Liver transplantation in metabolic disorders

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Abstract

Liver transplantation in pediatric patients represents about 10% of a total of 23.000 transplantations registred in the European Liver Transplantation Register (ELTR)since 1968. The pediatric patients show a specific spectrum of indications with cholestatic liver disorders ranking first, followed by hepatic based metabolic disorders. There has been a significant improvement of survival in transplantation since the early 80ies. The overall survival standard is nowadays in the range of 80%. There is a trend towards even better results in metabolic disorders.

The clinical presentation of liver disease caused by metabolic disorders shows a wide range from acute liver, cerebral, cardiac and renal failure to chronic end stage liver, kidney and heart disease potentially complicated by hepatocellular carcinoma. In many cases, the diagnosis of a underlying metabolic disorder is very difficult and time consuming so the decision to do a liver transplantation may be necessary before a final diagnosis is established.

Having these problems in mind, the consideration of absolute and relative contraindications for liver transplantation in metabolic disorders is even more difficult than it is already in cholestatic or inflammatory liver disorders. The individual evaluation of a patient suffering from a hepatic metabolic disorder must consider in addition the often dramatic restriction of quality of life due to rigorous dietary restrictions or other therapies. This makes clear that suitable methods to measure quality of life must be developed and applied in order to fulfill this goal.

The extension of indications for liver transplantation even to disorders with only partial defects in otherwise healthy livers was possible by using innovative surgical techniques such as partial, living related, split, in situ split and auxiliary orthotopic transplantation. These techniques allowed to reduce the mortality on pediatric waiting lists significantly without restricting the general donor pool. However, living related liver transplantation is handicaped by the heterozygous status of the parent donor. This plays a role especially in patients with progressive familial intrahepatic cholestasis (PFIC) and Wilson's disease. (Acta gastroenterol. belg., **1999**, 62, **300-305**).

Key words : liver transplantation, metabolic disorders.

Introduction

Liver transplantation in pediatric patients has shown a considerable growth in the last 20 years. Starting with single patient series in 1978, pediatric liver transplantation is performed in the range of 250 transplants a year as registered in ELTR (1). This development may be related to progress in surgical techniques, improvement in intensive care knowledge and better management of immunosuppressive therapy (2). With growing experience which is reflected by improving results with regard to survival rates, there was an increase of indications to be observed. Especially in the pediatric age group the challenge of treating metabolic disorders by dietary or palliative medical regimen made pediatricians think about replacement of the native diseased liver by a non diseased donor liver. This therapy equals in fact a gene therapy. Today, the result of these considerations is that hepatic based metabolic disorders rank second after cholestatic disorders in all pediatric transplantation indications (fig. 1).

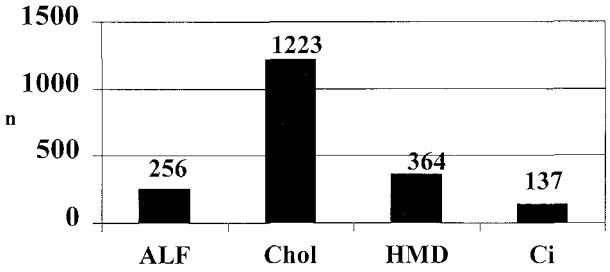

Fig. 1. — Indications for liver transplantation in pediatric patients aged up to 15 years as registred in the European Liver Transplant Register (1).

The classical scheme of indications and contraindications of liver transplantation has been cancelled since some time. At the beginning, only candidates with chronic end stage liver disease without multiorgan failure were accepted for transplantation. Hepato-pulmonary syndrome, hepato-renal syndrome, systemic infection, vascular malformation, systemic disease and even body weight below 10 kg were regarded as contraindications (2,3). Today, only active infection and significant pulmonary hypertension are regarded as contraindications (2). Systemic involvement of other organs in metabolic disorders for instance in cystic fibrosis, organic acidemias, mitochondrial respiratory chain defects are not regarded as absolute contraindications, since reports on good results after liver transplantation in these disorders have been published (4-7).

The shortage of donor organs was the limiting factor of transplantation in children only some years ago. The mortality on the waiting list was up to 25% (8). If all surgical innovative techniques such as living related, split-, in situ split and orthotopic auxiliary transplantation are considered, mortality on the waiting list is no longer a relevant problem (9). Using this extended donor pool for pediatric patients without reducing the number of donor organs for adult recipients, the inclusion of hepatic metabolic disorders in the list of

indications for liver transplantation is world wide accepted. The comparison between pediatric transplant programs in Europe and USA shows coincident figures (2,10).

In this expanding field of modern medicine the risk of approaching reasonable ethical limits or even crossing them by just applying medical techniques is high. Especially in metabolic disorders the individual evaluation of the risk / benefit ratio is essential. This review aims to give a rational approach to this difficult subject.

Indications

The hepatic metabolic disorders may present either as chronic or acute and stage liver disease (2,11). The chronic course may present as cirrhosis, cirrhosis and hepatocellular carcinoma (table 1). Other disorders may lead to chronic and acute failure of other organs than the liver. Finally, some of these metabolic disorders lead to acute liver failure with or without involving other organs (11).

Table 1. — **Indications for liver transplantation in different hepatic metabolic disorders**

Indication	Disorders
Cirrhosis	A1 ATD, CF, GSD III, IV, PFIC 1-3, Wilson's d.
Non-responders	GSD I, FHC, MMA, NHC, Tyrosinemia
Preemptive	Crigler-Najjar, Hyperoxaluria, Propionic acidemia, Urea cycle defects
Others	CF, Hyperoxaluria I, Tyrosinemia

From a pragmatic point of view, indications for liver transplantation in metabolic disorders may be derived from the natural course of the disease and its response to dietary or medical therapy and the risks of developing complications. According to these aspects, transplantation may be indicated in *cirrhosis, no response* to therapy, as preemptive treatment in patients at risk of undergoing complications and in patients with *hepatocellular carcinoma or chronic end stage renal disease* (table 1).

The individual evaluation of the risk / benefit ratio is mandatory in any patient whatever the underlying disorder is like (fig. 2). The knowledge of the natural course of the disorder determines the decision for transplantation primarily. On the other hand the large scale of phenotype expression of a given metabolic defect underlines the need for inidividual decisions. The understanding of whether or not there is a relation between clinical expression and molecular biology findings is not yet answered in many disorders (13).

The quality of life of a patient with metabolic disorder may be impaired by dietary regimen such as low protein diet in tyrosinemia (14), by phototherapy in Crigler-Najjar disease (12) or by partial biliary diversion in PFIC patients (15). On the other hand, there is no 100% survival guarantee after liver transplantation. The risk of suffering from cholestatic or viral liver disease after liver transplantation in a patient with only a partial liver function defect such as bilirubin conjugation in Crigler-Najjar disease must be balanced carefully against the risk of having a severe neurological defect due to Kernicterus. The impact of medical and surgical regimen before and after liver transplantation must be considered as well. The risk of hepatocellular carcinoma in many hepatic based metabolic disorders (table 1) must be balanced with the risk of lymphoproliferative disease under long-term immunosuppression (16) and the neurological, renal, cardiovascular and even hepatic complications (17).

Contraindications

Contraindications for liver transplantation have altered remarkably in the last years. Many conditions previously regarded as contraindications such as portal vein thrombosis, vascular anomalies, previous operations and body weight below 10 kg are now considered to be no contraindication per se (2). Multivariate analysis of predictors of the outcome of liver transplantation have shown that malnutrition, bilirubin and albumin serum concentration are significantly influencing the posttransplant outcome (18). So optimized timing of transplantation avoiding these risk constellations has become essential.

However, systemic infection is still an absolute contraindication. Living related transplantation yields the option to postpone transplantation until the recipient is treated effectively (19). Systemic disease is another contraindication, if cerebral, cardiac, pulmonary, renal or gastrointestinal involvement are not reversible under transplantation (2,7,20). Many hepatic metabolic disorders are found within this category : Organic acidurias, storage diseases, respiratory chain disorders and peroxisomal diseases (2,6,7,20). In cystic fibrosis, liver transplantation is accepted in end stage liver disease but compensated pulmonary function (5,21).

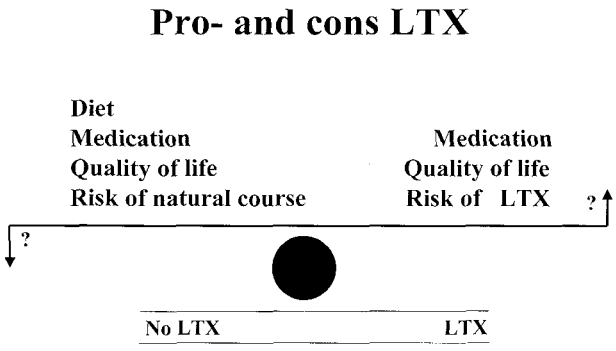

Fig. 2. — Balancing of conventional and surgical therapy in hepatic metabolic disorders

Surgical methods

In hepatic metabolic disorders LTX may be performed with different surgical techniques. In *cadaveric grafts*, the primary option in children below 15 kg body weight should be the split rather than the reduced size technique. This procedure saves the right liver lobe for an adult recipient. In pediatric recipient above this weight limit, a reight lobe of a small donor may be used. The outcome of both left lateral segment and right lobe recipient is best if the in situ split technique is used (20).

Living donation has been used in many patients suffering from hepatic based metabolic disorders. The basic question to be answered in these cases was wether or not the heterozygous donor will have disadvantages from loosing either 30% of his functional liver mass (left lateral segment) or even 60% if the right lobe is used. Even the recipient may have disadvantage by receiving a heterozygous liver (22).

A third surgical option in liver grafting may be the *orthotopic auxiliary transplantation.* This technique makes only sense in those metabolic disorders where no toxic compounds are produced in the remaining right lobe (23). These transplantations may be performed with cadaveric and living donated parental organs.

Results

The overall survival of patients transplanted for hepatic metabolic disorders trends to be better than in cholestatic diseases (1) (fig. 3). The 5 year survival of all pediatric patients is reported to be in the range of 70-86% (2). With regard to different hepatic metabolic disorders, the reported survival rates are varying between 45 and 100% (table 2-5).

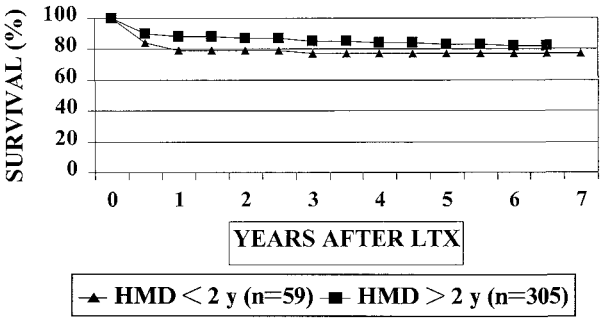

Fig. 3. — Results of liver transplantation in pediatric patients suffering from hepatic metabolic disorders as registred by ELTR (1).

Regarding the Kaplan-Meier survival curves after liver transplantation, it becomes clear that the first 2 months are the most critical ones. The losses of organs and patients are related to infections, multiorgan morbidity and surgical complications (17). These complications occur inthe range of 7–17% (17). Organ and patient losses due to rejection are almost neglectable.

The survival of these metabolic patients means a significant change of quality of life : Dietary restrictions are not longer necessary in GSD I, propionic acidemia, mitochondrial respiratory chain disorders, tyrosinemia and urea cycle defects. Phototherapy is no longer necessary in children with Crigler Najjar disease and plasmapheresis may be stopped in familial hypercholesterolemia. Medical therapy such as antioxidant therapy in neonatal hemochromatosis, NTBC in tyrosinemia and chelating agents in Wilson's disease are stopped but replaced by immunsuppression. In patients with chronic end stage liver disease symptoms and sequelae of cirrhosis disappear i.e. in a1 ATD, cystic fibrosis, PFIC 1,2 and 3, tyrosinemia and in Wilson's disease. The risk of developing a hepatocellular carcinoma is stopped as well.

In long-term studies after liver transplantation including patients with metabolic disorders, normal growth is observed in about 80% of patients (24,25). Normal pubertal development is reported after LTX, followed by normal pregnancies (26). Neurological defects however are not cured by transplantation (27).

The long-term effects of immunosuppression include those related to steroids such as stunting, obesity and bone disease, related to cyclosporin A such as gingiva hyperplasia, hirsutism, and related to both, cyclosporin A and tacrolimus such as neurotoxicity, arterial hypertension and nephrotoxicity (2). Oligo and monoclonal proliferation of EBV infected lymphocytes bear the risk of lymphoproliferative disease, especially if cytotoxic T-cell antibodies have been used (28,29).

Specific disorders

A1 ATD : (table 2) The indication for liver transplantation in this disorder has been overestimated for a long time. It has become clear after the Swedish longitudinal study that only 4% of homozygous PI ZZ type patients will require liver transplatation (30). The best prognostic indicator is the absence of neonatal cholestasis syndrome. There are specific complications such as arterial aneurisma, glomerulonephritis and hepato-pulmonary syndrome and in later life hepatocellular carcinoma which may complicate the disease. They must be taken into consideration for setting the indication for transplantation.The survival rate after LTX in these is reported to be 88% (31).

Table 2. — **Indications for liver transplantation in hepatic metabolic disorders presenting with cirrhosis**

Disease	Patients (%)	Survival (%)	Met. cure	Ref.
A1 ATD	4	88	complete	31
CF	14	75	partial	5
GSD III + IV	?	95	partial	34-35
PFIC	100	80-90	partial	22,43
WD	Pseudo-ALF	80	complete	46

Cystic fibrosis (CF) : (table 2), Cirrhosis will complicate the course of this disease in up to 20% of all patients. The prognosis of this focal cirrhosis however is difficult to predict, since portal hypertension and its complications rather than chronic liver failure are major causes of complications. The results of isolated liver transplantation with 75% are better than expected (5). In combined heart-lung and liver transplantation the results are more than 60% 5 year survival.

Crigler-Najjar disease (CND) : (table 4) The world registry of Crigler Najjar type I patients summarizes the experience of 57 patients. The outcome of these patients suggests to perform liver transplantation before the age of 6 years in order to avoid inevetible brain damage by Kernikterus (12). In some of these patients the option of auxiliary orthotopic liver transplantation has been used. The results are not as promising that this technique may be regarded as the ultimate choice (23).

GSD I : (table 3) Large adenoma are at risk of bleeding and perforation, hepatocellular carcinoma seems to be of less importance in these patients. Normally, these adenoma are either avoided or effectively treated by dietary regimen. Type Ib patients will not improve with regard to neutropenia after LTX (32,33).

Table 3. — **Indications for liver transplantation in hepatic metabolic disorders non responding to medical or dietary treatment**

Disease	Patients (%)	Survival (%)	Met. cure	Ref.
GSD I adenoma	rare	95	partial	32,33
FHC	rare	50	complete	36
MMA	rare	55	partial	40
NHC	50	70-80	Complete ?	38
Tyrosinemia	10 - ?	88-100	partial	44
WD	20 ?	80-90	complete	46

GSD III: (table 2) There are only anectdotal reports on liver transplantation in this disorder. The indication for transplantation was chronic end stage liver disease with hepatocellular carcinoma. Cardiomyopathy or myopathy were not observed (34).

GSD IV : (table 2) Since there are various phenotypes in this disorder, indication for liver transplantation should be derived from the clinical course (35). Neuromuscular and cardiac involvement must be excluded before transplantation.

Fam. Hypercholesterolemia (FHC) : (table 3) Patients non responding to medical and LDL apheresis therapy should be treated by liver transplantation before coronary heart disease makes a multiorgan transplantion necessary (36). Whether orthotopic auxiliary transplantation or a gene therapy of explanted hepatocytes will be a meaningful alternative to conventional transplantation or not is not yet to be decided.

Hyperoxaluria I : (table 4,5) The liver is the only organ responsible for the detoxification of glyoxalate by the alanine-glyoxylate aminotransferase. The removal of the defecient liver and it's replacement by a normal liver is the first rationale. Timing of liver transplantation may be difficult since most patients are diagnosed in chronic end stage renal disease only. In these patients the combined liver and kidney transplantation is necessary. The success of this combined transplantation is 80% after 5 years (37). In selected patients non responding to pyridoxine therapy a preemptive liver transplantation alone may be performed to cure the liver based metabolic defect avoiding chronic renal failure and systemic oxalosis. The patients treated so far have shown to profit from the transplantation without deterioration of kidney function under immunosuppression (38). Exclusive kidney transplantation has not been recommended for European patients (37).

Neonatal Hämochromatosis (NHC) : (table 3) This disorder has been reported up to now in about 100 cases. The clinical dramatic liver failure in a dystrophic newborn with high ferritine should initiate an antioxidant and chelating therapy. It is recommended that non-responders are proposed for liver transplantation within a few days. Results of liver transplantation in these patients is reported to be 70-80%. Since there might be a multifactorial cause of this disease, it may be possible that the medical cure is only partial (39).

Propionic acidemia (PA) : (table 4) This rare disorder may be controlled by dietary regimen. LTX is only recommended in those patients, where unexpected and severe decompensatione are observed (4).

Methylmalonaciduria (MMA) : (table 3) This rare disorder is responsible for neonatal death or progressive renal failure in combination with severe brain damage. Liver transplantation does not cure the disease, the decision for LTX must be based on individual evaluation findings (40).

Mitochondrial respiratory chain disorders (MRCD) : (table 4). This heterogenous group of defects is causing serious problems. The clinical manifestation may mimic acute liver failure of unknown origin. Because of the

Table 4. — **Preemptive liver transplantation in hepatic metabolic disorders**

Disease	Patients (%)	Survival (%)	Met. cure	Ref.
CN	100	95	complete	12
Hyperoxaluria I	?	100	complete	38
Propionacidemia	6	50	partial	4
MRCD	rare	45	partial	6
UCD	rare	?	partial	45

Table 5. — **Indications for liver transplantation in hepatic metabolic disorders presenting with hepatocellular carcinoma or renal failure**

Disease	Indication	Patients (%)	Survival (%)	Met. cure	Ref.
CF	Multiorgan-disease, HCC	Rare	64,5	partial	5,45
Hyperoxaluria I	Renal failure	50	80	complete	37
Tyrosinemia	HCC	1,4-18	80	partial	2,4

deleterious brain manifestation, which may manifest only after liver failure, the most important issue is to take this disorder into consideration. The results of liver transplantation are less favorable in the approximate 20 transplanted children, the survival being less than 50% (6). In the group of survivors there are still some severely handicaped children (own unpublished data).

Progressive familial intrahepatic cholestasis (PFIC) : (table 2) This disorder is a heterogenous group of bile acid transport defects, leading either to low or high gGT associated progressive familial cholestasis (41,42). The natural course is characterized by chronic end stage liver disease from infancy to adolescence. The low gGT patients may benefit from early surgical palliation, by which a cholecysto-entero-cutaneostomy may stop the progressive course of the disease (15). This procedure should be applied before the liver has become cirrhotic. Transplantation is the only way to cure patients with liver cirrhosis, living donation has not been successful in every patient (22, 43).

Tyrosinemia : (table 3) Therapy of this hepatic metabolic disorder has experienced a considerable change during the last years. The application of an herbicide NTBC may stop the progressive course of liver failure if applied early, as soon as the diagnosis is established. Experimental data suggest that this drug cannot prevent the development of hepatocellular carcinoma. Whether this holds true for human patients needs to be investigated by long-term observation. Today, liver transplantation is recommended for those patients, where no response to NTBC therapy is observed (2). Patients need careful examination under therapy in order to identify hepatocellular carcinoma either by imaging of nodular changes in the liver or by simultaneous monitoring of a fetoprotein (44).

Urea cycle defects : (table 4) These rare disorders are characterized by either acute fulminant manifestation in the neonatal period with excessive hyperammoniemia or by chronic course with acute decompensation caused by infections. The decision to transplant such a patient should be made before a brain damage is manifest. This risk is different for the different enzyme defects. The dietary regimen and application of either sodium benzoate or phenylbutyrate may be stopped after transplantation, though renal enzyme defects are still manifest (45).

Wilson's disease : (table 2,3). Indication for liver transplantation may be given in two situations. The majority of pediatric patients is at risk of presenting witha pseudo-acute-liver faliure, the minority will be candidates for liver transplantation by non-responding to chelating therapy.The acute fulminant presentation is most often a multiorgan failure complicated by hemolytic crisis. Results of liver transplantation are good despite this poor clinical condition (46). Living donation in these patients is difficult, since these patients are most often more than 15 kg and the parental donor is heterozygous.

Discussion

The heterogeneity of these disorders makes it very difficult to establish general proposals for therapy. The best way to optimized decisions is a close cooperation between metabolic and transplant centers. The potential of dietary and medical therapy must be balanced with the benefits of transplantation, risks of both therapeutic options must be considered as well. This can only by managed by such a close cooperation. The results of both therapeutic modalities should be measured by qualitiy of life analysis, which are now available (47,48).

The results of both therapeutic ways, the conventional and the surgical one have a strong influence on the individual proposal to the parents of these children. Many of these parents are at risk of having another child with the same disorder or have already experienced such a lethal course. Since the old borders of transplanting only those patients which will be definitely cured by transplantation has been abandonned, the ethical question in all disorders with multiorgan manifestation is very intriguing. Long-term results therefore have to be collected in order to answer those questions which we are not able to answer today.

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