Liver Transplantation for Inborn Errors of Metabolism and Genetic Disorders


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Inborn errors of metabolism or genetic disorders comprise 22% of referrals to the pediatric liver service at King's College Hospital, London (1). In the Cambridge/King's College Hospital liver transplantation program, 23% of children and 6% of adults receiving orthotopic liver transplantation have such liver disease (2). For such patients liver transplantation is now a very promising form of therapy (3). In this chapter we concentrate on aspects of the natural history and the effects of other forms of therapy, as well as on our experience of liver transplantation in three disorders: liver disease associated with α-1-antitrypsin deficiency, Wilson's disease, and tyrosinemia (fumaryl acetoacetate hydrolase deficiency) (Table 1). The role of liver and/or kidney transplantation in primary hyperoxaluria will also discussed. It will thus complement other chapters in this volume.

α-1-ANTITRYPsin DEFIcIENCY (GENOTYPE PIZZ)

α-1-Antitrypsin deficiency, coded for by a variant of a single polymorphic gene on chromosome 14, is inherited in an autosomal codominant fashion (4). It is one of the more common single-gene defects, occurring in about 1 in 2,000 to 1 in 7,000 newborns of European origin. The plasma deficiency of the glycoprotein is due to a block in secretion from the endoplasmic reticulum rather than a defect in the synthesis of the Z polypeptide.

The clinical features associated with the deficiency state are very variable, with

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1 Experience in the King's College Hospital, London, and Addenbrooke's Hospital, Cambridge. Program.
some having no overt disease, up to 20% developing liver disease of variable severity, and up to 60% developing emphysema. Although over 50% of infants with the deficiency state have abnormal biochemical tests of liver function and these remain abnormal in over 30% throughout the first 12 years of life, only 10 to 15% develop symptomatic liver disease (5). In 90% this takes the form of a conjugated hyperbilirubinemia with hepatosplenomegaly and disturbed biochemical tests of liver function presenting in the first 4 months of life. In 10% of these infants, a serious bleeding diathesis due to vitamin K malabsorption is an important component of their illness, frequently leading to permanent neurological abnormality (6). One to 2% present in later childhood or adult life with cirrhosis, with no history of prior jaundice in infancy (7). Emphysema usually has its onset in early adult life.

What causes the liver disease or determines its severity is unknown (8,9). α-l-Antitrypsin is a small monomeric glycoprotein (molecular weight 52,000) with three complex carbohydrate side chains. Circulating α-l-antitrypsin is only one of several antiproteases in the blood. It pervades tissue and is found in secretions. Its concentration increases with other acute-phase proteins under appropriate stress. In PiZZ individuals a single amino acid substitution in the polypeptide core is associated with the retention in the endoplasmic reticulum of α-l-antitrypsin deficient in carbohydrate side chains. Circulating concentrations of α-l-antitrypsin are only between 10 and 15% of normal but may rise to the lower limit of normal in stress, making phenotyping essential for diagnosis in the presence of liver disease. The physiological role of α-l-antitrypsin is unknown. In vitro, it inhibits elastase, collagenase, and leukocyte and bacterial proteases, including many that are critical in initiating or perpetuating components of the inflammatory response, such as complement activation, coagulation, and fibrinolysis. α-l-Antitrypsin is also formed by circulating mononuclear cells but not in sufficient concentration to affect the circulating concentrations. Whether these contribute to tissue concentrations is unknown (10). The accepted dogma is that emphysema is caused by the uninhibited action of proteases, activated particularly by cigarette smoking. The storage of α-l-antitrypsin within the endoplasmic reticulum of liver cells is not the cause of liver damage, since it is found

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TABLE 1. Liver transplantation for metabolic disorders

<table>
<thead>
<tr>
<th>Cambridge/King's series</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-l-Antitrypsin deficiency</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Primary oxaluria</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Proteorphyia</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>23</td>
</tr>
</tbody>
</table>
in PiZZ subjects with otherwise normal livers. A more likely hypothesis is that a tissue damage by proteases, however initiated, continues uninhibited because of lack of antiproteases. The situation may be aggravated by the production of oxidants by myeloperoxidase. Oxidants inactivate α-1-antitrypsin, further limiting its inhibitory capacity.

Liver transplantation in this disorder increases the serum α-1-antitrypsin concentration to the normal range and changes the phenotype to that of the donor (11). The features of end-stage cirrhosis are reversed. It is yet to be shown that liver transplantation will prevent the development of emphysema. The genesis of this may already be present, with over 10% of our patients having increased lung volumes in the first decade (12). Recombinant DNA technology using retroviruses has allowed the insertion of the normal α-1-antitrypsin gene into bacteria, yeasts, and bone marrow cells, but the glycoprotein produced is deficient in some of the carbohydrate side chains. The PiZ polypeptide has positively charged lysine replacing negatively charged glutamate at position 342. By inserting a second gene mutation which changes the amino acid at point 290 in the polypeptide chain from lysine to glutamate, the configuration of the peptide is restored to one that can be excreted in an experimental cell line (13).

To date α-1-antitrypsin for administration has been limited to plasma-derived material. It has a half-life of only 6 days. It has not been used in children with acute or chronic liver disease. Trials have been performed in adults with emphysema, confirming that it is possible to raise the serum concentration. Perhaps its use in infants with acute liver injury would inhibit the tissue-damaging cascade initiated by white cell protease, which activates coagulation, complement, and kallikrein production. Other possible antiproteases would include eglin C, aprotinin variants, and antioxidants such vitamin E. We are currently involved in a controlled trial of the use of colchicine as an anti-inflammatory, antifibrotic agent in this disorder. None of these therapies have an established role at present. There is thus no treatment for end-stage liver disease other than liver transplantation. The question is: When should this be done? In a few instances the liver disease in infancy is so severe that decompensated cirrhosis develops rapidly, with death as early as a few weeks of age. For such infants, should transplantation be considered?

The majority of patients recover from the acute hepatitis, the jaundice clears, and nutrition improves. A period of well-being follows. There is, however, persistent hepatomegaly with or without splenomegaly, and standard biochemical tests of liver function remain abnormal. In the course of the first decade, these will return to the normal range in approximately 25% of patients. Survival into the third decade without features of cirrhosis has been recorded in such patients. Approximately 25% die of cirrhosis, usually by 10 years of age. Features of decompensation appear up to 4 years prior to death; that is, the jaundice may return, the serum albumin drop, and diuretics may be required in controlling ascites. A further 25% with histologically confirmed cirrhosis remain in a compensated state with good growth and development throughout childhood despite persistently abnormal biochemical tests of liver function. In general, the prognosis of liver diseases is related to the severity and
duration of the acute hepatitis in early infancy, but in the individual patient the liver biopsy in the first 6 months of life is the best guide to prognosis. Those with the prospect of early death or cirrhosis can be identified by the changes seen in liver biopsies (i.e., marked portal tract changes with increased fibrosis, edema, or established cirrhosis). Such infants require reappraisal at regular intervals throughout childhood.

An important development in cirrhosis associated with α-1-antitrypsin deficiency is evidence of renal involvement, with a variety of glomerulonephropathies (14,15). Renal involvement may cause hematuria and/or proteinuria and contribute to hypoalbuminemia. The development of this renal complication does add to the difficulties after liver transplantation, particularly severe hypertension. It would seem desirable to proceed to liver transplantation before features of renal involvement are manifest.

We suggest that evaluation for liver transplantation should occur in infants with severe hepatic fibrosis in whom the cholestasis does not recede, and on the recurrence of jaundice, deteriorating coagulation studies, and/or falling serum albumin. Eleven of 15 children transplanted because of decompensated cirrhosis in 14 instances and severe growth failure in the other case are alive up to 5 years later. These required re-transplantation. After transplantation the serum α-1-antitrypsin phenotype is that of the donor, with concentrations in the normal range. The risk of future lung disease is unknown. No evidence of emphysema was found in four cases followed for more than 6 years after transplantation (11).

WILSON’S DISEASE

Wilson’s disease, an autosomal recessive disorder occurring worldwide with an estimated frequency of 1 in 50,000, is due to a defective gene on chromosome 13 (16). An abnormality in the transport and storage of copper results in copper accumulation and tissue damage. The exact pathogenesis is unclear. There is a defect in ceruloplasmin production, diminished biliary copper excretion with low concentrations of a high-molecular-weight copper-binding protein in bile (17). It has been postulated that this protein may inhibit copper reabsorption from the gut.

Early symptoms are frequently nonspecific and unless clinical signs of liver disease, or less commonly neurological abnormalities, are carefully sought for or abnormal liver function tests obtained, diagnosis is delayed for many months until jaundice or features of decompensated cirrhosis appear.

The initial presentation may be hemolysis or an apparent nephrotic syndrome. Symptomatic liver involvement in Wilson’s disease may mimic any form of acute or chronic liver disease. It is invariably fatal unless treated. Except in the four categories detailed below, α-penicillamine or other chelating agents, such as triethylene tetramine, together with a low copper diet, should adequately control liver damage, creating a stable compensated cirrhosis compatible with a good long-term prognosis. Oral zinc sulfate may also stabilize liver disease if the toxic side effects of these
drugs cause their withdrawal. Zinc has an antagonistic action against copper in many metabolic processes. Its inhibitory effect on copper absorption has been used to maintain a negative copper balance and to reverse abnormal biochemical and pathological abnormalities in patients already treated with penicillamine. These are reports in neurological literature of zinc being used as the sole mode of therapy.

Patients presenting with fulminant hepatic failure die, as do those with decompensated cirrhosis (18,19). If encephalopathy or severe hepatic decompensation occurs, hemofiltration or plasmapheresis may keep the patient alive until grafting is possible. For those with less severe liver disease we have developed a prognostic index (Table 2) based on the degree of abnormality of the prothrombin time, serum aspartate aminotransferase, and bilirubin concentration at the time of instituting therapy in 27 patients, 13 of whom died within 56 days of initiating treatment. It has correctly predicted the response to treatment in all but one subsequent case (see below). Patients with a prognostic index of 7 or greater should be referred for liver transplantation.

In one 12-year-old with decompensated cirrhosis and a prognostic index score of 9 we prescribed zinc sulfate 100 mg every 12 h, giving penicillamine in standard doses at the intervening 6 h. Gradually over the course of 2 months the liver function improved and subsequently returned to complete normality with a remission of all clinical features of liver disease. This has not occurred in other cases and we would not advocate this other than as a measure to be taken while waiting for an organ to become available.

Liver transplantation must also be considered for those who relapse because therapy has been stopped against medical advice. Hepatic decompensation occurs within 6 to 18 months and rarely (if ever) is it controlled by reinstituting penicillamine. Will such patients take immunosuppressants indefinitely? Following transplantation, serum ceruloplasmin levels return to normal over the course of 1–2 months. Radiolabeled copper studies show normal copper uptake by the liver graft with prompt biliary excretion. Kayser-Fleischer rings may be present for up to 2.5 years. Neurological abnormalities may improve rapidly, but some improvement may occur over the course of the next 4 years even in those with very advanced disease (20). Eight
of 14 patients transplanted at a mean age of 20 years (range 5.6 to 38.5 years) survived 6 months to 5 years after transplantation. Four were transplanted having had a fulminating presentation, the remainder having decompensated cirrhosis.

HEREDITARY TYROSINEMIA

The biochemical and diagnostic features and dietary treatment of hereditary tyrosinemia are considered elsewhere in this volume. Some clinical features should be emphasized. The acute form presents in the first 12 weeks of life with failure to thrive, vomiting, diarrhea, a cabbage-like odor, hepatomegaly, edema, ascites, splenomegaly, and a bleeding diathesis. Death from liver failure usually occurs by 8 months of age, with less than 10% surviving to 1 year (21,22). Such patients should be considered for transplantation if, despite conventional dietary and drug treatment, features of liver failure are not ameliorated or growth arrest occurs.

The chronic form may evolve from the acute or present with cirrhosis, renal tubular dysfunction, and hypophosphatemic rickets. Hepatocellular carcinoma develops on the basis of a macronodular cirrhosis in over 30% surviving beyond 2 years of age and is presumably likely to develop in all. Neither serum α-fetoprotein concentrations nor scanning by ultrasound, CAT, or NMR distinguish malignant transformation from regenerating nodules. It has been suggested that a “window of opportunity” for transplantation exists between 24 and 36 months of age. Although occasional survival into adult life has been described, there seems to be little reason to delay transplantation after the child weighs 10 kg or after 24 months of age if no extrahepatic metastasis has been identified. Our experience is limited to four patients, one of whom died of metastatic disease having received a transplant at 5.4 years, while those receiving transplants at 1.6, 2.1, and 7.4 years survive 1.5–2.5 years later.

PRIMARY HYPEROXALURIA TYPE I

Primary hyperoxaluria type I is an autosomal recessive disorder with a defect in hepatic metabolism leading to renal and cardiovascular damage. There is deficiency of peroxisomal alanine:glyoxylate aminotransferase (EC 2.1.44) in liver, kidney, and spleen. Glyoxylate accumulates and is metabolized to oxalate and glycolate. The oxalate is excreted in the urine, causing calcium oxalate nephrolithiasis, nephrocalcinosis, and renal failure (23).

Initially, renal transplantation was attempted for this disorder, but calcium oxalate causes early graft failure. This led to the introduction of liver and kidney grafting, which has proved successful. Another approach is to perform a liver transplantation, then to proceed to renal transplantation when the oxalate pool is diminished, so as to avoid renal allograft failure. It is important that transplantation be performed before severe cardiovascular disease arises due to systemic oxalosis. Eight patients with a median age of 19 years (range 10–28) have been transplanted in this program with five long-term survivors. The youngest had a combined kidney–liver transplant
with excellent renal and hepatic status 18 months later, although he continued to pass renal calculi for 9 months after the procedure. It particularly important to maintain a very high urinary output for the first few days post-transplant when the renal oxalate load is still very high (24).

**CYSTIC FIBROSIS**

With increasing long-term survival in cystic fibrosis, it has become recognized that between 10 and 20% of young adults develop features of cirrhosis. The major problems are alimentary bleeding from esophageal varices and massive splenomegaly with features of hypersplenism. Liver transplantation has been reported, with 50% surviving with a very good quality of life, without evident deterioration of pulmonary function (25). In at least one instance, combined liver–heart–lung transplant has been performed. In the United Kingdom, heart–lung transplant has been performed in over 60 patients with cystic fibrosis with 1-year survival rate of 60%. The majority of deaths are due to technical problems in the immediate post-transplant period, although some late deaths occur from an obliterative bronchiolitis. Cirrhosis may be well complicated in cystic fibrosis and its presence may only come to light after transplantation. The role of organ transplantation in this condition is at present less well defined than in other disorders, where there is less multisystem involvement.

**CONCLUSION**

Liver transplantation at present has a well-defined role in giving a good quality of life to patients with in an increasing range of metabolic disorders. It also gives new insight into the basic metabolic defects in many disorders and defines the hepatic contribution to their pathophysiology. Its place in management will require constant review as new forms of therapy evolve and as techniques of liver transplantation change.

**REFERENCES**


DISCUSSION

Dr. Otte: We have a patient suffering from α-1-antitrypsin deficiency who has hematuria and probably kidney damage. What is the future of the child if he is transplanted? Is it going to be reversible?

Dr. Mowat: We followed four patients who have had albuminuria and two of them had hematuria; over the course of 18 months it cleared.

Dr. Otte: For Wilson’s disease presenting as the fulminant form you mentioned that transplant should be done when the score was above 6. We have had a very poor experience with this kind of disease, and we have never been able to save a patient without a transplantation. I wonder how you would define the fulminant form. Is this a patient with neurological disorder or with hemolysis?

Dr. Mowat: The patients we have defined were those with encephalopathy, but any with a score of 7 or over would need a transplant, unless we have some better way of treating it. I
think these patients need very active intervention with hemofiltration and plasmapheresis while you try to get a liver. I think they should go right to the top of the list. As I described, we had five children who died within 5 days of admission.

Dr. Otte: Regarding the Crigler-Najjar syndrome, you said, and this is quite obvious, that transplantation should be performed before brain damage occurs. But how can you predict when brain damage is going to occur? If it has occurred it is too late; it is not reversible as far as I know, since there is destruction of the brain tissue. So do you refer to the age of the patient, or how else can you predict it? When are you going to consider having the child transplanted?

Dr. Mowat: I don’t think you can predict the brain damage. Our data base for serum bilirubin and brain damage goes back to the late 1940s, where we had a lot of experience with rhesus immunization. Since then there has been little new evidence, so we tend to go along with the belief that if we can keep the serum bilirubin less than 300 μmol/liter or 20 mg/dl, the risk of brain damage is relatively low. Professor Otte is quite right to be concerned about this because the children with Crigler-Najjar type I who have not died in infancy but have gone through to early adolescence very frequently develop neurological deterioration, even though the serum bilirubin may not have been higher than perhaps 250 μmol/liter. I try to keep my patients’ serum bilirubin below 200 μmol/liter, hoping that they have sufficient reserve to withstand a rise in bilirubin if they get an infection.

Dr. Buts: Do you believe that in Wilson’s disease there is a relationship between the blood level of ceruloplasmin and the severity of the disease?

Dr. Mowat: I have no evidence for this. The vast majority of our patients have unmeasurable ceruloplasmin and I am not aware of an association with the severity of liver disease.

Dr. Van Hoof: To avoid mental retardation in Crigler-Najjar disease, I think that weekly measurement of unconjugated bilirubin is insufficient. The rate of bilirubin production (destruction of heme) can be widely variable, and the transport of unconjugated bilirubin depends on the amount of albumin.

Dr. Mowat: A great deal of effort, particularly in the neonatal period, has gone into trying to get some estimate of reserve capacity for safe carriage of bilirubin. As far as I am aware, we have still no other measure that we can use successfully.

Dr. Sokal: I would like to add a comment about Crigler-Najjar disease. Although I am convinced that the only real therapy is liver transplantation, there is another potential way to help these patients. This has been done in neonates with hyperbilirubinemia due to ABO incompatibility. Administration of a heme synthesis inhibitor such as SN-protoporphyrin leads to a significant decrease in serum bilirubin levels. One child currently on our mailing list has been given this drug since he is not well controlled by phototherapy. His bilirubin level fell from 18 mg to 12 mg per 100 ml (308–205 μmol/liter) without additional phototherapy. However, he had photosensitivity and abnormal liver function tests which are possibly due to this drug; for this reason, this compound should not be recommended for general use, although it is likely to help some critical Crigler-Najjar patients on the waiting list for transplantation.

Dr. Mowat: Under these circumstances you don’t need to worry about liver damage. Does it have to be given by injection?

Dr. Sokal: No, it can be given orally.

Dr. Hobbs: I would like to make three comments. First, let me support you in that the protein reference units in Great Britain provide a monitoring service for Wilson's disease and there is no correlation between the residual ceruloplasmin level and the clinical severity. I would fully support Professor Mowat’s index, which is a sort of thing you need. Second, α1-antitrypsin deficiency was first described in 1963 by Laurell and Eriksson and was associated with lung disease. I believe that I was the first to describe it in association with angionecrotic renal disease.
in 1971. Three patients had to have renal transplants and one relapsed some years later. I must add that the disappearance of proteinuria or hematuria does not mean that the kidney has recovered. It just means that the leaky glomeruli have been fibrosed completely. But I am quite sure that having corrected the α-1-antitrypsin deficiency you are going to prevent further attacks. Third, I think there is a function for α-1-antitrypsin. Phylogenetically, it has evolved along with antithrombin III and has become a protein that is useful for survival. Its real function is the inhibition of white cell elastase, and it is the elastin destruction that results in the angionecrosis in the renal condition and in the destruction of the lung.