

Orthotopic Liver Transplantation in Children With Hepatic-Based Metabolic Disease

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SUCCESSFUL orthotopic liver transplantation provides a unique opportunity to study systemic effects of hepatic-based metabolic disease and to potentially provide a cure for previously often fatal illnesses. From May 9, 1981 through the next 12 months, 23 patients received orthotopic liver transplants. Children ranged from 7.5 months to 18 years of age. Each patient received cyclosporin-A (CyA) and steroids. Eight of the 23 patients had identifiable metabolic disease, and 3 of the 8 had associated hepatic neoplasms. Seven of the 8 patients had evidence of correction of the underlying metabolic defect or showed clinical improvement. The eighth patient died prior to documenting correction of the defect.

Metabolic indications for transplantation included: alpha-1-antitrypsin (A₁AT) deficiency (4), glycogen storage disease type I (GSD I) (with adenomas) (1), hereditary tyrosinemia (with hepatocellular carcinoma) (1), Sea Blue Histiocyte syndrome (with hepatocellular carcinoma) (1), and Wilson's disease (1). Two of the 8 patients died. Each had A₁AT deficiency. One died 6 weeks after transplant due to an hepatic abscess, and the other died 3.5 months after transplant secondary to a cerebral hemorrhage.

Patients with A₁AT deficiency are summarized in Table 1. All patients had end-stage liver disease and/or severe portal hypertension. Three of the 4 patients had abnormally low levels of A₁AT (2 with Pi ZZ and 1 with Pi SZ). Each of these 3 patients had periodic acid-Schiff stain positive and diastase-resis-

tant granules in hepatocytes. A fourth patient, OT 226, had a normal A₁AT level and was Pi MZ. Her liver did not demonstrate the characteristic intracytoplasmic granules. Post-transplant, 3 of the 4 patients had normal A₁AT levels and, where measured, assumed the Pi type of the donor. OT 203 died prior to measuring his A₁AT level and Pi type. Notably, the 2 patients who died had no evidence of granule accumulation in transplanted liver.

GSD I was diagnosed in OT 218 after presenting with acidosis, hypoglycemia, growth failure, and hepatomegaly. She had a sibling who died of the same disease at 2.5 years of age. At 8 years of age she underwent a portocaval shunt, which helped her growth but did not improve her hypoglycemia. She required frequent daytime feedings and continuous nocturnal nasogastric feedings. She developed progressive hepatomegaly, poor growth, and hepatic tumor nodules. She hemorrhaged into the tumor nodules, developed encephalopathy, and was transplanted in February of 1982.

Postoperatively she developed mild hyperglycemia that resolved within 48 hr. She maintained clinically normal glucose homeostasis on 3 normal meals per day and no nocturnal feedings. Six weeks posttransplant, detailed carbohydrate metabolic studies confirmed a normal 24-hr fast, normal oral glucose tolerance test, and a brisk response to parenterally administered glucagon. She is now leading a virtually normal life at home.

Hereditary tyrosinemia, Fanconi's renal tubular disease, and rickets were diagnosed in OT 206 at 1 year of age. Strict dietary therapy normalized her serum amino acids and corrected the renal defect with healing of her rickets. In July 1981 she was discovered to have hepatocellular carcinoma and developed progressive liver failure with markedly elevated alpha-fetoprotein (AFP) levels. She was

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Table 1. Liver Transplantation For Metabolic Disease

OT	Age (Years) Sex	Diagnosis	Pretransplant	Posttransplant	Current Status	Follow-up (Months)
192	10 ♂	A ₁ AT	A ₁ AT 44, Pi SZ	A ₁ AT 174 Pi MM	Well, bili 0.6	13
201	4 ♂	A ₁ AT	A ₁ AT "LOW," Pi ZZ	A ₁ AT "NL"	Died 6 weeks, liver abscess	
203	18 ♂	A ₁ AT	A ₁ AT "LOW," Pi ZZ	A ₁ AT NOT DONE	Died 3½ mo., cerebral hemorrhage	
226	4 ♀	A ₁ AT	A ₁ AT 157 Pi ZZ	A ₁ AT 85 MM	Well, bili 1.3	4
218	16 ♀	GSD I	Nocturnal Feeds, Liver Tumor, poor growth	NL 24 hr fast, OGTT, glucagon stimulation	Well, bili 0.5	3
206	2 ♀	Tyrosinemia	Cirrhosis, dietary restriction, liver tumor, high αFP	NL amino acids, αFP, regular diet, no tumor	Well, bili 1.1	8
222	7 ♀	Sea Blue Histiocyte	Cirrhosis, neurodegenerative disorder, liver tumor	No tumor, neurologic improvement	Well, bili 0.8	5
202	13 ♂	Wilson's	Ataxia, Cogwheel rigidity, liver and renal failure, coma, Cu 65 μg/dl ceruloplasmin 4 mg/dl	Normal intellect, mild bilateral foot drop	Well, bili 0.7 Cu 99 μg/dl ceruloplasmin 27 mg/dl	10

A₁AT, alpha - 1 - antitrypsin (deficiency) (mg/dl); Pi, protease inhibitor type; NL, normal; Bili, total bilirubin (mg/dl); GSD I, glycogen storage disease, type I; αFP, alpha fetoprotein; Cu, serum copper, normal 80-120 μg/dl; ceruloplasmin, normal 20-40 mg/dl; oral glucose tolerance test.

transplanted on 11/13/81. Urine and plasma amino acids remained normal postoperatively without any dietary restriction, and her AFP levels fell to zero by 3 weeks after transplant. In addition, there has been no evidence of recurrent tumor. She has had problems of hypertension and rejection, both of which have been controlled, and is now leading a virtually normal life.

OT 222 was diagnosed as having a variation of the Sea-Blue Histiocyte syndrome in November 1981 after evaluation for progressive hepatic disease and a degenerative neurologic disorder. Hepatosplenomegaly was discovered at 2-3 months of age, and evaluation for an etiology was unfruitful. Liver enzymes were twice normal. Bone marrow and ophthalmologic exams were normal. Liver biopsy at 5 months of age demonstrated cirrhosis without cholestasis. She had a single myoclonic seizure at that time. She developed normally until 5 years of age when parents noted an unsteady gait, tremor, and a paresis of upward gaze. She had hyperactive deep

tendon reflexes, mild hypertonicity, dysdiadochokinesia, extensor plantar reflexes, mild truncal ataxia with a normal mental age. At 6 years of age she developed cogwheel rigidity. Repeat ophthalmologic exam and ceruloplasmin were normal, and CAT scan of the head demonstrated mild cerebral atrophy. Electroencephalogram was consistent with a metabolic disorder. Leukocyte lysosomal enzymes, hepatic sphingomyelinase, and hepatic sphingomyelin were normal. An occult hepatocellular carcinoma was discovered without evidence of metastases. In November 1981, a bone marrow demonstrated foamy histiocytes characteristic of Sea-Blue Histiocyte syndrome. On 2/24/82, OT 222 underwent hepatic transplantation without complications save for moderate postoperative hypertension. She was discharged 3 weeks posttransplant on CyA and prednisone.

Nearly 4 months posttransplant her neurologic status has significantly improved. Prior to transplant she could not stand independently from a chair and could walk short

distances only with the aid of a walker. Peg board exercises were extremely frustrating. Currently, she is walking short distances without the walker, only holding someone's hand, and is able to get up independently from her seat. She can place pegs in the board with greater facility. Teachers describe her as having more stamina, being more vocal, and socially interactive. Current liver enzymes and bilirubin are normal.

OT 202 was an almost 13-year-old boy in a gifted class in school when he developed subacute hepatitis diagnosed as Wilson's disease. Despite d-penicillamine therapy, he developed progressive liver failure, ataxia and cogwheel rigidity, gastrointestinal hemorrhage, ascites, encephalopathy, and hepatorenal syndrome requiring dialysis. On 9/20/81 he underwent orthotopic liver transplantation with rapid improvement in his sensorium and renal failure. His hospital course was marked by gradual improvement in his neurologic function, although a mild right hemiparesis was noted. He had persistently high urinary copper excretion (182–434 $\mu\text{g Cu/g Cr}$) with normalization of ceruloplasmin (27 mg/dl) by 4 weeks posttransplant. Penicillamine challenge did not significantly increase urine copper excretion. Currently, the patient is in his regular advanced class in school and has only a mild bilateral footdrop as his only neurologic residua. Liver function tests are normal on CyA and prednisone.

DISCUSSION

Orthotopic liver transplantation for hepatic-based inborn errors of metabolism offers a unique opportunity to correct previously often fatal disorders. In our 4 patients with A_1AT deficiency, liver transplantation led to assumption of the donor Pi type and/or normalization of the serum A_1AT level where measured. Two patients were heterozygous (MZ, SZ) and assumed a homozygote MM state posttransplant. These data confirm similar information reported by Hood et al.¹ on 7 patients who underwent liver transplantation with A_1AT deficiency. Long-term follow-up

of Hood's patients as well as our patients reveal no tendency toward reversion to the original phenotype, diminution of serum levels of A_1AT , or development of other complications of A_1AT deficiency.² It is impossible to state, however, if these patients may escape complications during longer follow-up.

Never before has anyone with GSD I been able to lead a life with virtually normal glucose homeostasis. Our patient is the first with GSD I treated with liver transplantation. Postoperatively she demonstrated clinically normal carbohydrate metabolism. More formal testing³ confirmed the clinical impression, revealing only minor perturbations of slightly prolonged glycemic phase to parenteral glucagon, perhaps reflecting the effect of her low-dose steroid therapy. While liver transplantation appears to correct the hepatic-based glucose-6-phosphatase deficiency, it perhaps should be held in reserve for those patients who have failed vigorous medical therapy or have developed irreversible and progressive liver disease. Also, while the hepatic defect is corrected with transplantation, no evidence to date exists as to whether other organs affected by the enzyme deficiency show any benefit from hepatic transplantation.

Our patient OT 206 with hereditary tyrosinemia is the second patient with this disorder to be transplanted, and the longest survivor (8 months). Fisch and Starzl⁴ reported one other patient who normalized serum tyrosine and urinary metabolites as early as 48 hr posttransplant. Their patient died after 3 months of sepsis and portal vein thrombosis. Our patient has no clinical evidence of any residual metabolic defect. Ongoing studies, however, are continuing to search for such defects remaining in other organs, since the long-term implications of hepatic transplantation in tyrosinemia are not known. Perhaps with the improved survival of liver transplant patients,⁵ it may be warranted to consider transplantation prior to the onset of lethal complications as malignancy or hepatic failure.

The Sea-Blue Histiocyte syndrome is char-

acterized by the presence of blue, foamy histiocytes in the bone marrow. Patients may have progressive neurologic deterioration after a period of normal development characterized by ataxia, vertical supranuclear ophthalmoplegia, dementia, and often seizures along with visceromegaly with an as yet undetermined intracellularly stored substance.⁶ Our patient had normal liver sphingomyelin and normal leukocyte sphingomyelinase activity, suggesting this disorder may not be a variant of Niemann-Pick disease. In addition, she did not demonstrate dementia, although it may have been early in her clinical course. Despite a lack of basic understanding of the pathophysiology, it appears that the defect may be hepatic-based, and that liver transplantation may have some beneficial effect on halting neurologic deterioration, and perhaps may reverse neurologic impairment. Much work remains to further elucidate this unusual problem.

Neurologic impairment was clearly reversed in the patient with Wilson's disease. Liver transplantation clearly reversed the metabolic defects of copper metabolism as well. Groth et al.⁷ reported 2 teenage boys who underwent transplantation for Wilson's disease. One had neurologic involvement that slowly improved over the following 17 months. These patients, like ours, demonstrated normalization of serum copper and ceruloplasmin. Hepatic copper, not yet measured in our patient, was normal in Groth's 2 patients. It appears that liver transplantation may normalize the biochemical abnormalities in Wilson's disease, and perhaps more dramatically,

may reverse the neurologic deterioration suffered by these patients.

Overall, it appears that orthotopic liver transplantation may be an effective mode of therapy for hepatic-based and often fatal inborn errors of metabolism. While underlying metabolic defects may be corrected, long-term effects of transplantation in these disorders are not known and require further observation. In addition, with survivors of such disorders potentially living to reproductive adulthood, genetic counselling becomes increasingly important for these patients and their families.

ADDENDUM

Since the submission of this manuscript, patient OT 222 with the Sea-Blue Histiocyte syndrome has had a plateau of neurologic improvement 11 months posttransplant. Subsequent bone marrow examination still demonstrates storage histiocytes and there is evidence of a small amount of storage material in the Kupffer cells of the transplanted liver. Because Kupffer cells in the transplanted liver are of recipient origin, it is not surprising that metabolic defects possibly originating in reticuloendothelial cells are not corrected by hepatic transplantation. Although the metabolic defect in the Sea-Blue Histiocyte is unknown, results in our patient suggest that it is not liver-based.

Patient OT 202 with Wilson's disease has continued neurologic improvement with resolution of his foot drop 15 months posttransplant. Hepatic copper in the liver homograft is normal.

REFERENCES

1. Hood JM, Koep LJ, Peters RL, et al: *N Engl J Med* 302:272, 1980
2. Starzl TE: Personal communication
3. Malatack JJ, Finegold DN, Roe TF, et al: (in preparation)
4. Fisch RO, McCabe ERB, Doeden D, et al: *J Pediatr* 94:592, 1978
5. Starzl TE, Klintmalm GBG, Porter KA, et al: *N Engl J Med* 305:266, 1981
6. Neville BGR, Lake BD, Stephens R, et al: *Brain* 96:97, 1973
7. Groth CG, Dubois RS, Corman J, et al: *Transplant Proc* 5:829, 1973