Liver Transplantation for the Budd-Chiari Syndrome

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A retrospective study was performed that analyzed 23 patients who had an orthotopic liver transplantation for the Budd-Chiari syndrome with end-stage liver disease. Patient follow-up was as long as 14 years. The technical considerations relevant to the Budd-Chiari syndrome were discussed. There have been no serious complications of postoperative anticoagulation. Three patients, all of whom died, had recurrence of the Budd-Chiari syndrome. No other patient has had evidence of recurrent Budd-Chiari syndrome on postoperative liver biopsies. One-, 3-, and 5-year actuarial survival was 68.8%, 44.7%, and 44.7%, respectively. It was concluded that orthotopic liver transplantation is the most effective treatment for patients with the Budd-Chiari syndrome and end-stage liver disease.

The Budd-Chiari syndrome is a poorly defined spectrum of disease ranging from a veno occlusive disorder with small vessel occlusion to thrombosis of the major hepatic veins and/or inferior vena cava. A wide variety of underlying disorders and risk factors such as paroxysmal nocturnal hemoglobinuria (PNH), polycythemia vera and other myeloproliferative diseases, tumors, amoebic abscesses, congenital venal caval webs, oral contraceptives, and pregnancy have been reported to cause the syndrome, although most cases of the syndrome have been attributed to cryptogenic causes.1,2 More recently antithrombin III deficiencies, lupus anticoagulants, and occult myeloproliferative diseases have been suggested to comprise a part of the cryptogenic category.3-5 Attempts at treatment have included anticoagulation, thrombolysis, portasystemic shunts, and liver transplantation. Although liver transplantation removes the cirrhotic liver disease, it may not cure the underlying thrombotic disorder. Recurrence of Budd-Chiari lesions in a transplanted liver has been previously described.6 In an additional report of 17 patients from Cambridge who had liver transplants for Budd-Chiari, only one patient who was on anticoagulation therapy had a late death that may have been related to the underlying thrombotic disorder.7 We have described another large group of patients who have had liver transplants for end-stage liver disease secondary to the Budd-Chiari syndrome to discuss the long-term prognosis, to report the results of postoperative anticoagulation therapy, and to describe the technical problems associated with this disease.

Materials and Methods

Patients

Twenty-three patients were transplanted for the Budd-Chiari syndrome between 1974 and 1988. The transplants performed before 1981 were performed at the University of Colorado Medical Center in Denver, Colorado, and those after 1981 were performed at the Presbyterian-University Hospital in Pittsburgh, Pennsylvania. This represented 1.3% of patients undergoing liver transplantation during this time period. The diagnosis was confirmed by postresection pathologic examination in all patients. The ages at time of transplantation varied from 13 to 48 years, with a median age of 30 years. Three patients were male and 20 were female.

The patients were diagnosed with the Budd-Chiari syndrome an average of 2.3 years (SD ± 2.7 years) before their transplants. The underlying etiologies (Table 1) included paroxysmal nocturnal hemoglobinuria in 1, polycythemia vera in 3, essential thrombocytosis in 1, and...
## TABLE 1. Summary of Patient Data

<table>
<thead>
<tr>
<th>OLTx No.</th>
<th>At Op.</th>
<th>OLTx</th>
<th>Etiology</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>22</td>
<td>11/28/74</td>
<td>Polycythemia vera</td>
<td>Alive</td>
<td>No anticoagulation, 2 children post-transplant, liver biopsy 1986 normal</td>
</tr>
<tr>
<td>174</td>
<td>20</td>
<td>3/25/80</td>
<td>Oral contraceptive lupus anticoagulant thrombocytosis</td>
<td></td>
<td>Died 6/81 multiple thrombotic postoperative events without anticoagulation, no thrombotic events for 1 year on anticoagulation; recurrent Budd-Chiari when anticoagulation stopped for a procedure</td>
</tr>
<tr>
<td>179</td>
<td>21</td>
<td>6/5/80</td>
<td>Oral contraceptive</td>
<td>Alive</td>
<td>No anticoagulation, no thrombotic events</td>
</tr>
<tr>
<td>181</td>
<td>16</td>
<td>8/23/80</td>
<td>Unknown</td>
<td>Died 4/82</td>
<td>Retransplanted for chronic rejection, no recurrent Budd-Chiari, died of candidiasis</td>
</tr>
<tr>
<td>270</td>
<td>28</td>
<td>12/11/82</td>
<td>Oral contraceptive</td>
<td>Died 1/83</td>
<td>Aspergillus pneumonia</td>
</tr>
<tr>
<td>371</td>
<td>31</td>
<td>3/18/84</td>
<td>Unknown</td>
<td>Died 1/87</td>
<td>Died from recurrent Budd-Chiari; one episode of subtherapeutic anticoagulation</td>
</tr>
<tr>
<td>385</td>
<td>40</td>
<td>4/20/84</td>
<td>Unknown</td>
<td>Alive</td>
<td>Liver biopsy 4/86 normal</td>
</tr>
<tr>
<td>511</td>
<td>22</td>
<td>4/4/85</td>
<td>Oral contraceptive</td>
<td>Alive</td>
<td>Hepatic artery thrombosis 9/85, subtherapeutic anticoagulation, not retransplanted</td>
</tr>
<tr>
<td>624</td>
<td>35</td>
<td>10/9/85</td>
<td>Polycythemia vera; oral contraceptive</td>
<td>Died 12/85</td>
<td>Pseudomonas pneumonia</td>
</tr>
<tr>
<td>733</td>
<td>38</td>
<td>3/2/86</td>
<td>Polycythemia vera</td>
<td>Died 3/86</td>
<td>Candidiasis</td>
</tr>
<tr>
<td>735</td>
<td>36</td>
<td>3/4/86</td>
<td>Unknown</td>
<td>Died 4/86</td>
<td>Cecal perforation</td>
</tr>
<tr>
<td>736</td>
<td>13</td>
<td>3/4/86</td>
<td>Cysteamine</td>
<td>Alive</td>
<td>No anticoagulation, no thrombotic events</td>
</tr>
<tr>
<td>919</td>
<td>40</td>
<td>10/12/86</td>
<td>Unknown</td>
<td>Alive</td>
<td>Liver biopsy 2/87, normal</td>
</tr>
<tr>
<td>1151</td>
<td>30</td>
<td>7/4/87</td>
<td>Unknown</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>1230</td>
<td>35</td>
<td>9/13/87</td>
<td>Essential thrombocytosis</td>
<td>Died 11/87</td>
<td>Pseudomonas pneumonia</td>
</tr>
<tr>
<td>1247</td>
<td>25</td>
<td>9/25/87</td>
<td>Oral contraceptive</td>
<td>Died 9/87</td>
<td>Intraoperative death from pulmonary emboli</td>
</tr>
<tr>
<td>1281</td>
<td>29</td>
<td>10/31/87</td>
<td>PNH</td>
<td>Died 11/87</td>
<td>OLTx #1: primary nonfunction OLTx #2: thrombosed hepatic artery OLTx #3: thrombosed hepatic and portal vein, Aspergillus in thrombus artery</td>
</tr>
<tr>
<td>1478</td>
<td>48</td>
<td>4/12/88</td>
<td>Unknown</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>1487</td>
<td>25</td>
<td>4/19/88</td>
<td>Oral contraceptive</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>1693</td>
<td>21</td>
<td>9/9/88</td>
<td>Oral contraceptive</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>1709</td>
<td>35</td>
<td>9/22/88</td>
<td>Unknown</td>
<td>Alive</td>
<td>OLTx #1: primary nonfunction</td>
</tr>
<tr>
<td>1755</td>
<td>42</td>
<td>10/30/88</td>
<td>Unknown</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>1774</td>
<td>32</td>
<td>11/10/88</td>
<td>Lupus anticoagulant</td>
<td>Alive</td>
<td></td>
</tr>
</tbody>
</table>

OLTx, orthotopic liver transplantation.  
PNH, paroxysmal nocturnal hemoglobinuria.
cysteamine administration for the treatment of cystinosis in 1. Seven of the patients had a significant history of oral contraceptive use. Two of these patients had an antithrombin III deficiency and two had a protein C deficiency, but each of these had an accompanying deficiency of other coagulation factors that made a decrease in hepatic synthetic function the likely cause. Two patients had associated lupus anticoagulants. The cause in the remaining nine (39%) patients was cryptogenic.

The patient with PNH was diagnosed 10 years before symptoms of end-stage liver disease began. The patients with myeloproliferative disorders were diagnosed 6 years before liver disease became clinically significant in 1, during the work-up for Budd-Chiari syndrome, which was 1 year before operation, in 1, and 7 years after operation in 1 patient who had no known cause at the time of transplantation.

The Budd-Chiari syndrome was initially diagnosed by clinical presentation and a liver biopsy with or without a venogram in 74%, and only by a venogram in 26%. An ultrasound added diagnostic confirmation in 14 of 15 (93%) of the patients in whom it was used.

In more recent patients the venogram was not performed unless there was a diagnostic question after liver biopsy and ultrasound had been performed. Nuclear magnetic resonance imaging has added additional confirmation in all eight patients it was used on during the last 2 years.

Five of the patients had a history of previous portal caval shunts and four had had peritoneal venous shunts placed. Three patients had been treated unsuccessfully with anticoagulants and thrombolysis. Prior thrombotic events had occurred in 3 patients (a deep venous thrombosis in 1, a pulmonary emboli in 2, 1 of whom required thoracotomy and embolectomy, and a sagittal sinus thrombosis in 1). The sagittal sinus thrombosis presented as a severe headache.

Indications for orthotopic liver transplantation included end-stage liver disease with intractable ascites in 52%, recurrent variceal bleeds in 43%, encephalopathy in 47%, spontaneous bacterial peritonitis in 9%, and hepatorenal failure in 34%. One of the patients was intubated in the intensive care unit and was placed on vasopressors immediately before transplantation. The decrease in synthetic function of the liver was not as severe as that in many other causes of end-stage liver disease. The average prothrombin time was 14.9 seconds (SD ± 0.7), the average bilirubin was 4.3 mg/dL (SD ± 3.2), and the average albumin was 2.8 am/dL (SD ± 0.69).

**Technical Considerations**

At operation 30% of the patients were found to have dense adhesions between the liver and diaphragm surrounding the suprahepatic inferior vena cava (IVC). Almost all of the patients had severe portal hypertension. The dissection was usually very difficult due to the large liver size and typically enlarged caudate lobe. The average liver volume on preoperative Cat scan was 2441 cc (SD ± 752 cc). Portal bypass was usually instituted early in the operation before most of the liver dissection to decrease the blood loss related to the severe portal hypertension. In some cases the connective tissue around the suprahepatic IVC was so dense that it could not be safely encircled to apply a clamp. In these cases the infrahepatic IVC was ligated and oversewn and the liver was then dissected in a retrograde fashion up to the suprahepatic inferior vena cava, as has been previously described, with the remainder of the operation preceding in the standard fashion. The suprahepatic vena caval cuff was fashioned in some cases by dissecting superiorly up to the right atrium. This was done through the diaphragm (Fig. 1). A thoracic extension was not necessary in any of the patients. The average intraoperative blood loss was 21.8 units (SD ± 17.6).

**Anticoagulation**

Most patients within the last 5 years were given dextran 40 at 20 cc/hour beginning immediately after operation and continuing for five days. Twenty-five hundred units of subcutaneous heparin was begun on postoperative day 1 if the prothrombin time was less than 18 seconds and there was no postoperative bleeding. When the patients' clinical courses were stable with no future plans for invasive procedures, the patients' were converted to Warfarin anticoagulation. This was done an average of 4.6 days (SD ± 6.2) after operation. Two patients who had early deaths and were never put on Coumadin...
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(DuPont, Wilmington, DE) due to a coagulopathy were excluded from this calculation. When an invasive procedure such as a liver biopsy or operation was planned, the patients were converted to heparin anticoagulation with a partial thromboplastin time between 1.5 and 2 times control, which was stopped shortly before the procedure and restarted 6 hours after the procedure if there seemed to be no significant bleeding.

Results

Pathologic Findings In the Native Liver

Thrombosed main hepatic veins were found in the native liver pathologic specimens in 83% of the patients. Four (17%) also had nonocclusive thrombus in their IVC. One of these four livers had membranous webs in the retrohepatic IVC in addition to thrombosed hepatic veins and cirrhosis. Typical histologic findings were central lobular congestion and necrosis with dilation of the sinusoids, obliteration of central veins, varying degrees of central-to-central and central-to-portal bridging fibrosis, and organized thrombus in branches of the main hepatic veins.

Recipient Survival

Overall 16 of 23 (69.5%) of the patients survived the initial hospitalization, including all six operated on during 1988. One-, 3-, and 5-year actuarial survival was 68.8%, 44.7%, and 44.7%, respectively. This compared with 1-, 3-, and 5-year survivals of 69%, 61%, and 57.6%, respectively, in the age-matched population of all transplanted patients in the Pittsburgh–Denver experience. This difference did not achieve statistical significance using the generalized Wilcoxin (Breslow) Method. The P value was 0.50. Using this method, the patients transplanted within the last year were excluded from the calculation. Included were Colorado patients from the precyclosporine era in which 1-year overall survival in adults was approximately 25%.

Causes of Death

Causes of early death included Pseudomonas, Candida, and Aspergillus pneumonias, sepsis from a cecal perforation secondary to an ileus despite colonoscopic decompression, an intraoperative death from a massive pulmonary emboli and, in one patient, a thrombosed hepatic artery and portal vein. Late deaths were caused by systemic candidiasis after a retransplant for chronic rejection in one patient and recurrent Budd-Chiari in two patients.

Disease Recurrence

Recurrence of the Budd-Chiari Syndrome or postoperative thrombotic complications of the hepatic vessels occurred in three patients who were studied at autopsy. One patient suffered thrombosis of her hepatic artery and portal vein 1 week after operation. The thrombus in both grew aspergilli. This patient, with an underlying etiology of PNH, had thrombosed the hepatic artery in a previous graft four days after operation despite therapeutic levels of anticoagulation. In a second patient, the recurrent Budd-Chiari syndrome occurred acutely after Coumadin was held for a procedure without interim heparin therapy. On autopsy, more than 1 year after transplantation, the liver showed evidence of previous recurrent Budd-Chiari syndrome with fibrous occlusion of multiple central and sublobular hepatic veins, old thrombi in the hepatic artery and left renal vein, as well as recent thrombi in the portal vein, IVC, hepatic veins, and pulmonary artery. This patient had been started on Coumadin after transplantation after she had recurrent postoperative mesenteric thromboses with intestinal infarction, multiple pulmonary emboli, and thrombosis of the superior vena cava. She had remained asymptomatic on Coumadin for more than 1 year despite several subtherapeutic prothrombin times. An initial extensive evaluation did not show an etiology for her hypercoagulability and repeated evaluation just before stopping her Coumadin dosage for the procedure showed a thrombocytosis possibly related to a myeloid stem disease and a lupuslike inhibitor of the coagulation system. This patient has been previously reported.6

The third patient, who died from a recurrent Budd-Chiari syndrome, was therapeutically anticoagulated except for one four-day period 4 months before she was admitted with a fever and elevated liver enzymes. After admission she had a rapid clinical deterioration. On autopsy she was found to have severe old and recent intrahepatic hepatic vein thrombosis. The other vessels were patent. She had a cryptogenic etiology for her Budd-Chiari syndrome.

The patient who died of candidiasis after a retransplant for chronic rejection 1.5 years after her first transplant had no evidence of recurrent Budd-Chiari syndrome on pathologic exam of her first allograft.

Biopsy of the liver has been performed in a number of the patients after operation. Patient 93 had a liver biopsy 12 years after operation that showed no evidence of recurrence of Budd-Chiari despite not being treated with anticoagulation. She was diagnosed with polycythemia vera 7 years after transplantation. Patient 385 had a liver biopsy 2 years after operation that showed no evidence of recurrent Budd-Chiari. No other patient has had evidence of recurrent Budd-Chiari in a biopsy. However most of their biopsies were done within 1 month of transplantation.

Anticoagulation and Thrombosis

No patient has had a serious complication caused by anticoagulation. The patients' anticoagulation treatment
has been followed closely either in the liver transplantation clinic or by their local physicians. The prothrombin times have been steadily maintained between 18 and 20 seconds with occasional drops to 15 and peaks to 24 seconds.

Postoperative thrombotic events occurred in the three patients previously mentioned and in two additional patients. One had a splenic vein thrombosis that led to variceal bleeding and was successfully treated with a splenectomy. This was the earliest patient with the longest follow-up, now 14.5 years. Her transplantation was on November 28, 1974. She was not treated with anticoagulation medication. Another patient suffered thrombosis of her hepatic vein 5 months after operation. Her prothrombin time was 14 to 15 seconds at that time. She developed multiple hepatic abscesses and was treated with surgical drainage after refusing retransplantation. She is now doing well 4 years after the hepatic artery thrombosed.

Discussion

Budd-Chiari is a syndrome of decreased hepatic outflow caused by varying degrees of hepatic venous occlusion. It may present acutely with right upper quadrant pain, ascites, and hepatomegaly, or gradually over a period of months or years, with slowly increasing ascites and/or variceal bleeds. The liver becomes progressively more congested and the majority of untreated patients eventually die from the complications of end-stage liver disease. In the study by Tavill et al., the mortality rate in 19 patients was 89%, with all 17 deaths occurring within 3.5 years of symptom onset.

Medical treatment with thrombolysis and/or anticoagulation has been successful in a small number of patients. Warren et al. reported successful treatment with streptokinase in one patient with 4 months of follow-up. Greenwood reported an initially successful outcome in one patient treated with urokinase who later rethrombosed and died of a variceal bleed 1.5 years later. Although there have been reports of successful thrombolytic therapy months after symptoms began, thrombolysis usually works better if used soon after thrombosis has occurred. This is not practical in most Budd-Chiari patients because they generally present with a long history of symptoms. In Parker’s study only 20% of the patients presented with less than a 1-month history of symptoms. Powell-Jackson et al. described streptokinase or heparin treatment in five patients with a 1-to-6 week history of symptoms. Treatment was successful in only one of the five patients and this patient was found to have cirrhosis on liver biopsy 10 years later. Her Budd-Chiari occurred secondary to trauma and she was treated with heparin. McDermott et al. reported two patients with Budd-Chiari secondary to oral contraceptives who gradually improved with only anticoagulant treatment. Millikan et al. described one patient who experienced recanalization of his hepatic veins after only diuretic treatment. This patient initially only had partial hepatic vein occlusion.

Surgical alternatives to treatment have included peritoneal venous shunts, portal-systemic shunts, and orthotopic liver transplantation. Peritoneal venous shunts have palliated the symptoms of massive ascites but have been unsuccessful in decreasing the mortality rate from the underlying progressive liver disease. Cameron documented two patients who developed histologic liver fibrosis after being treated with working Leveen shunts, as well as one patient who died of liver failure with a Leveen shunt. Some of these patients survived for several years.

Surgical treatment with portal systemic shunts has been considered the treatment of choice in patients well enough to undergo surgery, although in some studies comparing medical and surgical treatment the groups were acknowledged not to be comparable, with the sickest nonoperable patients receiving medical treatment only. McCarthy reported an 86% mortality rate after a mean survival of 6 months in 14 medically treated patients versus a 31% mortality rate in a very mixed group of 16 surgically treated patients with another four of the surgically treated patients having ongoing hepatic disease. In Ahn’s study of 30 patients, the 2-year survival rate in the medically treated group was 9%, versus 54% in the surgically treated group. This did not achieve statistical significance due to the small numbers, but a subgroup of surgically treated patients in which the IVC obstruction was also treated did have a significantly better survival rate (77% at 2 years). The number of different surgical procedures to treat Budd-Chiari has been reported to be as high as 23 and the results reported from different institutions have varied greatly. Inferior vena caval webs are common in the Orient and can often be treated with different types of membranotomy, but this form of Budd-Chiari is very uncommon in the United States and was not represented at all in our series. The most commonly used procedures in the United States are the side-to-side portacaval shunt and the mesocaval shunt, when the IVC and portal vein are patent, and the mesoaortial shunt when the IVC is stenosed or thrombosed, with a patent portal vein. The mesocaval shunt has often been used when the enlarged caudate lobe made portacaval exposure very difficult.

The successful results with these surgical procedures range from 30% to 92%, with the majority having survival rates in the 60%-to-75% range. In Cameron’s report of 12 patients operated on for Budd-Chiari, two of five patients with mesocaval shunts did well with some improvement in sinusoidal congestion on postoperative biopsy. Of seven patients given mesoaortial shunts, three of seven were successful, but two of these three thrombosed and had to be redone. Of six patients who had portacaval shunts for Budd-Chiari reported in Milan, two of six died of liver failure and four are alive at 6, 25, 27, and 29 months without encephalopathy. Ahn had estimated survival.
In our own series the 1-, 3-, and 5-year actuarial survival rates were 68.8%, 44.7%, and 44.7%, respectively. This group of patients had many high risk problems, including previous failed shunt surgery, thrombosed portal veins, and severe portal hypertension. Most of the deaths have occurred during the initial hospitalization, most often from pneumonia and other forms of sepsis. There has been a trend of improvement with no deaths during the initial hospitalization in the six patients transplanted for Budd-Chiari during 1988.

There was a second mortality rate peak during the first 2 years after operation from thrombotic complications, but this was seen in the earlier years of the study and was at least partially due to anticoagulant management. The technical aspects of a liver transplantation for Budd-Chiari have sometimes differed from transplantation for other diseases. Dense adhesions around the suprahepatic IVC often make a retrograde hepatic dissection the safest method and have allowed the dissection to be done without extension of the operation into the chest in all patients. The development of veno-venous bypass in 1983 had a major impact in this subgroup of transplant patients due to the severe portal hypertension that is usually found with Budd-Chiari. For this reason the veno-venous bypass is usually instituted before the liver dissection is undertaken.

Recurrence of the Budd-Chiari syndrome was seen in two resected liver allografts examined 2.8 and 1.2 years after transplant. Both of these patients had at least one documented period of subtherapeutic anticoagulant treatment. One other allograft in a patient adequately anticoagulated was examined after 1.5 years and had no evidence of Budd-Chiari recurrence. In patient 93 the biopsy at 12 years showed no sign of Budd-Chiari recurrence despite no anticoagulant treatment. It is not possible to know if recurrent Budd-Chiari would have been prevented in those patients who developed recurrence if they had been anticoagulated adequately at all times or if the underlying disease would have caused the problem anyway. It is clear that anticoagulant treatment was essential in some of the patients based on the experience of thrombotic episodes occurring with anticoagulant withdrawal, as well as with reported thrombotic episodes without anticoagulation therapy that did not recur with anticoagulation. If the Budd-Chiari syndrome is caused by anti-thrombin-III or protein C deficiency or by another protein made in the liver, then liver transplantation may be curative in this group of patients and they may not require postoperative anticoagulation. A patient with homozygous protein C deficiency who was cured with liver transplantation has been reported from Pittsburgh.

However, until a subgroup is well defined that does not require anticoagulation, all post-transplant Budd-Chiari patients should be therapeutically anticoagulated. We experienced no anticoagulant complications with close fol-
low-up of all patients. Based on the Cambridge experience in which only 1 of 16 anticoagulated patients had a late thrombotic-related death and in our experience in which 3 of 23 patients had recurrent Budd-Chiari syndrome, at least one of which was not adequately anticoagulated, it certainly seems that liver transplantation is indicated for the Budd-Chiari syndrome when associated end-stage liver disease is present. The underlying disease should be treated as much as is possible.

In summary 23 patients in our experience who had liver transplantation for the Budd-Chiari syndrome were reviewed. Orthotopic liver transplantation for the Budd-Chiari syndrome can be done with acceptable morbidity and mortality rates that seem to be improving. In patients with end-stage liver disease and Budd-Chiari it is the treatment of choice. Further long-term follow-up of patients with shunt surgery for Budd-Chiari, as well as with transplantation for Budd-Chiari, will be needed to determine the best treatment for patients with the Budd-Chiari syndrome and intermediate degrees of liver failure.

References