

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

ORIGINAL ARTICLE

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RÉSUMÉ

Neuf centres ont rapporté 15 cas de transplantation hépatique pour maladie de Rendu-Osler-Weber avec atteinte hépatique. Six cas sont rapportés ici afin d'analyser les aspects techniques et hémodynamiques spécifiques.

Malades et méthodes — Cinq femmes et 1 homme ont été transplantés pour maladie de Rendu-Osler-Weber. Le tableau prédominant était une maladie biliaire dans 3 cas, une hypertension portale dans 2 cas et une insuffisance cardiaque dans 1 cas. L'hémodynamique systémique était mesurée par sonde de Swann-Ganz en début et en fin de transplantation.

Résultats — La transplantation nécessitait la transfusion de 16 à 88 culots globulaires (médiane = 59 culots) et durait de 11 à 15 heures (médiane = 13 heures et 15 minutes). Les 6 malades avaient un syndrome hyperkinétique en début d'intervention. En fin d'intervention, on observait une augmentation significative de la pression artérielle moyenne (de 66 ± 2 à 72 ± 6 mm Hg, $p < 0,05$), et une diminution significative du débit cardiaque (de $9,2 \pm 3$ à $5,7 \pm 0,5$ L/mn, $p < 0,05$). Deux malades sont décédés à J2 et J11 et quatre sont vivants 3 à 7,5 ans (médiane = 4 ans 9 mois) après transplantation avec une fonction hépatique normale et sans symptomatologie cardio-vasculaire.

Conclusion — La transplantation pour maladie de Rendu-Osler-Weber est une intervention difficile. En cas de succès, elle est curative sur l'hépatopathie et le syndrome hyperkinétique.

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 mmHg, $p < 0.05$), whereas cardiac output (from 9.2 ± 3.0 to 5.7 ± 0.5 L/mn, $p < 0.05$) 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.

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 ligation 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

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

Parameter	Patient n° 1	Patient n° 2	Patient n° 3	Patient n° 4	Patient n° 5	Patient n° 6
Age (yrs)/sex (M/F)	38/F	41/F	49/F	38/F	67/M	48/F
Predominant syndrome ^a	Biliary	Portal hypertension	Biliary	Biliary	Portal hypertension	Cardiac failure
Ascitis	No	Yes, infected	No	No	Yes	No
Esogastric varices or hypertensive gastritis	No	Yes	No	Yes	Yes	No
History of biliary surgery	Cholecystectomy, Operated abscess, Repeated abscess drainage	Abscess drainage due to diffuse lithiasis	No	Cholecystectomy Endoscopic sphincterotomy Operated abscess	No	No
Alkaline phosphatases (IU/L)	203	190	337	145	716	325
GGT (IU/L)	464	235	87	1168	283	221
Bilirubin (µmole/L)	344	14	249	24	36	97
ASAT/ALAT (IU/L)	92 /57	54 /32	54 /34	53 /54	34 /12	407 /359
PT (% normal)	96	66	74	100	55	61
Serum albumin (g/L)	30	31	25	44	23	33
Diagnostic criteria of Rendu-Osler-Weber disease [28]	— Family history — Epistaxis	— Family history — Telangiectasia — Epistaxis — Organ involvement — esophagus — colon	— Family history — Telangiectasia — Epistaxis — Organ involvement — lung — esophagus — colon	— Family histo — Organ involvement — brain	— Family history — Telangiectasia — Epistaxis — Organ involvement — stomach	— Family history — Telangiectasia — Organ involvement — stomach — small bowel

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

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, inflammatory bowel disease, negative serology for hepatitis B and C viruses, and negative autoimmune screen (anti-tissue, anti-nuclear, anti-smooth muscle and anti-mitochondria antibodies).

According to the classification established by Garcia-Tsa et al. [5] (table I), 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 ascitis 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 prior to transplantation. Echocardiography demonstrated a hyperkinetic state in all patients. One patient (n° 5) had a transjugular intrahepatic portosystemic shunt (TIPS) due to severe portal hypertension with intractable ascitis and esophageal varices with red signs. The TIPS had probably occluded 2 months prior to transplantation due to serious aggravation of the hyperkinetic state. The classic morphology were performed in all 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.

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

Parameter	Patient n° 1	Patient n° 2	Patient n° 3	Patient n° 4	Patient n° 5	Patient n° 6
Transplantation date	3/03/1994	1/16/1997	1/24/1997	7/28/1997	11/05/1998	02/04/2001
Transfusions						
BU/FFP/PU (n/n/n)	16/32/ 0	18/14 /0	61/91 /45	4 /80/10	88/64 /12	77/82/40
Extra-corporeal circulation	Cavo-jugular	Porto-cavo-jugular	Porto-cavo-jugular	Porto-cavo-jugular	Cavo-jugular	Porto-cavo-jugular
Duration of cold ischemia	11 h 20 min	9 h 38 min	12 h 53 min	7 h 37 min	10 h 49 min	10 h 12 min
Duration of operation	15 h	13 h 30 min	15 h	11 h	11 h 30 min	13 h
Weight of native liver (g)	2640	1840	2460	2300	2160	1500

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

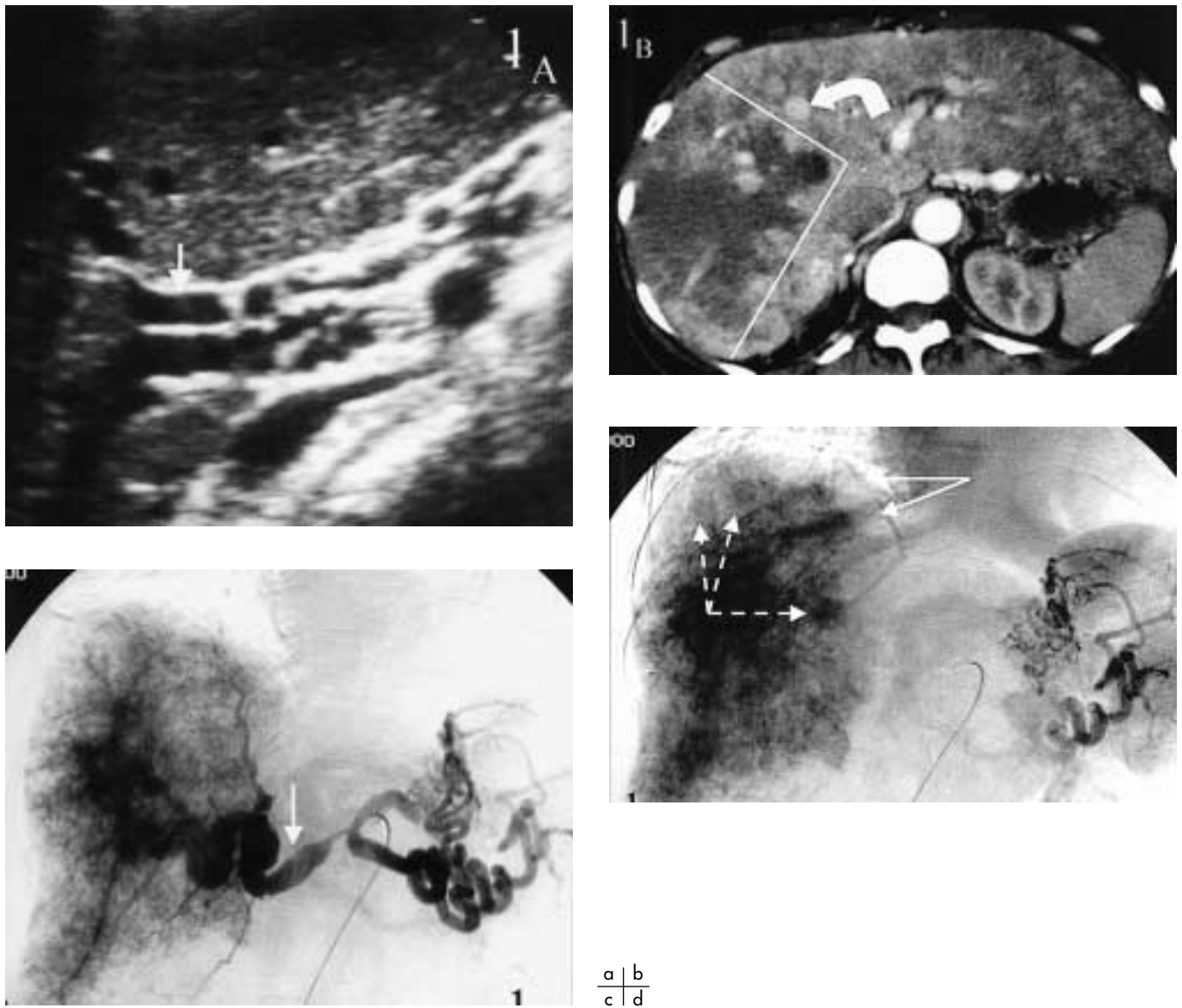


Fig. 1 – Illustration of morphological tests of Rendu-Osler-Weber's disease with liver involvement.
 a) Voluminous hepatic artery at ultrasound (arrow);
 b) arteriohepatic vein fistula (the hepatic artery and the hepatic veins are both opaque: arrow) with defective hepatic perfusion (hypodense triangle);
 c) large hepatic artery on arteriography;
 d) opacification of the supra-hepatic veins (solid arrows) while the splenic artery is still opacified suggesting arterio-suprahepatic fistula. Hypervascular pseudonodules (broken arrows).

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 ($n^{\circ} 4$) 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 ($n^{\circ} 1, 3, 4$) 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 ± 2 to 72 ± 6 mmHg ($p < 0.05$) and cardiac output declined significantly from 9.2 ± 3 to 5.7 ± 0.5 L/min ($p < 0.05$). The declines in central venous pressure (from 9.0 ± 1.8 to 7.0 ± 1.4 mmHg),

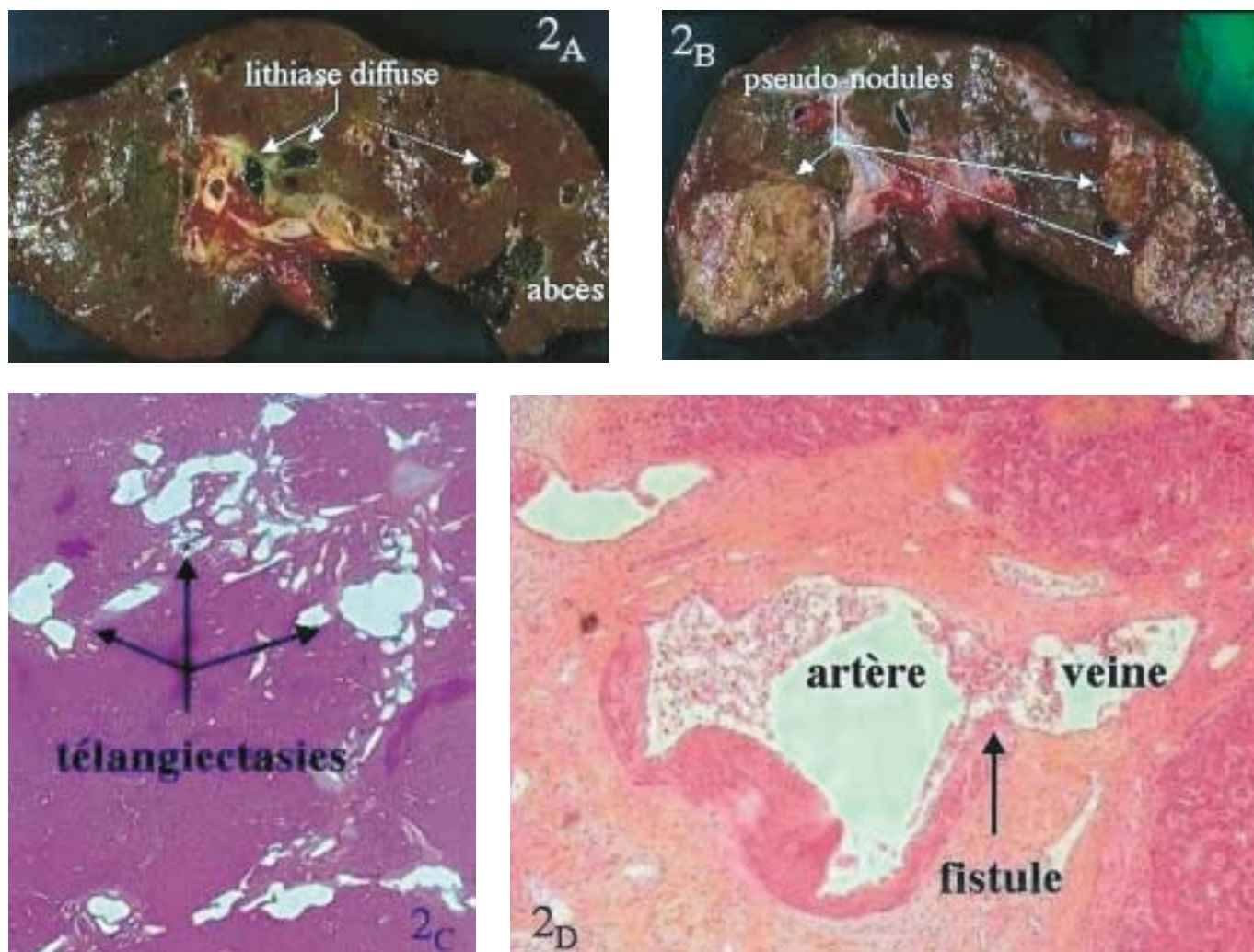


Fig. 2 – Macro and microscopic appearance of the liver in Rendu-Osler-Weber's disease with liver involvement.

- a) diffuse intrahepatic lithiasis with a scar from angiocholitis;
- b) pseudonodules;
- c) telangiectasias;
- d) arteriovenous fistula.

mean pulmonary arterial pressure (from 22.3 ± 5.9 to 21.7 ± 3.9 mmHg) and wedge pressure (from 15.4 ± 5.1 to 12.7 ± 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 2380g) for the patients' weight (44-72 kg, median 54.5kg). All exhibited irregular bands of fibrosis with scattered telangiectasias. 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

Table III. – Liver transplantation for Rendu-Osler-Weber's disease: 15 reported cases.

	Sex (M/F)/Age (yrs)	Predominant syndrome	Peroperative Transfusion n blood units	Outcome
Bauer, 1995 [26]	F, 33	Biliary + Cardiac failure	na	Living, 24 months
Saxena, 1998 [34]	F, 43	Biliary	Massive	Living, duration not given
Mc Inroy, 1998 [38]	F, 31	Biliary	na	Living, duration not given
Odorico, 1998 [39]	F, 48 F, 47	BiliaryBiliary	na ^a na	Living, 12 months Living, 9 months
Boillot, 1999 [27]	F, 36 F, 50 F, 42	Biliary + Cardiac failure + PHTBiliary + ascites + PHTCardiac failure + PHT	2679	Living, 65 months Living, 53 months Living, 29 months
Le Corre, 2000 [28]	F, 40	Cardiac failure	na ^b	Living, 1 months
Garcia-Tsao, 2000 [5]	F, NA	Biliary	Massive	Death D0, hemorrhage
Hillert, 2001 [47]	F, 39	Biliary	na	Living, 12 months
Pfizzmann, 2001 [29]	F, 45 F, 69 F, 54 F, 55	Biliary + PHTCardiac failureCardiac failure + PHTCardiac failure	nananana	Living, 65 months Living, 21 months Living, 16 months Living, 12 months

PHT = Pulmonary arterial hypertension, na = data not available. ^a rupture of the spleen at portal clamping. ^b peroperative blood loss = 1200 ml.

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 for Rendu-Osler-Weber disease has varied from 1 to 65 months (median, 15.5 months).

The hemodynamic parameters in our patients were comparable with those observed in the more severe forms of Rendu-Osler-Weber disease [27-29, 49-52]. Partial correction of the hyperkinetic syndrome observed in our six patients confirms the results from other teams [27-29].

Currently, experience shows that the following « principles » can be set down to improve the transplantation technique :

1) Concerning general anesthesia, Pfizzmann et al. [29] proposed per- and postoperative infusion of nitrates and prostacycline (epoprostenol) to lower pulmonary arterial

pressure and dopamine and dobutamine at cardioprotective doses.

2) Primary ligation of the hepatic artery can improve peroperative systemic hemodynamics [27, 28].

3) The liver can be mobilized more safely with venovenous extracorporeal circulation [27, 29].

4) Rapid removal of the liver, facilitated by venovenous extracorporeal circulation, can limit the need for vascular filling and lower the risk of septic emboli in patients with cholangitis [27].

5) 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-Weber 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.

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