Liver Transplantation in Hemophilia A

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Four patients with hemophilia A have undergone liver transplantation in our institution, three successfully. The first was a 21-year-old man with chronic active hepatitis (CAH) in whom the effects of previous abdominal operations prevented the satisfactory technical insertion of the new liver. He died intraoperatively. The second patient was a 15-year-old boy with CAH who began to synthesize factor VIII coagulant activity (F VIII:C) within 18 hours of successful liver transplantation and has continued to do so for almost 2 years (F VIII:C range 0.89 to 3.20 U/mL). The first 2 months of his postoperative course were complicated by infections, but since that time he has done well and has returned to school. The third patient was a 48-year-old man with portal fibrosis and severe ascites. He synthesized F VIII:C (range 0.96 to 1.50 U/mL) within six hours after reestablishment of circulation through the new liver. His postoperative course was complicated by numerous infections, and he died with sepsis and an acquired immunodeficiency-like syndrome 4 months after transplantation. The fourth patient was a 47-year-old mild hemophiliac with CAH who produced adequate factor VIII:C levels following transplantation (range 0.79 to 2.80 U/mL). These patients demonstrate that liver transplantation in hemophiliacs with end-stage liver disease may be lifesaving and results in correction of the F VIII:C deficiency and associated hemorrhagic tendency.

WHILE the site of production of human factor VIII coagulant activity (F VIII:C) has been unclear, data generated during the past two decades have consistently implicated the liver as the primary site of synthesis. This was accomplished utilizing liver perfusion techniques[1-3] and orthotopic hepatic transplantation into hemophiliac dogs.[4] However, others have suggested that the spleen[5-7] or lung[8] were important as well. Recent immunohistologic advances have localized F VIII:C primarily to the liver[9-10] and in particular to hepatic sinusoidal cells.[10] Whether these cells are the site of synthesis or are merely serving a storage function is not known. By recombinant DNA techniques,[11-14] F VIII:C messenger RNA has been demonstrated in the hepatocyte[14] as well as the kidney, although the latter was not identified as a site of origin.[15] The first successful human orthotopic liver transplantation in a F VIII-deficient hemophiliac was recently reported in a letter from this laboratory.[16] The new liver reversed the F VIII:C defect. The purpose of this report is to describe in detail the orthotopic liver transplantation in four F VIII:C-deficient hemophiliacs. All patients were advised of procedures and attendant risks, in accordance with institutional guidelines, and gave informed consent. In the three who survived the surgery, F VIII:C levels normalized, and their bleeding problems resolved.

CASE PRESENTATIONS

Patient 1 was a 21-year-old white, moderately F VIII:C-deficient hemophiliac who had received multiple infusions of F VIII concentrate in the past and had developed severe hepatic dysfunction. When first tested his blood showed antibody to hepatitis B surface antigen (anti-HBs), although no definite history of acute hepatitis could be obtained. A biopsy diagnosis of CAH was made in 1973; variceal bleeding became evident in 1976; and he underwent a splenectomy and a side-to-side portacaval shunt. In 1977 he had an appendectomy for a perforated appendix and in 1979 a cholecystectomy for cholelithiasis. During the last 6 years of his life he had frequent episodes of hepatic encephalopathy in addition to hemophilia-associated symptoms such as intramuscular (IM) hematomata and hemarthroses. Preoperative laboratory tests are shown in Tables 1 through 3. After a thorough evaluation the patient was accepted for transplantation; a donor liver became available approximately 6 weeks later; and the procedure was performed on May 13, 1982. Intraoperatively he utilized 15,950 units of F VIII concentrate. The technical aspects of the transplant were greatly complicated by foreshortened recipient vessels, a result of previous operations, which made the construction of vascular anastomoses difficult. Venovenous bypass during the anhepatic phase, which decompresses the portal circulation, was not being used at that time. When the portal and caval venous circulations were occluded, the intestines became edematous, and uncontrollable bleeding ensued. A total of 55 units of RBCs and 61 units of fresh frozen plasma were transfused, but the patient died on the operating table.

Patient 2 is a 16-year-old white, severely F VIII:C-deficient hemophiliac who had been treated with F VIII concentrate since early childhood. During the first year of life he had severe hepatitis B, which he transmitted to both parents. Subsequently hepatitis B surface antigen (HBsAg), anticore antibody (anti-HBc), and antibody to hepatitis B e antigen (anti-HBe) persisted. Additional laboratory tests are shown in Tables 1 through 3. In February 1984 he developed liver enzyme elevations that may have represented non-A, non-B (NANB) hepatitis or possibly a concurrent delta agent infection. In October 1984 he developed severe thrombocytopenia, which resolved following splenectomy. A simultaneous liver biopsy showed CAH. Postoperatively he developed a pancreatogastrocutaneous fistula that persisted for several months. Liver transplantation and repair of the fistula were performed on March 5, 1985. There was a small accumulation of ascites, but little difficulty was encountered during the transplant procedure, which required only four units of RBCs. The fistula repair included excision of numerous sinus tracts and required eight units of RBCs. During the operative and immediate postoperative period he was given 14,160 units of heat-treated F VIII concentrate. Eighteen hours postoperatively F VIII infusions were discontinued, and the F VIII:C levels

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Table 1. Coagulation Studies

Test	Normal Range	Patient 1 3/5/85* 3/8/85†	Patient 2 3/5/85;* 2/14/85; 3/25/85†		Patient 3 10/19/85;* 10/9/85; 10/28/85†		Patient 4 6/30/86;* 6/17/86; 7/9/86†	
Prothrombin time (s)	10-13	16.6	10.9	11.1	14.4	11.3	14.0	12.6
Activated partial thromboplastin time (s)	24-34	107.0	39.0	31.9	53.9	29.8	60.7	46.8
Thrombin time (s)	13-18	40.4	30.5	13.0	27.5	17.3	20.7	22.0
Reptilase time (s)	13-18	50.4	35.1	—	33.6	—	29.9	—
Euglobulin lysis time (min)	120 or >	90	240	240	15	150	90	210
Ethanol gel (0-4)	0	0	2	1	0	0	0	—
Protamine gel (0-4)	0	0	2	0	0	1	0	—
Wellcotest (μg/mL)	0	0	>40	>10<40	>40	0	0	—
Staph clumping titer	1-4	0	0	8	128	0	0	0
Platelet count ($10^3/\mu L$)	150-450	73	344	414	130	183	50	130

*Date of surgery.

†Dates of tests.

thereafter remained normal or supranormal. On the ninth postoperative day he underwent revision of the bile duct reconstruction (initially performed during the transplantation), and on the 28th postoperative day a subphrenic abscess was drained. Both procedures were performed without F VIII replacement therapy, and no excess bleeding was encountered. Pre-operative and postoperative coagulation findings are shown in Tables 1 and 2.

Six weeks postoperatively he was discharged, and since that time he has maintained F VIII:C levels of 0.89 to 3.20 U/mL. He was given 20 vials (100 mL) of hepatitis B immune globulin (HBIG) intraoperatively and postoperatively. His HBsAg has remained positive except for several weeks (beginning about five weeks postoperatively) when it was negative and anti-Hbs appeared. Since then he has remained positive for HbsAg, anti-Hbs, and the antibody to delta agent. He returned to temporary employment in the summer of 1985 and returned to school in the fall of 1985.

Patient 3 was a moderately obese, 48-year-old white, severely F VIII:C-deficient hemophiliac on home treatment with F VIII concentrate as needed since 1973. Since that time his bilirubin, SGPT (ALT), and SGOT (AST) had been intermittently elevated and his anti-HBs had been positive. The patient had a strong history of alcohol abuse in the past but discontinued its use in 1974. Liver biopsy in 1976 showed portal fibrosis with fatty changes and early nodule formation. His liver disease was moderately stable until July of 1985 when there was a marked increase in girth due to development of massive ascites. The spleen was enlarged; the gallbladder was contracted and contained gallstones. Subsequent progressive jaundice, malaise, accumulation of ascites, and poor response to diuretics heralded further clinical deterioration. Pre-operative and postoperative laboratory findings are shown in Tables 1 through 3. The patient was evaluated favorably for liver transplantation, and the procedure was performed on October 19, 1985. Twelve liters of ascitic fluid were removed. He received 17,290 units of heat-treated F VIII concentrate and ten units of RBCs intraoperatively. Postoperatively the patient received no F VIII concentrate, and his factor VIII:C level ranged from 0.96 to 1.50 U/mL. An episode of postoperative bleeding of unknown cause necessitated a repeat laparotomy. No excessive operative bleeding was encountered, and no F VIII concentrate was required. The patient suffered a mild rejection crisis and was successfully treated with OKT3 (Ortho Pharmaceuticals, Raritan, NJ) monoclonal antibody (MoAb) therapy. The rejection crisis was followed by pneumocystis carinii pneu-

Table 2. Coagulation Factor Assays (Pre- and Post-Liver Transplant)

Factor		Patient 1 Pre	Patient 2 Pre	Patient 2 Post	Patient 3 Pre	Patient 3 Post	Patient 4 Pre	Patient 4 Post
		3/03/82	8/27/84	3/19/85	3/11/81	11/1/85	6/17/86	7/15/86
VIII:C	U/mL*	0.02†	0.01†	1.75†	0.01†	1.15†	0.10†	2.80†
vwF	U/mL*	10.0	6.24	3.68	1.06	6.24	2.32	3.36
RCF	U/mL*	4.35	3.75	4.64	0.97	4.20	3.40	2.76
		5/13/82	2/14/85	3/25/85	10/09/85	10/28/85	6/17/36	7/9/86
I	mg/dL	180	375	420	240	270	160	440
II	U/mL*	0.3	0.78	0.90	0.48	0.70	0.46	0.80
V	U/mL*	0.57	0.80	0.96	0.36	1.25	0.22	0.44
VII	U/mL*	0.18	0.68	0.66	0.23	0.60	0.35	0.58
VIII:C	U/mL*	0.11‡	1.30‡	1.20†	0.33‡	1.40†	0.10†	1.10†
IX	U/mL*	0.11	0.95	1.00	0.26	0.86	0.48	0.90
X	U/mL*	0.49	0.80	1.05	0.68	0.58	0.56	1.05
XI	U/mL*	0.15	0.39	0.63	0.24	0.52	0.19	0.55
XII	U/mL*	0.36	0.91	0.66	0.67	0.78	0.43	0.63

*Normal range, 0.5 to 1.5 U/mL.

†Not treated with F VIII.

‡Treated with F VIII.

Table 3. Preoperative Hepatitis Serologies, Liver Function Tests, and Anti-HIV Results

Test	Patient 1	Patient 2	Patient 3	Patient 4
HBsAg	0	+	0	0
HBeAg	ND	–	ND	ND
Anti-HBe	ND	+	ND	ND
Anti-delta	ND	+	ND	ND
Anti-HBs	+	0	+	+
Anti-HBc	+	+	+	+
Bilirubin (mg%):				
Total	5.0	3.5	25.1	3.0
Direct	3.0	1.4	12.7	0.9
SGOT (AST) (IU)	202	313	120	48
SGPT (ALT) (IU)	80	79	62	26
Anti-HIV ELISA	+	+	+	–
Western blot	+	+	+	ND

ND, not done.

monia, which resolved with trimethoprim-sulfamethoxazole therapy. Subsequently a cytomegalovirus infection resolved without treatment. Four months postoperatively he developed *Escherichia coli* and pseudomonas sepsis, to which he succumbed despite parenteral antibiotics and intensive care.

Patient 4 is a 47-year-old mildly F VIII:C-deficient hemophiliac who had a F VIII:C level of 0.10 U/mL and a history of CAH secondary to NANB hepatitis accompanied by episodes of variceal bleeding, encephalopathy, and cholecystitis. Liver transplantation was performed on June 30, 1986 with 17,120 units of heat-treated F VIII concentrate and eight units of RBCs transfused intraoperatively. Preoperative and postoperative coagulation findings are shown in Tables 1 and 2. No factor VIII replacement was given postoperatively, and the new liver began synthesizing F VIII:C within four hours after the procedure. His postoperative course was complicated by a mild rejection episode, which was also treated successfully with OKT3 MoAb, and the patient was discharged approximately 8 weeks postoperatively after maintaining F VIII:C levels between 0.79 and 2.80 U/mL.

DISCUSSION

Successful liver transplantation in the hemophiliacs presented here not only reversed the hepatic failure but also corrected the coagulation defect of hemophilia A. These results demonstrate that hemophilia should not be a contraindication for the procedure and that resolution of the hemophilia, except for genetic transmissibility, should be expected. Therefore consideration of this procedure as a feasible, albeit difficult option should be given to the small but significant number of hemophiliacs who suffer from end-stage liver disease. The fatal outcome of Patient 1 suggests that scarring and fibrous changes after abdominal surgical procedures, especially shunting procedures and splenectomy, may make liver transplantation difficult or impossible and should be avoided. Whether or not the presence of human immunodeficiency virus (HIV) antibodies in a transplant candidate will alter the selection process remains to be determined. Three of these four patients were HIV antibody positive, and one of the three suffered from opportunistic infections typical of acquired immunodeficiency syndrome (AIDS) or the immunosuppressed post-transplantation state.[17] The diagnostic criteria of the Centers for Disease Control (CDC), however, exclude the diagnosis of AIDS in patients receiving immunosuppressive agents. At this point exclusion of anti-HIV-positive hemophiliacs for liver transplant consideration seems to be premature.

Although liver transplantation with its attendant risks and requirements for lifelong immunosuppression cannot be recommended as a treatment for hemophilia per se, it clearly may avert imminent death in hemophiliacs with end-stage liver disease and also appears to cure the coagulation defect. Future prospects for the availability of recombinant F VIII:C products may decrease the present high risk of transmissible liver disease[18] and eventually obviate the need for liver transplantation in hemophilia.

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