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LIVER TRANSPLANTATION FOR METABOLIC LIVER DISEASES

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Metabolic liver diseases result in accumulation or deposition of excessive amounts of metabolic products that lead to cirrhosis and subsequent liver failure. The defect may lie in the hepatocytes, as in Wilson disease and glycogen storage diseases, or the liver may be affected by deposition of substrates secondary to their increased concentration in plasma as a result of increased exogenous intestinal absorption (e.g., primary or hereditary hemochromatosis) or increased administration (e.g., secondary hemochromatosis). Whatever the cause, the accumulation of metabolic products in the liver may result in cirrhosis and the consequences thereof. These can result in chronic or acute liver failure. Most of these diseases also involve organs other than the liver, thus adding complexity to the management of such cases.

Hereditary (primary) hemochromatosis (HH) and Wilson disease are the prototype metabolic liver diseases for which liver transplantation (LTx) is commonly indicated and shall form the basis of this review.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis is a genetic disease characterized by increased intestinal absorption of iron, eventually leading to its increased deposition in parenchymal organs, such as the liver, heart, and pancreas.

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This inability to limit iron absorption is inherited as an autosomal recessive trait associated with the HLA-B3, B7, and B14 histocompatibility antigens. Homozygotes alone develop the disease, and iron loss in menstruation and pregnancy may protect women.[12] It affects approximately 1 in 400 of the white population[3] and manifests as hepatic cirrhosis, hepatomegaly, diabetes mellitus, heart failure, and a leaden-gray skin pigmentation. Other manifestations include arthropathy and impotence. The diagnostic criteria include increased iron stores, mainly in parenchymal (non-RE) cells; absence of an identifiable basis for secondary iron overload; and a family history of hemochromatosis.[34]

Diagnosis is confirmed by an elevated serum ferritin level (> 400 μg/L), plasma iron, and highly saturated plasma iron binding capacity. Perl's Prussian blue stain of liver biopsy helps to grade hepatic iron overload. Hepatic iron index (HII) expresses the abnormal rate of hepatic iron accretion (hepatic iron concentration [HIC] in micromoles per gram dry weight divided by age in years). An HII of more than 2.0 in the absence of prior phlebotomy therapy or significant gastrointestinal bleeding, regardless of the presence of cirrhosis,[16] points to the diagnosis of HH. Noninvasive methods of diagnosis include computed tomography scanning, which shows increased attenuation of the liver produced by electron-dense storage iron. Magnetic resonance imaging may be used to measure hepatic iron content, and induced magnetic field by stored iron can be established by a superconducting quantum interference device technology. Standard diagnostic criteria[16] include an HIC of more than 4500 μg/g dry weight, calculated HII of more than 2.0, increased stainable iron in the liver (Perl's Prussian blue stain, grade 3+ or 4+), and more than 4 g iron removed by phlebotomy (> 16 U blood). Feder et al[16] recently reported mutation of a novel major histocompatibility complex (MHC) class 1-like gene in patients with hereditary hemochromatosis. Using full haplotype analysis, they identified a 250-kilobase region more than 3 megabases telomeric of the MHC that is identical by descent in 85% of patient chromosomes. The *HLA-H* gene was identified within this region and was noted to contain two missense alterations, one of which was found homozygous in 83% of 178 patients with hemochromatosis diagnosed using standard criteria.[16, 39] The gene is located on the short arm of chromosome 6 telomeric to the HLA A3 locus. The most important mutation is the *cys 282 tyr* substitution. The diagnostic value in the screening of patients with possible hemochromatosis and in establishing this diagnosis is being evaluated at this time.

Weekly phlebotomy of 500 mL (250 mg iron) blood until serum iron is normal is the treatment of choice in patients with HH. Chelation therapy with deferoxamine mesylate is used to treat secondary hemochromatosis. Patients with established cirrhosis manifest with symptoms and signs of portal hypertension, and the condition predisposes to hepatocellular carcinoma, which occasionally is the presenting feature.

Indications for Liver Transplantation in Patients with Hemochromatosis

Deterioration of end-stage liver disease and its manifestations of portal hypertension, namely gastrointestinal bleeding, encephalopathy, or ascites, in the presence of lack of response to chelation therapy or suspicion of hepatocellular carcinoma (HCC) are the most common indications for LTx in patients with HH. The reported prevalence of primary liver cancer in HH ranges from 7.5% to 36.0%,[1, 19, 23] and primary liver cancers are estimated to be the cause of death in as many as 45% of HH patients. In a series of 37 HH patients undergoing LTx, primary liver cancer was found in 10 patients; 8 patients had HCC, and 2 patients had cholangiocarcinoma. Incidental primary liver cancer was found in 7 of 10 patients.[23] Actual 1-year survival rate after LTx was 58% in this series; infections or sepsis were the cause of death in 10 of 13 patients (mean survival, 2.9 mo).

In their report, Farrell et al[15] established that cardiac and infectious complications are the most common causes of mortality after LTx in patients with HH. Deferoxamine given intravenously at the time of cardiac events has occasionally resulted in significant improvement and ultimate long-term survival.[4] In a series of 37 HH patients undergoing LTx, the diagnosis of HH had been suspected in only 13 (35%), indicating the necessity of increased index of suspicion for this disease in patients presenting with end-stage liver disease.[23] Kilpe et al[20] from the Health Care Financing Administration reported a 1-year survival rate of 54% after LTx in 56 patients with HH compared with an overall survival rate of 79%. Other series have reported similar results.[11]

Strategies to Reduce Mortality of Patients with Hereditary Hemochromatosis

Early diagnosis by screening and early histologic confirmation before episodes of gastrointestinal bleeding complicate the diagnosis. Vigorous iron depletion by phlebotomy or chelation therapy[15] may decrease the risk for cardiac complications after LTx for HH. The recently described genetic marker for HH[16, 39] will possibly make the diagnosis and screening of asymptomatic cases more accurate and easy to implement. Active research is currently being conducted in this field. A thorough preoperative evaluation of transplant candidates is mandatory to assess myocardial function and rule out sepsis to avoid increased postoperative mortality and morbidity.

Overall Results of Liver Transplantation for Patients with Hereditary Hemochromatosis

In a series presented by Power et al[35] none of the five patients who were followed up for 4 years after LTx for HH showed evidence of

recurrent iron overload; however, long-term follow-up is required to establish the risk for hepatic iron reaccumulation in these patients.[53] Others speculate that lack of iron deposition in transplanted livers could indicate that the primary defect for HH is in the liver and not in the gut as previously proposed, and this defect would be corrected with LTx.[22, 33] Cases of recipients who inadvertently received livers from donors with presymptomatic HH have been reported that surprisingly showed a decrease in HIC over time.[2, 9, 21] In another series of six patients from Pittsburgh, Pillay et al[30] reported absence of iron reaccumulation during the entire follow-up period in five survivors as evidenced by postoperative liver biopsies. In a review, Grace[17] addressed the difficulty of drawing conclusions about recurrence of hemochromatosis following LTx at present. HH may coexist with alcoholic cirrhosis or hepatitis C,[32] and the long-term outcome of these patients and the individual impact of each of these coexisting conditions have yet to be determined. Deteriorating cardiac condition in these patients calls for evaluation for a combined heart and liver transplantation.[51]

WILSON'S DISEASE

Wilson disease (WD) is a familial syndrome first described by Wilson in 1912. It is characterized by involuntary movements, tremors, spasticity, mental symptoms, and cirrhosis and is associated with accumulation of copper in the brain and liver and secondary renal changes. The WD gene is located on chromosome 13 and very likely encodes a copper-transporting P-type ATPase protein. The deficiency of this gene product is likely to lead to lack of copper incorporation into ceruloplasmin and defective biliary secretion of copper. WD is an autosomal recessive disease with gene frequency of approximately 0.4%.[55]

Deficiency of the plasma copper protein, ceruloplasmin, caused by impaired synthesis, is observed in 96% of WD gene homozygotes and 20% of heterozygous carriers of one WD gene.[52] The main metabolic defect is impairment of copper biliary secretion, which leads to its accumulation in the body. This metabolic defect associated with a low ceruloplasmin level is responsible for the various adverse events observed in patients with this condition.

Pathogenesis

Accumulation of copper first in the liver, followed by other organs, such as the brain, and the secondary effects of increased copper excretion by the kidneys lead to a pathologic syndrome typical of WD.[52] Copper deposition in the liver leads to its enlargement and development of steatosis. These changes progress to periportal, and later to bridging, fibrosis. It is postulated that steatosis and accumulation of copper in the liver exert a fibrogenic stimulus encouraging collagen deposition and

subsequent development of cirrhosis. Basal ganglia involvement in the brain leads to their increased pigmentation and cystic degeneration, and cortical white matter involvement may lead to degenerative changes in the cortex and the development of central pontine myelinolysis. Renal effects of increased copper excretion manifest as hypercellularity of glomeruli, nephrocalcinosis, and functional renal tubular defects (Fanconi syndrome).

Clinical Presentation

WD may present as chronic hepatitis in younger patients with symptoms of lassitude, fatigue, upper abdominal pain, jaundice, and features of portal hypertension. Sometimes, elevated aminotransferases can be the only manifestation. Other findings include splenomegaly, hypersplenism, and endocrine abnormalities. Another clinical presentation is fulminant hepatic failure that necessitates urgent LTx. These patients usually present with evidence of acute hemolysis and renal failure. This diagnosis should be entertained in young adolescents presenting with these features. Striking absence of sensory disturbances in the presence of dystonia, resting and intentional tremors, dysarthria, dysphagia, and abnormal gait are characteristic neurologic problems associated with WD. Kayser-Fleischer rings caused by deposition of copper in Descemet's membrane of the cornea are present in 40% to 60% of patients with symptoms of liver disease. Other abnormalities present in patients with WD include osteomalacia, intra-articular calcifications, disorders of spinal curvature, and skin pigmentation. Kayser-Fleischer rings are less common in children, especially those who present with fulminant hepatic failure.

A high probability of WD exists when a patient under 40 years of age presents with hepatic, neurologic, or psychiatric disturbances. Diagnosis is confirmed if a sibling has WD and liver chemistry shows elevated aminotransferases and below normal serum ceruloplasmin levels[52]; however, 5% of WD patients have normal ceruloplasmin levels, although these are in the low-normal range. Elevated serum copper levels are particularly useful in the diagnosis of WD in patients presenting with acute hepatic failure. These patients may have low-normal levels of serum ceruloplasmin and absent Kayser-Fleischer rings. Other diagnostic studies include serum copper, hepatic copper, and measurement of radiocopper incorporation into ceruloplasmin. Increased urinary copper excretion of more than 100 μg/24 h points to the diagnosis.[52] Quantitative copper estimation in liver biopsy is also a diagnostic criterion, and more than 250 μg hepatic copper per gram of dry weight of liver confirms the diagnosis, although patients with cholestatic liver disorders (i.e., primary biliary cirrhosis or primary sclerosing cholangitis) may also present with elevated hepatic copper and have Kayser-Fleischer rings. The recently described genetic marker for WD will probably facilitate the screening and diagnosis of this condition.

Treatment

Medical treatment in the form of chelation therapy with D-penicillamine (1 g orally daily) with pyridoxine 25 mg/d is started as soon as the diagnosis is confirmed. Sensitivity to D-penicillamine is seen in some patients, manifesting as rashes, fever, lymphadenopathy, and granulocytopenia or thrombocytopenia, and responds to a temporary discontinuation of the drug. 2,3-Dimercaprol or trientine (triethylene tetramine dihydrochloride)[42] may be used in patients with poor responses to D-penicillamine. Some patients with WD have been treated with zinc salts,[6] up to 300 mg of elemental zinc,[6, 52] and other investigators have used thiomolybdates.[26] The mainstay of medical therapy is periodic follow-up with clinical, hematologic, and biochemical examination to assess hepatic and neurologic recovery. A progressive decrease in the urinary excretion of copper and free serum copper concentration over time indicates a good prognosis.[61] Cessation of medical therapy may result in a rapid and irreversible hepatic and neurologic deterioration[56, 61] with acute hepatic failure that necessitates urgent LTx.

Surgical management of portal hypertension by transjugular intrahepatic portosystemic shunting (TIPS) or by surgical decompression is indicated in patients with recurrent or uncontrolled variceal bleeding that is unresponsive to standard conservative measures of sclerotherapy or banding. It is also indicated in patients who are unable to undergo LTx.

Indications for Liver Transplantation in Patients with Wilson Disease

Acute hepatic failure associated with hemolysis and hypercupremia and advanced cirrhosis and hepatic insufficiency unresponsive to an adequate trial of chelation therapy and supportive measures[5, 10, 14, 27, 28, 38, 49, 50, 61] are the most common indications for LTx in patients with WD. Use of a prognostic index based on the degree of abnormality of serum aspartate aminotransferase (AST), bilirubin, and prothrombin time on admission to select patients for LTx has been shown to be a good predictor of outcome following LTx.[28, 29] Refractory extrahepatic manifestations, such as neurologic deterioration in the absence of severe hepatic disease, are also an indication for LTx.[8, 24, 31, 43, 49]

The overall survival rate of WD with LTx has been reported to be 72% at 3 months to 20 years.[14, 43] Postdilution hemofiltration[36, 37] or heterotopic liver transplantation[47] has been reported to serve as a good bridge to treat WD patients with severe liver impairment, pending LTx. The overall outcome of patients receiving LTx for WD depends much on the severity of decompensation preoperatively and the disease presentation. In the series by Schilsky et al,[43] LTx for WD patients presenting with fulminant hepatitis was associated with 90% survival. The authors attribute this to younger mean age (17.4 $\pm$ 5.1 y) and the relatively short duration of the illness (2 d–12 w). The importance of early diagnosis, with its characteristic features of hepatic insufficiency associated with

nonimmune hemolysis and a rather low serum aminotransferase and alkaline phosphatase activity, is not commensurate with the extent of hepatocyte necrosis, and timely intervention with LTx is critical to ensure a good outcome[25, 40, 43] and cannot be overemphasized.

Liver transplantation for patients with WD associated with chronic hepatic insufficiency and failure of medical treatment has an overall survival rate of 72% in the group of patients with hepatic insufficiency.[43] The timing of LTx for patients on medical therapy depends on lack of biochemical and clinical evidence of improvement. In general, LTx should be considered for such patients 3 months after the onset of medical treatment.[43]

Patients who undergo LTx for severe progressive liver insufficiency or fulminant hepatic failure (FHF) precipitated by noncompliance to medical treatment have comparable results if LTx is appropriately timed. LTx in patients with neurologic manifestations of WD is associated with some improvement of central nervous system abnormalities.[7, 43–45] Chelation therapy with D-penicillamine or trientine may be required to be continued in selected patients after LTx, especially for persistence of neurologic symptoms caused by excessive copper deposition. This is thought to mobilize copper deposited in brain and cornea, the latter being evidenced by the disappearance of Kayser-Fleischer rings.[41, 43, 46] Cases have been reported, however, of certain patients in whom LTx does not lead to neurologic improvement.[18] Therefore, realistic considerations should be given when discussing the outcome of such a major surgical procedure with the patient and the family.

Eghtesad et al[13] reviewed 45 patients (19 males and 26 females) with WD who underwent LTx at the Thomas E. Starzl Transplantation Institute. Follow-up period ranged from 4 to 26 years. A total of 30 patients (67%) received LTx for FHF, and 15 (33%) for chronic liver failure. A total of 19 (42%) patients were younger than 18 years of age at the time of LTx. Only one patient received LTx for chronic liver failure. The overall 1-year survival rate in this series was 75.5% (69% for FHF, 87% for chronic liver disease). The actuarial 10-year survival rate was 71%, with late deaths secondary to infectious complications.

Neurologic manifestations of WD and response to LTx were evaluated in the same group. Of the 17 patients who received LTx in the presence of severe neurologic manifestations, 13 (76%) survived. A total of 10 of the survivors proceeded to complete neurologic recovery. The authors concluded that LTx can result in significant improvement of neurologic manifestations of WD, and timely intervention with LTx in patients with unsatisfactory response to medical therapy may prevent irreversible neurologic damage.

Technical Considerations During Liver Transplantation

Patients with WD can present with FHF and, often, FHF is the presenting feature of the disease. In these situations, the diagnosis is

rapidly established by biochemical markers, a family history of WD, and a liver biopsy (conventional or transjugular if the patient is coagulopathic). Because of the rapidity of onset of liver failure and resulting portal hypertension, portosystemic collaterals are lacking. These patients need to be optimized before transplantation with blood products and a quick workup to determine optimum candidacy. The LTx is usually done in a "piggyback" fashion with or without systemic venovenous bypass. A temporary portacaval shunt is constructed before hepatectomy to decompress splanchnic circulation and prevent intestines from becoming congested as a result of the lack of collateral circulation. In situations in which an organ donor is not available or social and cultural issues do not allow retrieval of organs from cadaveric donors, living-related or unrelated LTx is indicated as a life-saving measure.[54]

FUTURE DIRECTIONS

Rapid advances in cellular transplantation and molecular biology have resulted in new treatment modalities of hepatocyte transplantation[5] and gene therapy. These could potentially be used to treat patients with less-advanced disease. These novel management strategies are predicted to provide more cost-effective therapy[57–59]; however, the efficacy and longevity of these modalities are yet to be determined.

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