Liver transplantation for intrahepatic Rendu-Osler-Weber’s disease:
the Paul Brousse hospital experience

Daniel AZOULAY (1), Sophie PRECETTI (2), Jean-François EMILE (3), Philippe ICHAI (1), Marie-Christine GILLON (4), Jean-Charles DUCLOS-VALLÉE (1), Selim VISDA (1), René ADAM (1), Denis CASTAING (1), Didier SAMUEL (1), Henri BISMUTH (1)

(1) Département de Chirurgie Hépato-Biliaire, (2) Service de Radiologie, (3) Département d’Anesthésie, (4) Service d’Anatomopathologie, Hôpital Paul Brousse, Université Paris-Sud, UPRES 1596, IFR 89.9, Villejuif.


SUMMARY
Nine centers have reported 15 cases of liver transplantation for Rendu-Osler-Weber’s disease with liver involvement. Six cases are reported to analyse the specific technical and hemodynamical aspects.

Patients and methods — Five women and 1 man were transplanted for Rendu-Osler-Weber’s disease. The clinical presentation was biliary disease in 3 cases, portal hypertension in 2 cases, cardiac failure in 1 case. Systemic hemodynamics were assessed at the beginning and at the end of the transplantation procedure.

Results — The procedure lasted from 11 to 15 hours (median = 13 hours and 15 minutes). Blood transfusion during the procedure varied from 16 to 88 blood units (median = 59 blood units). Six patients had hyperkinetic syndrome at the beginning of the procedure. At the end of transplantation, mean arterial pressure significantly increased (from 66 ± 2 to 72 ± 6 mm Hg, p < 0.05), whereas cardiac output (from 9.2 ± 3.0 to 5.7 ± 0.5 L/min, p < 0.05) significantly decreased. Two patients died at D2 and D11 and 4 are alive 3 to 7.5 years (median = 4 years 9 months) after transplantation with a normal liver function and without any cardiac symptoms.

Conclusion — Liver transplantation for Rendu-Osler-Weber’s disease is a difficult procedure. When successful, liver transplantation is curative of both the liver disease and the hyperkinetic state.

Liver transplantation for intrahepatic Rendu-Osler-Weber disease or hereditary hemorrhagic telangiectasia is an autosomal dominant vascular anomaly characterized by the presence of multiple small telangiectases of the skin, mucous membranes, digestive tract, brain, and other organs causing focal dilatation of the post-capillary venules and direct arteriovenous shunts of larger vessels without intermediary capillaries associated with recurrent episodes of bleeding [1]. Hepatic involvement is observed in 8 to 31% of patients [2-5]. This prevalence is probably underestimated due to the lack of sensitivity of methods used to search for vascular malformations and the variable penetrance of the large number of genes involved but not fully identified [3, 4, 6, 7]. Garcia-Tsao et al. [5] identified three main types of expression of hepatic disease depending on the predominance of heart failure, portal hypertension, or biliary disease. To date, treatment in most patients with hepatic disease has been limited to symptomatic care by embolization, calibration [8], or ligature of the hepatic artery to reduce heart flow [9-19].

There have been 106 cases of hepatic Rendu-Osler-Weber disease reported in the literature: 30 patients were asymptomatic [4, 20-25] and 76 were symptomatic. According to the Garcia-Tsao classification established for 69 symptomatic patients [5], 43 (40.5%) had heart failure [4, 5, 9-13, 15-17, 19, 21-23, 26-33], 13 (12%) had portal hypertension [5, 14, 17, 27, 34-37] and 13 (12%) had biliary disease [5, 23, 29, 38-41]. Among the seven non classified patients, four presented encephalopathy [24, 42, 43] and three atypical symptoms [44-46]. Fifteen liver transplantations have been performed for Rendu-Osler-Weber disease in nine centers [5, 26-29, 34, 38, 39, 47]. We report here six cases of liver transplantation for
Rendu-Osler-Weber disease and analyze hemodynamic and hepatic outcome.

Patients and methods

Between 1994 and 2001, six patients, five women and one man, median age 48 years, (range, 38-66), underwent liver transplantation for Rendu-Osler-Weber disease. Patients n° 1 and 4 were sisters (tables I and II).

Liver involvement was confirmed in all six patients by the presence of diffuse intrahepatic telangiectases and arteriovenous malformation visualized on the celiomesenteric arteriogram. All patients also exhibited at least two of the following extrahepatic involvement diagnostic criteria: epistaxis, cutaneomucosal telangiectases, and family history of Rendu-Osler-Weber disease [48]. Intercurrent liver disease was ruled out by the absence of chronic alcoholism, intravenous drug use, in three patients (n° 1, 3, 4) had predominant biliary disease with repeated episodes of cholangitis with or without intrahepatic abscesses and two patients (n° 2, 5) had predominant severe portal hypertension with intractable ascites and digestive tract bleeding due to recurrent rupture of esophageal varices despite well-conducted endoscopic treatment (patient n° 5 also had pulmonary artery hypertension). One patient (n° 6) had high-output cardiac failure with cholangitis. Embolization or ligation of the hepatic artery had not been attempted in any of the patients (figure 1).

Systemic hemodynamics

Right heart catheterization was performed with a Swann-Ganz catheter. Measurements were taken on the operating table before incision and at the end of the procedure before transfer to intensive care.

Rendu-Osler-Weber disease : the Paul Brousse hospital experience

Table I. – Main characteristics of 6 liver transplant recipients for Rendu-Osler-Weber’s disease with liver involvement.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient n° 1</th>
<th>Patient n° 2</th>
<th>Patient n° 3</th>
<th>Patient n° 4</th>
<th>Patient n° 5</th>
<th>Patient n° 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)/sex (M/F)</td>
<td>38/F</td>
<td>41/F</td>
<td>49/F</td>
<td>38/F</td>
<td>67/M</td>
<td>48/F</td>
</tr>
<tr>
<td>Predominant syndrome*</td>
<td>Biliary</td>
<td>Portal hypertension</td>
<td>Biliary</td>
<td>Biliary</td>
<td>Portal hypertension</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Ascitis</td>
<td>No</td>
<td>Yes, infected</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Esophageal varices or hypertensive gastritis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>History of biliary surgery</td>
<td>Cholecystectomy, Operated abscess, Repeated abscess drainage due to diffuse lithiasis</td>
<td>No</td>
<td>Cholecystectomy</td>
<td>Endoscopic splanchnic Endoscopic sphincterotomy</td>
<td>Operated abscess</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatases (IU/L)</td>
<td>203</td>
<td>190</td>
<td>337</td>
<td>145</td>
<td>716</td>
<td>325</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>464</td>
<td>235</td>
<td>87</td>
<td>1168</td>
<td>283</td>
<td>221</td>
</tr>
<tr>
<td>Bilirubin (µmole/L)</td>
<td>14</td>
<td>249</td>
<td>24</td>
<td>36</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>ASAT/ALAT (IU/L)</td>
<td>92 /57</td>
<td>54 /32</td>
<td>54 /34</td>
<td>34 /34</td>
<td>407 /359</td>
<td>407 /359</td>
</tr>
<tr>
<td>PT (%)</td>
<td>96</td>
<td>66</td>
<td>74</td>
<td>100</td>
<td>55</td>
<td>61</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>30</td>
<td>31</td>
<td>25</td>
<td>44</td>
<td>23</td>
<td>33</td>
</tr>
</tbody>
</table>

According to the Garcia-Tsao et al. classification [5].

Table II. – Main parameters of liver transplantation in 6 patients with Rendu-Osler-Weber’s disease.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient n° 1</th>
<th>Patient n° 2</th>
<th>Patient n° 3</th>
<th>Patient n° 4</th>
<th>Patient n° 5</th>
<th>Patient n° 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BU/FFP/PU (n/n/n)</td>
<td>16/32/0</td>
<td>18/14/0</td>
<td>61/91 /45</td>
<td>4 /80/10</td>
<td>88/64 /12</td>
<td>77/82/40</td>
</tr>
<tr>
<td>Duration of cold ischemia</td>
<td>11 h 20 min</td>
<td>9 h 38 min</td>
<td>12 h 53 min</td>
<td>7 h 37 min</td>
<td>10 h 49 min</td>
<td>10 h 12 min</td>
</tr>
<tr>
<td>Duration of operation</td>
<td>15 h</td>
<td>13 h 30 min</td>
<td>15 h</td>
<td>11 h</td>
<td>11 h 30 min</td>
<td>13 h</td>
</tr>
<tr>
<td>Weight of native liver (g)</td>
<td>2640</td>
<td>1840</td>
<td>2460</td>
<td>2300</td>
<td>2160</td>
<td>1500</td>
</tr>
</tbody>
</table>

BU/> FFP/PU = blood unit/fresh frozen plasma units/platelet units.
Statistical analysis

The non-parametric Wilcoxon test was used to compare pre- and postoperative hemodynamic measurements (StatView 4.5s, Abacus Concepts, Inc., Berkeley CA, USA). Differences with $P < 0.05$ were considered significant.

Results

Reanalysis of the operation reports revealed that the native liver was oversized, distended and difficult to mobilize in all six patients. The surgeon described a difficult dissection in all patients due to the hypertrophy and collateral arterial network aggravated by prior operations and/or severe intra-abdominal portal hypertension. Under these conditions, venovenous extracorporeal circulation was instituted in all patients (table II). The pericardium had to be opened in one patient (n° 4) to control the suprahepatic vein. Blood transfusion during the procedure varied from 16 to 88 blood units (median, 59). Mean operative time (after anesthesia induction) varied from 11 to 15 hours (median, 13 hours 15 minutes). The liver was removed as rapidly as possible after instituting venovenous extracorporeal circulation for the three patients (n° 1, 3, 4) with cholangitis in order to avoid septic emboli. In all 6 patients the retrohepatic hepatic vena cava was resected for whole-liver transplantation.

Hemodynamic measurements

All six patients exhibited a severe hyperkinetic state before transplantation. Compared with measurements made at the beginning of the operation, mean arterial pressure increased significantly at the end of the procedure, from $66 \pm 2$ to $72 \pm 6$ mmHg ($p < 0.05$) and cardiac output declined significantly from $9.2 \pm 3$ to $5.7 \pm 0.5$ L/min ($p < 0.05$). The declines in central venous pressure (from $9.0 \pm 1.8$ to $7.0 \pm 1.4$ mmHg),

Fig. 1 – Illustration of morphological tests of Rendu-Osler-Weber’s disease with liver involvement.

a) Voluminous hepatic artery at ultrasound (arrow);
b) arteriohepatic vein fistula (the hepatic artery and the hepatic veins are both opaque: arrow) with defective hepatic perfusion (hypodense triangle);
c) large hepatic artery on arteriography;
d) opacification of the suprahepatic veins (solid arrows) while the splenic artery is still opacified suggesting arterio-suprahepatic fistula. Hypervascular pseudonodules (broken arrows).
mean pulmonary arterial pressure (from $22.3 \pm 5.9$ to $21.7 \pm 3.9$ mmHg) and wedge pressure (from $15.4 \pm 5.1$ to $12.7 \pm 2.5$ mmHg) were not significant.

**Mortality**

Two patients died during the postoperative period. The first (patient n°5°) had severe encapsulating peritonitis prior to surgery and required 88 blood units during surgery. Brain death ensued on day 2 postop in this patient despite normal liver function. The CT scan performed just before death revealed massive hemorrhage in the cerebral ventricles with no visible vascular anomaly. Autopsy could not be performed. A hemostatic gastrostomy had to be performed during the procedure in the second patient (n°6) due to rupture of a gastric arteriovenous malformation. This patient’s liver function had returned to normal levels on day 11 postoperatively when rapidly fatal (2 hours) massive gastric bleeding developed. At last follow-up (3-7.5 years, median 4 years 9 months) the four other patients were living at home with normal liver function and no cardiovascular disorder. None of the four survivors developed late extrahepatic complications of Rendu-Osler-Weber disease.

**Histology**

The native livers were oversized (1500-2640 g, median 2380 g) for the patients’ weight (44-72 kg, median 54.5 kg). All exhibited irregular bands of fibrosis with scattered telangiectases. There were no signs of cirrhosis. Localized areas of ischemic and septic necrosis, scars of healed abscesses, and diffuse intrahepatic biliary sludge and/or biliary stones were observed in the livers of the patients with cholangitis (figure 2).

**Discussion**

Liver transplantation provided long-term cure of hepatic and cardiac disease in four patients with Rendu-Osler-Weber disease. One patient died from cerebral hemorrhage two days after surgery and another from severe bleeding of a gastric arteriovenous malformation 11 days after surgery.

Biliary involvement has been frequently observed in reported cases of transplantation (table IV) and was also observed in four of our six patients but this probably reflects a bias due to recruitment in a hepatobiliary and liver transplantation surgery unit. It can be postulated that nodular transformation and fibrosis...
in Rendu-Osler-Weber disease as well as biliary ischemia induced by arteriovenous fistulization can cause compression or stricture of the large bile ducts favoring stasis, infection, and lithiasis [40, 41].

Other teams have reported 15 liver transplantations in 15 women aged 31 to 69 years (median, 44.5) with Rendu-Osler-Weber disease [5, 26-29, 34, 38, 39, 47] (table III). Of these 15 patients, 10 had symptomatic cholangitis [5, 26, 27, 29, 34, 38, 39, 47], seven had heart failure [26-29], and six had pulmonary hypertension [27-29]. Intraoperative blood transfusion was reported in detail or mentioned for six patients [5, 27, 28, 34] and was massive in three of these six [5, 27, 34], with one death [5]. One other patient [39] required splenectomy due to rupture of the spleen when the portal vein was clamped. The considerable amount of blood loss in our patients (median intraoperative transfusion = 59 blood units) was directly related to the presence of a collateral hepatic arterial network aggravated by prior procedures and/or severe intra-abdominal portal hypertension. Indeed, procedures proved difficult as shown by the median duration of cold ischemia (13.25 hours). By comparison, primary liver transplantations in our center require 9 blood units and 8.5 hours cold ischemia. For the 12 out of 14 survivors reported in the literature, long-term survival after liver transplantation was triggered by the development of new arteriovenous malformations and has to be repeated in some patients ; more importantly, it can also cause rupture of the spleen at portal clamping. 4) Pre-, per-, or postoperative prophylaxis in patients with severe arteriovenous malformations remains a major challenge, as demonstrated by our one death subsequent to uncontrollable rupture.

Ligation, calibration, and embolization of the hepatic artery has been proposed for the treatment of the cardiac and hepatic consequences of Rendu-Osler-Weber disease [9-19, 31]. Ligation and calibration have been abandoned by nearly all teams. The improvement in systemic hemodynamics obtained with arterial embolization is only temporary because it induces the development of new arteriovenous malformations and has to be repeated in some patients ; more importantly, it can also cause hepatic or biliary necrosis where mortality can reach 20% [5, 15, 17, 29, 39, 53]. We discussed arterial embolization before deciding to perform transplantation in our patients. This option was not retained for any of them because of these drawbacks and in order to prevent damage to the hepatic artery in these transplantation candidates. Furthermore, among the 15 transplant recipients reported in the literature, the decision to undertake transplantation was triggered by the development of ischemic cholangitis, or by an aggravation of a pre-existing cholangitis in six patients who had undergone embolization [29, 39, 47] or ligation of the hepatic artery [34] to lessen flow in the hepatic artery. The TIPS performed in patient n° 5 was a conceptual error. Actually, the portal shunt could only worsen the patient’s hyperkinetic state by further increasing the pre-load [17, 54, 55].
Conclusion

Liver transplantation is the treatment of choice for Rendu-Osler disease in patients with severe hepatic involvement leading to local disorders, diffuse cholangitis or portal hypertension, and/or perturbed hemodynamics causing high-output cardiac failure. Transplantation is curative for the liver disease and for the hyperkinetic syndrome. The difficulties encountered during the operative procedure may be overcome, at least partially, by adhering to principles based on the physiopathology of the disease. Indications and modalities of hepatic artery embolization should be revisited taking into account the possibility of subsequent curative liver transplantation.

REFERENCES


