Primary Biliary Cirrhosis in the Era of Liver Transplantation

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Primary biliary cirrhosis (PBC) is a slowly progressive chronic cholestatic liver disorder. PBC affects 47,000 patients in the United States, and 3,500 new cases of the disease are reported annually. Ursodeoxycholic acid (UDCA) can prevent disease progression, but many patients ultimately need liver transplantation because of serious complications.

Presentation

More than 60 percent of patients with PBC are asymptomatic at the time of diagnosis. Such patients are identified when raised levels of alkaline phosphatase, gamma glutamyl transferase and cholesterol are found during a routine checkup. Most patients are female, and they usually range in age from 40 to 50 years. Hepatosplenomegaly is present in up to 30 percent of cases, but the physical examination is otherwise unremarkable.

Some patients present with fatigue or pruritus. Fatigue is related to poor sleep quality and depression, rather than to the severity of the disease. Pruritus is often debilitating and can precede the onset of jaundice by many months. Features of autoimmune disorders such as Sjogren's syndrome, scleroderma and arthritis are prominent; jaundice is the presenting symptom in fewer than 5 percent of cases. Patients occasionally present with variceal bleeding, which sometimes is a consequence of nodular transformation of the liver early in the course of the disease.

Diagnosis

Cholestatic liver chemistry tests, an elevated antimitochondrial antibody test (AMA) and a typical liver biopsy can establish the diagnosis. Marked elevations of IgM occur in 70 percent of cases, probably because of aberrant B cell activation.

Abdominal imaging can help to exclude the possibility of biliary tract obstruction. A liver biopsy can help to stage the disease and serial samples can assist in determining the prognosis. Biopsies can be most helpful when specimens contain at least 10 portal triads, minimizing sampling error. Patients should undergo screening for esophageal varices if the platelet count falls below 200,000/ml along with a serum bilirubin of 1.6 mg/dl and an albumin below 4g/dl. Hepatocellular carcinoma is increased in patients with PBC, so individuals with longstanding disease should undergo periodic screening for this condition.

Treatment

UDCA delays progression of the disease and prolongs survival free of liver transplantation, particularly in individuals with early disease who respond to therapy. The optimal dosage is 13 to 15 mg/kg body weight, and side-effects are few. Other drugs that have received study include azathioprine, which had no benefit, and steroids including budosinide, which led to an improvement in histology and liver chemistry tests, although side-effects were considerable. Cyclosporine, methotrexate, mycophenolate mofetil and retuximide have not shown clear benefit.

Liver Transplantation

Liver transplantation should be considered in patients who become jaundiced, particularly when the serum bilirubin exceeds 5 mg/dl. It also should be entertained if there is variceal hemorrhage, refractory pruritus or recurrent bone fractures. At Northwestern Memorial, these individuals are placed on the United Network for Organ Sharing waiting list for cadaveric transplantation. If the patient’s MELD score does not seem to be an adequate reflection of disease progression, living donor liver transplantation can be considered. This procedure can make a liver available to the patient before the disease

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Living Donor Liver Transplantation: Lessons Learned

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LIVER transplantation is the preferred modality of treatment for patients with liver failure, both acute and chronic, as well as for those with certain inborn errors of metabolism. Unfortunately, the supply of organs from deceased donors has not met the demand, and mortality on the transplant waiting list is rising. Despite attempts to maximize the deceased organ pool by accepting organs from more marginal donors, splitting livers and taking other such desperate measures, the gap continues to widen.

In 1997, the first adult living donor liver transplant (ALDLT) was performed in the United States. We performed our first ALDLT at Northwestern Memorial Hospital in 1998. Initial enthusiasm for this procedure was fueled by excellent results in pediatric recipients. However, it became evident fairly quickly that the procedure was much more involved for the donor of an adult recipient, given that the right lobe of the donor was needed for transplant. By 2001, almost a thousand ALDLT had been performed in the United States. However, two facts were emerging: There were at least three donor deaths in the United States alone and some in Europe as well; and the outcomes of the recipient procedure using a live donor graft did not seem to be as good as those using a full-sized liver from a deceased donor. Therefore, the National Institutes of Health initiated a national study, comprising nine transplant centers in the United States, in an attempt to answer two fundamental questions about ALDLT: What are the risks to the donor? And, is the recipient operation equivalent to that involving a full-sized liver from a deceased donor? The study was called “Adult-to-adult living liver” or “A2ALL.”

The seven-year study is now entering its sixth year. The first part of the study, now almost completed, included a retrospective analysis of all ALDLT performed at the nine participating institutions prior to initiation of the prospective cohort. As of May 31, 2008, 1,582 patients were enrolled: 680 in the retrospective cohort and 902 in the prospective cohort. To date, only the retrospective cohort has been analyzed, resulting in eight publications in major journals. I will focus on three of these.

**First, what about donor complications?**

A recent report by the A2ALL consortium showed that there were four deaths in living donors out of 217 donors reviewed retrospectively. One of these deaths could be directly attributed to the surgery and occurred 21 days after transplantation. The other three deaths occurred 486, 670 and 702 days after transplantation, and the causes were a train accident, suicide and substance overdose, respectively. One could argue that the last two deaths might have been related to psychiatric effects of living donation and that these donors should have been ruled out, but there was no evidence of psychiatric illness at the time of donation. There have been no other donor deaths reported in the subsequent 521 living donors enrolled in the study. What about donor complications other than death? First, mean length of stay for the four deaths was seven days with a standard deviation of three days. Of these, 339 were not re-hospitalized, 38 had one re-hospitalization, and eight and six donors had two and greater than two re-hospitalizations, respectively. Sixty-two percent of donors (243) experienced no complications, whereas out of 148 donors who experienced complications, 21 percent, 10 percent, 4 percent and 3 percent experienced one, two, three or greater than three complications, respectively. Of those who experienced complications, 106 complications were considered minor (Clavien grade 1); 103 complications required some intervention (Clavien grade 2); and eight complications were associated with a more protracted course (Clavien grade 3): one biliary complication, five abdominal wall complications such as hernia requiring repair, and two patients with significant and debilitating upper extremity neuropathia (14 other patients had transient upper extremity neuropathia). The only factor statistically associated with any complication was significant transfusion of red blood cells, indicating a difficult operation, given that the vast majority of live donors do not receive blood transfusions.

**Second, what about recipient complications?**

Another report from the A2ALL consortium showed that although the overall complication rates in recipients of living donor livers were comparable to those in recipients of livers from deceased donors, four significant complications occurred more frequently in living donor recipients: bile leak (32 percent vs. 10 percent), unplanned re-operation (26 percent vs. 17 percent), hepatic artery thrombosis (6.5 percent vs. 2.3 percent) and portal vein thrombosis (2.9 percent vs. 0 percent). However, the study found that there was a “learning curve” for ALDLT that included the first 15 to 20 procedures at each of the nine participating centers, and in fact once the learning curve was conquered, the surgical complications in ALDLT were similar to those in deceased donor liver transplantation. This learning curve has now been confirmed by a study of non-A2ALL centers.

**Third, what about recipient outcomes other than surgical complications?**

The most significant study from the A2ALL consortium summarizes recipient outcomes. Out of 808 cases that were evaluated, 389 recipients underwent ALDLT in the A2ALL retrospective cohort; 91 died after ALDLT. In addition,

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Liver Disease in the Obese Patient

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Obesity has reached epidemic proportions in the United States and many other developed nations. In the United States, the number of obese (BMI > 30) and extremely obese individuals (BMI > 40) has increased to 31 to 33 percent and 3 to 7 percent of the population, respectively. As a result, the incidence of diabetes and the metabolic syndrome has increased in parallel. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome, which is characterized by obesity, diabetes, hypertension and dyslipidemia. NAFLD affects about one-third of the general population and has quickly become the most common etiology of abnormal liver tests and an increasingly common cause of cirrhosis. The histological spectrum of NAFLD ranges from simple steatosis to steatohepatitis (NASH), which can progress to cirrhosis in approximately 20 percent of patients.

The severity of obesity is related to the risk of having advanced fibrosis and cirrhosis in subjects with NASH. (Table 1) Obesity is associated with insulin resistance, which promotes a pro-inflammatory state in the body and may thus facilitate fibrosis and progression to cirrhosis. The distribution of adiposity in obesity also is of critical importance because not all fat is metabolically equivalent. Patients with the metabolic syndrome and NAFLD more commonly have a predominantly truncal fat distribution, which corresponds to an increase in visceral adipose tissue. Visceral adipose tissue is less well differentiated and secretes an abundant number of potentially injurious cytokines. In addition, free fatty acids from visceral fat depots are released directly into the portal vein and liver. Other fat depots, such as dorsocervical lipohypertrophy (DCL), may predict insulin resistance or extent of liver injury. In a study of 123 patients with NAFLD, 28.5 percent were found to have DCL. While waist circumference correlated best with metabolic risk, the presence of DCL correlated with severity of steatohepatitis.

Although most patients with NAFLD have abnormal liver chemistry tests, abnormalities can be mild or transient and, in a sizable number of patients, persistently normal. This can make screening for liver disease in obese patients more challenging. However, clinical studies in the United States and Europe have shown that risk factors such as age > 45, BMI > 30 and the presence of diabetes can predict the severity of NASH irrespective of transaminase elevation. Treatment for NAFLD is challenging. The cornerstone of therapy is weight loss, which ameliorates the other components of the metabolic syndrome as well. (Table 2) Drug therapy for NASH is not yet approved and, when it is, it is unlikely to be a “one-size-fits-all” pill. Medical regimens will be tailored to the individual patient’s co-morbid conditions. The thiazolidinediones have emerged as a promising option, but there are safety concerns that dictate these drugs be reserved only for carefully selected patients. Bariatric surgery holds promise as a treatment for many patients with NASH who are unable to lose weight, but is certainly not the answer for all. Surgically induced weight loss is effective in improving or eliminating the metabolic syndrome and can significantly attenuate or eliminate liver injury in patients with NASH.

Looking to the future, there are many potential therapeutic targets with several drugs currently under investigation that may hold promise for the treatment of NASH. One of these agents is pentoxifylline, found to be effective in pilot studies. At Northwestern Memorial, we have just completed the interim analysis of a double blind-placebo controlled trial of pentoxifylline in NASH patients and found an improvement in both ALT and histology in patients who received pentoxifylline for 12 months. We also have ongoing clinical trials involving bariatric surgery patients studying the role of adipose tissue in liver disease injury and progression.

For further information, please contact Jeanne Gottstein, clinical research coordinator, at 312-908-5902.

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becomes too severe for transplantation to succeed.
The five-year survival rate is 80 percent, with rapid improvement in the quality of life. PBC does recur in a few cases, recognized by redevelopment of cholestatic liver chemistry tests despite adequate immunosuppression. Liver biopsy usually helps to establish the diagnosis. Graft loss is not a common outcome. Some complications of PBC, particularly osteopenia, require years of therapy to achieve stability.

Living Donor Liver Transplantation: Lessons Learned  (Continued from Page 2)

249 recipients underwent deceased donor liver transplantation (DDLT) because the living donor evaluated was not deemed suitable; 54 died after DDLT. And, 99 patients whose donors also were not deemed suitable died without a transplant. Some recipients who were candidates for ALDLT received cadaveric transplants while waiting. The study found that once the centers were beyond their institutional learning curves, patients receiving ALDLT had a 64 percent lower risk of death. Furthermore, the study found that significant predictors of mortality included center experience, MELD score at transplantation, a diagnosis of HCC and recipient age.

Summary:
Donor complications are being catalogued by the A2ALL study. They include minor, major and life-threatening complications. Donor death directly attributable to the donor procedure is infrequent but can occur. Recipient complications resemble those of liver transplantation from deceased donors only after an institutional learning curve of 15 to 20 cases. Finally, if a patient receives ALDLT at a center that has passed its learning curve, the chance of survival is much improved. Of note, we have performed more than 150 living donor liver transplants at Northwestern Memorial Hospital.²

REFERENCES:
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2. Donor morbidity paper (Ghobrial, recently accepted)
3. Recipient morbidity (Olthoff, annals of surgery)
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