presence of intrahepatic arteriovenous malformations and to detect shunting. For patients who had undergone liver biopsies, we obtained the slides and reexamined the specimens.

**RESULTS**

**Clinical Characteristics**

The 19 patients (14 women and 5 men) had a median age of 55 years, with a range of 34 to 74 years (Table 1). All 19 patients had a family history of hereditary hemorrhagic telangiectasia, and 3 had a family member with symptomatic liver involvement. Ex-

cept for one patient, who had a base-line cardiac index of 2.9 liters per minute per square meter, all the patients had a hyperdynamic circulation (cardiac index, 4.2 to 7.3 liters per minute per square meter). All the patients were found to have an enlarged hepatic artery on angiographic or CT studies. The patients were followed for a median of 25 months (range, 6 to 56).

We identified three distinct clinical presentations: high-output heart failure, portal hypertension, and biliary disease (Table 1).

**High-Output Heart Failure**

Eight patients had an elevated cardiac output, an elevated pulmonary-capillary wedge pressure, and a presentation consistent with the presence of heart failure. All eight patients presented with shortness of breath in the absence of anemia or clinically significant pulmonary arteriovenous malformations. Two of the eight patients had peripheral edema; seven had a liver bruit. One patient had an elevated alkaline phosphatase level and biliary cysts on CT scanning. The median cardiac index was the highest in this group of patients (6.8 liters per minute per square meter). The six patients who underwent angiography had shunting from the hepatic artery to the hepatic veins (Fig. 1).

Medical therapy included salt restriction, diuretics, antihypertensive agents, antiarrhythmic agents, and digoxin, as clinically indicated. After a median period of 24 months, the symptoms of heart failure were stable in four patients and had improved in three. None improved without therapy. One patient had incapacitating heart failure; hepatic arterial embolization was performed to decrease the shunting from the hepatic artery to the hepatic veins. Although the heart failure improved, hepatobiliary necrosis and sepsis developed, and the patient died. In one of the patients with stable heart failure, who had a normal alkaline phosphatase level and no cysts at presentation, pain developed in the right upper quadrant, with an elevated alkaline phosphatase level and a cystic lesion visible on a CT scan. Endoscopic retrograde cholangiography revealed an abnormal biliary tree with saccular dilatations. The patient died from biliary sepsis shortly after undergoing the endoscopic study.

**Portal Hypertension**

Six patients had an elevated hepatic sinusoidal pressure, with ascites in four and gastrointestinal hemorrhage in two (from gastroesophageal varices in one patient and from gastrointestinal telangiectases in the other). Three patients had gastroesophageal varices. The hepatic venous pressure gradient was markedly elevated in the four patients in whom it was measured. The other two patients had portosystemic collaterals and nodularity of the liver on CT scanning. Angiography was performed in four patients, one of whom had shunting from the hepatic artery to the

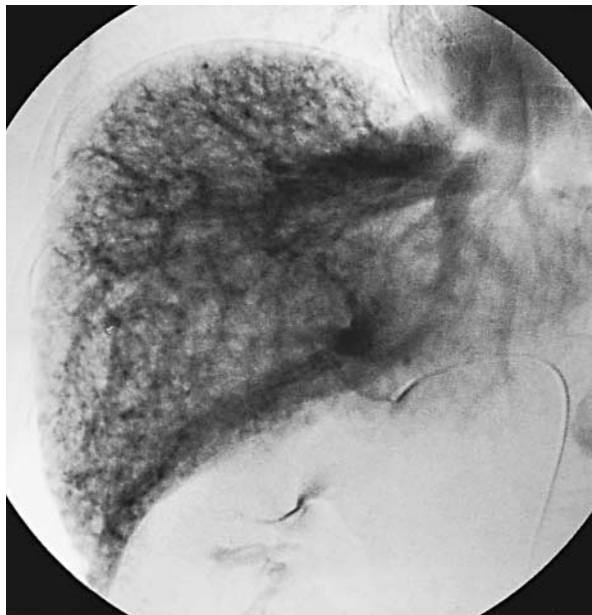
**TABLE 1. CHARACTERISTICS OF 19 PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA AND LIVER DISEASE, ACCORDING TO THE CLINICAL PRESENTATION.**

CHARACTERISTIC	HEART FAILURE (N=8)	PORTAL HYPERTENSION (N=6)	BILIARY DISEASE (N=5)
Age			
Median	59	67	48
Range	34-72	56-74	36-55
Female sex	6	3	5
Symptoms and signs at presentation (no. of patients)			
Shortness of breath	8	0	0
Abdominal pain	1	0	2
Intractable chronic gastrointestinal bleeding	0	3	0
Liver bruit	7	1	2
Ascites	0	4	0
Alkaline phosphatase (U/liter)			
Median	94	100	355
Range	47-142	87-369	153-1066
Bilirubin (mg/dl)*			
Median	0.5	0.6	0.5
Range	0.2-1.6	0.3-1.3	0.2-6.1
Albumin (g/dl)			
Median	4.1	4.0	4.1
Range	3.7-4.5	2.7-4.4	3.4-4.8
Prothrombin time (sec)			
Median	12.6	12.6	11.7
Range	12.1-12.8	12.0-13.3	10.9-13.2
Cardiac index (liters/min/m <sup>2</sup> )			
Median	6.8	4.6	5.5
Range	5.8-7.3	4.2-5.5	2.9-6.6
Pulmonary-capillary wedge pressure			
No. of patients	6	4	4
Median (mm Hg)	17.0	9.0	11.3
Range (mm Hg)	14.0-22.0	7.0-16.0	5.0-15.5
Hepatic-artery-to-hepatic-vein shunting (no. of patients/total no.)	6/6	0/4	1/2
Hepatic venous pressure gradient			
No. of patients	5	4†	4
Median (mm Hg)	2	20	2.5
Range (mm Hg)	1-7	17-24	1-8

\*To convert values for bilirubin to micromoles per liter, multiply by 17.1.  
 †Three of the patients had endoscopically confirmed esophageal varices.



A



B

**Figure 1.** Hepatic Arteriogram in a Patient Who Had Hereditary Hemorrhagic Telangiectasia and High-Output Heart Failure, with a Cardiac Index of 7.0 Liters per Minute per Square Meter of Body-Surface Area.

The liver parenchyma has a hypervascular pattern (Panel A), with early opacification of the hepatic veins (Panel B). These findings indicate the presence of shunting from the hepatic artery to the hepatic veins.

portal vein. None had detectable shunting from the hepatic artery to the hepatic veins.

After a median period of 19 months, the condition of two patients had improved: in one, ascites resolved with diuretic treatment; in the other, ascites resolved after the placement of a peritoneovenous shunt and did not recur despite the subsequent removal of the shunt. In the two patients who did not have ascites initially, it developed on follow-up. Four patients died: one from metastatic lung cancer diagnosed at the time of variceal hemorrhage (which had been controlled with variceal ligation) and three from intractable gastrointestinal bleeding due to mucosal telangiectases. In two of these four patients, ascites became intractable. Treatment of ascites and gastrointestinal hemorrhage with the placement of a transjugular intrahepatic portosystemic shunt was unsuccessful, as previously reported.<sup>6</sup> A high alkaline phosphatase level, liver cysts, and gram-negative sepsis developed in one of the four patients who died.

#### Biliary Disease

Five patients had elevated alkaline phosphatase levels and radiographic evidence of bile-duct abnormalities similar to those in Caroli's disease, a congenital malformation of the developing biliary tree (ductal plate),<sup>7</sup> or those in sclerosing cholangitis. Two of the patients presented with severe fatigue, two with pain in the right upper quadrant, and one with a history of jaundice and fever; three patients also had pruritus. All five patients had liver-enzyme abnormalities consistent with the presence of cholestasis. This group had the highest alkaline phosphatase levels (median value, 355 U per liter; range, 153 to 1066). CT scans showed liver cysts in two patients, in one of whom the cyst was described as a focal biliary dilatation (Fig. 2). In the other three patients, CT scans showed dilated intrahepatic bile ducts, and in two of the three, the findings were confirmed by endoscopic retrograde cholangiography. One of the two patients who underwent angiography had shunting from the hepatic artery to the hepatic veins, but to a lesser degree than in the patients with heart failure.

After a median period of 30 months, the liver-enzyme levels had improved spontaneously in two patients; in one of the two, the abdominal pain had also resolved. One patient continued to have fatigue and abnormal liver-enzyme values. One patient had atrial fibrillation followed by the development of heart failure, which responded to medical therapy. In another patient, ascites developed and the synthetic function of the liver deteriorated. She died from severe intraoperative bleeding during an unsuccessful attempt at liver transplantation.

#### Histologic Features of Liver-Biopsy Specimens

Eight liver biopsies were performed in seven patients (Table 2). Six had been performed before the



**Figure 2.** Abdominal CT Image in a Patient with Pain in the Right Upper Quadrant and an Elevated Alkaline Phosphatase Level. The liver is enlarged and hypervascular. A cystic mass with branches indicates the presence of a biliary cyst.

patients were referred to our center (four percutaneous and two wedge biopsies). Two biopsies were performed at our center with the transjugular approach. Although no bleeding complications occurred after the percutaneous biopsies, two of the four patients had severe, protracted pain. Abnormal ectatic vessels were seen in all the biopsy specimens except for one (a small specimen). Biliary abnormalities were present only in the patients with biliary disease, and sinusoidal fibrosis was present only in the patients with portal hypertension. Nodularity was present in seven patients. Six of these patients had alternating areas of regeneration and atrophy (nodular hyperplasia), and five of the six had thick fibrous bands along ectatic vessels. This combination of regeneration and fibrosis was misinterpreted as cirrhosis in two cases (both involving small specimens). Only one patient was considered to have true cirrhosis. Biopsy was not performed in the eight patients with heart failure.

### DISCUSSION

Hereditary hemorrhagic telangiectasia is an uncommon autosomal dominant disorder characterized by abnormal vascular structure. Telangiectases that consist of focal dilatations of postcapillary venules and arteriovenous malformations are the characteristic lesions in this disorder. Like the telangiectases, the arteriovenous malformations lack capillaries and form direct connections between arteries and veins, but they are much larger.<sup>1</sup>

The liver has a unique vascular supply. Blood enters the liver from two sources, the portal vein and the hepatic artery, merging at the level of the hepatic sinusoids and exiting through the hepatic veins. In pa-

**TABLE 2.** HISTOLOGIC FEATURES OF EIGHT LIVER-BIOPSY SPECIMENS FROM SEVEN PATIENTS, ACCORDING TO THE CLINICAL PRESENTATION.

FEATURE	PORTAL HYPERTENSION (N=3)	BILIARY DISEASE (N=5)*
Ectatic vessels	3	4
Biliary abnormalities		
Periductal fibrosis	0	3
Bile-duct necrosis	0	1†
Sinusoidal fibrosis	2	0
Nodularity		
Absent	0	1
Regeneration alternating with atrophy (nodular hyperplasia)	3	3
True cirrhosis	0	1
Fibrosis along ectatic vessels	3	2‡

\*Two of the biopsies were performed seven years apart in one patient. The specimen from the first biopsy was initially reported to be normal, but reexamination showed some ectatic vessels and alternating areas of regeneration and atrophy. The specimen from the second biopsy was reported to be cirrhotic, but reexamination showed nodular hyperplasia with fibrous tissue along ectatic vessels — findings consistent with the presence of “pseudocirrhosis.”

†The presence of a biliary concretion indicated bile leakage and calcification.

‡One of the three patients with nodular hyperplasia did not have fibrosis along ectatic vessels.

tients with hereditary hemorrhagic telangiectasia, liver involvement predominantly results in shunting from the hepatic artery to the hepatic veins. Angiography and corrosion cast studies have also shown the presence of anastomoses between the hepatic artery and the portal vein.<sup>8</sup> Although difficult to demonstrate angiographically, shunting between portal and hepatic veins has been demonstrated histologically.<sup>9</sup> In the presence of marked shunting from the portal vein, only the hepatic artery supplies blood to the liver. The presence of hepatic necrosis after hepatic-artery embolization supports the presence of shunting from the portal vein to the hepatic veins.

Martini<sup>10</sup> classified patients with hepatic disease due to hereditary hemorrhagic telangiectasia into three subgroups according to the histologic features of the hepatic disease: patients who had telangiectases with fibrosis or cirrhosis, those who had cirrhosis without telangiectases, and those who had telangiectases without fibrosis or cirrhosis. The patients in the second group probably had chronic post-transfusion hepatitis that was unrelated to hereditary hemorrhagic telangiectasia.

According to our review of the literature since 1978, there have been reports on a total of 83 patients with hereditary hemorrhagic telangiectasia and liver involvement; 30 of the patients were asymptomatic,<sup>4,11-16</sup> and 53 were symptomatic. Forty-four of the symptomatic patients could be classified as having one of the three

presentations we identified in our study: 32 had heart failure,<sup>4,12-14,17-32</sup> 7 had portal hypertension,<sup>29,32-37</sup> and 5 had biliary disease.<sup>14,38-40</sup> Of the nine patients who could not be classified, four presented with encephalopathy<sup>9,15,41</sup> as a result of portal-to-hepatic-vein shunting, two presented with abdominal angina due to mesenteric arterial "steal" through pancreaticoduodenal arteries,<sup>42</sup> and three had clinical findings that were difficult to characterize,<sup>43-45</sup> although one of the three<sup>45</sup> may have had biliary disease.

The particular clinical manifestation of liver involvement in patients with hereditary hemorrhagic telangiectasia may depend on the predominant type and size of shunt as well as on the effects of an abnormal hepatic blood supply. The majority of such patients have a hyperdynamic circulation resulting from arteriovenous shunting, portovenous shunting, or both. Practically all patients with high-output cardiac failure have shunts from the hepatic artery to the hepatic veins. Chronic high flow from such shunts eventually leads to heart failure. Other factors related to diastolic dysfunction, such as older age, hypertension, and coronary artery disease, may play a part in precipitating heart failure.

A shunt from the hepatic artery to the portal vein leads to portal hypertension, but such shunts have not been reported in all patients with hereditary hemorrhagic telangiectasia who have portal hypertension due to liver involvement. All our patients who underwent hepatic-vein catheterization had an increased pressure gradient, indicating the presence of sinusoidal hypertension and therefore a sinusoidal or postsinusoidal site of increased resistance. Increased sinusoidal blood flow can lead to increased deposition of fibrous tissue and nodularity — findings associated with the "arterialization" of the portal vein.<sup>46</sup> An alternative and perhaps more likely explanation is that the liver undergoes nodular transformation, also known as "pseudocirrhosis."<sup>47</sup> Nodular hyperplasia is characterized by the presence of regenerative nodules that compress the surrounding liver parenchyma. These nodules, unlike those in true cirrhosis, are not delimited by fibrous septa. An association between hereditary hemorrhagic telangiectasia and nodular hyperplasia of the liver has been reported previously.<sup>9</sup> Chronic ischemia, such as that which occurs with an arteriovenous or portovenous shunt, causes atrophy of the involved liver acinus. Adjacent acini, with an intact blood supply, undergo compensatory hyperplasia, resulting in micronodularity<sup>48,49</sup> and portal hypertension.

The biliary tree obtains its blood supply from the peribiliary plexus that arises from the hepatic artery. Arteriovenous shunts may cause hypoperfusion of the peribiliary plexus and ischemic necrosis of extrahepatic or intrahepatic bile ducts, or both, with the subsequent development of a biliary stricture. This process has been described in association with the hepatic arterial instillation of chemotherapeutic drugs<sup>50</sup> and

after liver transplantation.<sup>51</sup> Ischemia can also lead to biliary necrosis and the formation of cysts that contain bile. Alternatively, since some cases resemble Caroli's disease, it could be postulated that abnormalities in vascular formation at the ductal plate arrest the normal development of the bile-duct system. The reported coexistence of hereditary hemorrhagic telangiectasia and polycystic kidneys in one patient<sup>37</sup> is consistent with this possibility.

Notably, as we found and as others have reported,<sup>14,24,28,30,32,37,38</sup> the clinical manifestations of liver involvement overlap and may fluctuate over time, with spontaneous exacerbations and remissions. The reason for spontaneous improvement is unclear. It may depend on changes in shunting patterns or on the presence of reversible conditions (e.g., anemia or atrial fibrillation). In some cases, pregnancy, which causes a hyperdynamic circulatory state, has precipitated heart failure, with resolution after delivery.<sup>23</sup>

Seven of our patients had undergone liver biopsy. In retrospect, this potentially risky procedure was unnecessary, since histologic examination of the liver is not helpful in establishing the presence of liver involvement or in classifying the type of liver disease in patients with hereditary hemorrhagic telangiectasia.

Hepatic-artery embolization or ligation has been performed in patients with hereditary hemorrhagic telangiectasia and liver involvement.<sup>17,18,20,21,24,25,27,29-31,35</sup> Even though this procedure has ameliorated the symptoms of heart failure or splanchnic steal, it may cause hepatic or biliary necrosis, or both, as we and others have found,<sup>25,29,30,42</sup> and should therefore be used only under special circumstances, provided that shunting from the portal vein to the hepatic veins is ruled out.

Liver transplantation has been performed in six patients with liver disease due to hereditary hemorrhagic telangiectasia<sup>28,32,37,40</sup> with good results, although excessive intraoperative bleeding was noted in two of the patients.<sup>32,37</sup> We attempted liver transplantation in one patient, who died from hemorrhaging during the surgery.

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