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Liver transplantation and cell therapies for inborn errors of metabolism

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Abstract Liver transplantation is now very successful with >85 % long term survival into adult life. When considering the impact of liver transplantation for metabolic disease two independent factors need to be considered; whether or not the defect causes liver disease and whether or not it is confined to the liver. When considering transplantation many factors need to be considered including the local success of transplantation, the impact of the metabolic disease on the patient and family and the potential for future therapeutic developments. Where transplantation is undertaken for a liver based defect there is a lifelong complete correction of the defect. Where there is a residual extrahepatic defect this will have an impact on the outcome of liver transplantation and the severity of this defect must be considered as part of the transplant assessment process. Access to a multi-disciplinary team with expertise in metabolic disease, liver disease and other relevant organ based specialists is crucial. Most children will receive transplantation from cadaveric donor but living related transplantation from a heterozygote parent is usually safe and effective. Auxiliary liver transplantation has a small but useful role where partial correction of the defect is helpful and there is a future prospect of gene therapy. The first-generation of hepatocyte transplants have shown proof of principle but to date have had a rather modest and temporary metabolic effect. Stem cells may have the potential to produce a more sustained and significant metabolic correction, but must be shown to be effective in controlled trials.

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Introduction

Liver transplantation is one of the outstanding successes of high technology medicine. Paediatric liver transplantation can now offer a 1 year survival of >90 % of whom the vast majority will survive into adulthood with a good quality of life(McKiernan 2011). Since the introduction of liver transplantation, inherited metabolic disorders have been the indication in approximately 15 % of cases(Arnon et al 2010).

These indications however are never static. Liver transplantation is not a "cure" but rather a disorder in itself with a defined acute mortality and a future attrition rate mostly related to the lifelong need for immunosuppression. In an individual child and family the therapeutic decision has to incorporate the contemporary local success of transplantation, the impact of the metabolic defect on the child and the family, the natural history of the defect and whether any new therapies are available or potentially available. As a result, an inherited defect that may be a contraindication to transplantation in one era may be a definite indication in another and vice versa.

Assessment for liver transplantation is a formal process carried out by the transplant multi-disciplinary team. This team should be widely based and incorporate paediatricians, surgeons, anaesthesists, nurses, social workers, play therapists and psychologists. The team should be supported by a metabolic expert where metabolic disease is the indication and should be able to call on other relevant organ based specialists as required. The process involves a comprehensive evaluation to assess fitness and suitability for transplantation in parallel with providing age appropriate information to the child and their family. This usually follows an

outpatient review and is usually undertaken over 4–5 working days, but the pace should be individually determined.

In considering the indication and outcome of liver transplantation in metabolic disease two independent factors need to be considered; firstly whether or not the metabolic defect causes liver disease and secondly whether or not the defect is confined to the liver. This results in four categories of disorders to consider (Table 1).

Category 1. Intrinsic liver disease with defect confined to the liver

In this group the indication for transplantation is usually made depending on the severity of the liver disease rather than that of the intrinsic metabolic defect. These indications are well established (Table 2). Where the defect causes a significantly higher risk of developing hepatocellular carcinoma (HCC), e.g. in Tyrosinaemia, transplantation maybe indicated at an earlier stage than if it were based on the severity of liver disease alone.

For this category the outcome of transplantation will reflect the success of the transplantation programme, the clinical status of the child at transplant and possibly the age at transplant. Liver transplantation for acute liver failure is less successful than elective transplantation(Sze et al 2009). The effect of age at transplantation is more unpredictable. Liver transplantation in early infancy is less successful, but considering it is usually indicated for acute liver failure and is associated with prolonged waiting times this is not so surprising. Beyond 6 months old, age at transplantation has little impact on outcome. Children with established liver disease usually have some degree of portal hypertension and hence tolerate the effect of portal vein clamping relatively well.

For survivors of transplantation there is a lifelong correction of the metabolic defect and the long term prognosis is similar to that of contemporary liver transplantation for other indications(Arnon et al 2010).

Category 2. Intrinsic liver disease with an extrahepatic defect

The indication for transplantation in this category will usually be as in category 1, i.e. primarily based on the severity of the liver disease. The metabolic correction of the defect will be immediate and prolonged but long term survival will reflect not just the success of transplantation but the nature of the extrahepatic disease. When counselling families the fact that liver transplantation will not be “curative” should be highlighted.

Timing of transplantation may also be impacted by the extrahepatic defect. Decision making in cystic fibrosis associated liver disease (CFLD) highlights the complexities involved. In CFLD transplantation needs to be undertaken while there is sufficient pulmonary reserve to support transplantation. This may necessitate transplantation prior to the development of end stage liver disease especially if there is deteriorating pulmonary function and therefore a risk of missing the window of suitability. Post transplantation there is some short term improvement, or at least stabilisation, in pulmonary function but the natural history of the disease is unchanged in the medium term (Dowman et al 2012). Many young people with cystic fibrosis will eventually develop progressive pulmonary dysfunction which will be life limiting without lung transplantation. So if they underwent liver transplantation too early, they may not have developed end stage liver disease prior to the onset of pulmonary insufficiency and hence overall patient survival may not be significantly improved. However, the improved quality of life following successful liver transplantation also needs to be factored into this complex equation.

Another group of diseases that fall into this category are mitochondrial liver diseases. Mitochondrial liver diseases may be due to inherited disorders of respiratory chain proteins or to abnormalities of mitochondrial DNA assembly. Unfortunately these disorders are usually multisystemic and when the presentation is with acute liver failure the outlook is very poor. Liver transplantation for acute liver failure due to a multisysytemic defect does not prevent, and may even hasten, neurological deterioration. This is not just an individual tragedy but in an era of organ shortage results in the denial or delay of transplantation to someone else. The challenge is to exclude untreatable disorders as quickly and accurately as possible without denying lifesaving liver transplantation to those who could benefit.

Rapid and accurate characterisation of the underlying defect is increasingly feasible and more is known about the natural history of this group of disorders. Liver transplantation is contra-indicated where liver failure is due to; Valproate induced liver failure, mutations in Polymerase γ, Twinkle and deoxyguanine kinase with neurological involvement(Mindikoglu et al 2011; Sokal et al 1999). On the other hand, children presenting with chronic liver disease due to isolated respiratory chain defect may have an excellent outcome following transplantation. Similarly some children with mitochondrial DNA depletion due to mutations in MPV-17 have good quality long term survival albeit often complicated by peripheral neuropathy. Where the underlying defect in mitochondrial DNA cannot be defined a systematic multidisciplinary assessment including evaluation of extrahepatic involvement is important so that individualised advice can be given to affected families.

In general for this group of disorders timing of liver transplantation is dependent on the severity of the liver disease but pre-emptive transplantation should be avoided because of the extrahepatic defect. A careful individualised

Table 1 Categories of metabolic liver disease when considering liver transplantation

	Liver disease	No significant liver disease
Defect confined to the liver	α1 antitrypsin deficiency (PiZZ)	Crigler-Najjar syndrome
	Tyrosinemia type 1	Primary hyperoxaluria type 1
	Wilson's disease	Urea cycle disorders (ASL excepted)
	PFIC types 2 and 3	Familial hypercholesterolaemia
	Urea cycle disorders : ASL	Hemophilia(s)
	GSD type I (for tumours)	Factor VII deficiency
	Cholesterol ester storage disease	Protein C and S deficiencies
	Indian childhood cirrhosis	Complement factor H deficiency
		GSD type Ia, (metabolic control)
		Acute intermittent porphyria
		Familial amyloid polyneuropathy
Extrahepatic defect	GSD III and IV	Methylmalonic academia
	Erythropoietic protoporphyria	Propionic acidemia
	Lysosomal storage diseases	Maple syrup urine disease
	Cystic fibrosis	GSD I non A, (metabolic control)
	Respiratory chain disorders	
	PFIC 1	

multidisciplinary transplant assessment process should be undertaken and the outcome of transplantation in this group of disorders should be continuously audited.

Category 3. No intrinsic liver disease with defect confined to liver

This category utilises transplantation as a highly effective and realistic form of gene therapy. In individual disorders the decision on transplantation should be assessed by a multidisciplinary team taking into account the success of transplantation, the prognosis of the underlying metabolic defect, the quality of life associated with treatment of the disease for the child and the family and the risk of irreversible disease in other organs including kidney, brain and heart.

In children without liver disease the technical aspects of transplantation, especially removal of the native liver are usually straight forward. However these children have not had pre-existing portal hypertension and are sensitive to the haemodynamic effect of portal vein clamping and hence more susceptible to early liver dysfunction. As a result surgical expertise and selection of suitable high quality donor organs are particularly crucial to success.

Urea cycle disorders

There is now extensive experience with transplant for this group of diseases. It results in a complete functional correction of the metabolic defect, allowing a normal diet with no risk of hyperammonaemia. There is also protection against further neurological damage and there may even be functional benefit to pre-existing impairment. What is harder to measure is the transformation of quality of life for their families with the removal of the omnipresent threat of metabolic crisis. Parents find their role changing from that of a vigilant carer and advocate to a more traditional parental one.

Transplantation should be considered early where there is severe disease and ideally before any neurological insult. Ideally transplantation should be planned from 6 months which allows maximisation of medical therapy, aggressive vaccination and by this age the technical risks of transplantation have minimised (Leonard and McKiernan 2004).

Table 2 Indications for liver transplantation due to liver disease

Life expectancy: anticipated length of life <18 months (because of liver disease)
Unacceptable quality of life (because of liver disease)
Growth failure or impairment due to liver disease
Reversible neuro-developmental impairment due to liver disease.
Likelihood of irreversible end organ damage
(neurological, renal, respiratory or cardiovascular depending on underlying disorder)
Risk of malignancy

Primary hyperoxaluria type 1

This is a disorder due to deficiency of hepatic alanine glycoxalate transaminases. This leads to overproduction of oxalate which results in nephrocalcinosis and urolithiasis which may in turn cause renal insufficiency. As renal insufficiency progresses, oxalate accumulates resulting in systemic oxalosis. Unfortunately at the time of presentation end stage renal disease may have developed and then the only curative treatment is combined liver and kidney transplantation. Where renal failure has developed there will inevitably be some evidence of systemic oxalosis with the risk of cardiovascular, bone and haematological complications.

Liver transplantation completely corrects the defect, but in the presence of end stage renal failure the huge accumulated oxalate load must be excreted via the grafted kidney. This is associated with a significant risk of recurrent renal oxalosis. In severely affected infants with renal failure organ combined transplantation may be unrealistic. A staged procedure, with early liver transplantation to prevent further oxalate accumulation followed by renal transplantation when feasible (approximately 10 kg), may be the only option. However cardiovascular complications of systemic oxalosis may still develop following liver transplantation while on dialysis. Unsurprisingly pre-emptive liver transplantation prior to the development of end stage renal disease has a much better outcome (Perera et al 2011). Ideally liver transplantation should be undertaken when there is evidence of progressive renal disease despite maximal medical treatment but before glomerular filtration rate falls below 50 ml/min/1.74 m^2.

Atypical haemolytic uraemic syndrome

This may result from genetic defects in a number of complement factors, most commonly factor H and rarely factor I. These disorders have a high risk of progression to end stage renal disease but unfortunately commonly recur following isolated renal transplant. The majority of complement factors are synthesised within the liver and combined liver and kidney, or isolated liver, transplant results in complete correction of the defect. The success of transplantation is dependent on using pre- and peri-operative plasma exchange to prevent fatal, uncontrolled complement activation in the peri-operative period. The indications for combined liver kidney transplantation are to treat renal failure and to reduce the risk of renal recurrence. Isolated liver transplantation may be occasionally indicated when plasma exchange is not feasible or tolerated (Saland et al 2009). The availability of Eculizumab, a monoclonal antibody blocking C5 activation and the formation of the pathogenic membrane attack complex, provides a new treatment strategy. This agent may have the potential to prevent renal recurrence and to replace plasma exchange therapy, but its longterm safety and efficacy remain to be determined (Zuber et al 2012).

For survivors of transplantation there is a lifelong correction of the metabolic defect and the long term prognosis is similar to that of contemporary liver transplantation for other indications unless irreversible pre-transplant complications have occurred.

Category 4. No liver disease and extrahepatic defect

These disorders largely consist of the organic acidaemias and type 1 non A glycogen storage disease. The indications for liver transplantation will be similar to those of category 3. The likely long term outcome will be related not just to the success of transplantation but the severity of the extra hepatic defect. To date, however these appear manageable in propionic acidaemia but sadly the risk of neurological deterioration appears to be still present in children with methylmalonic acidaemia(Leonard et al 2001). The experience is much more positive in maple syrup urine disease. Here liver transplantation only replaces about 10 % of normal activity, but the functional correction is much more complete, resulting in normal peripheral amino acid homeostasis. This results from the anatomical position of the liver receiving both portal venous and arterial inflow, allowing the regulated metabolism of amino acids arising from dietary sources and from muscle turnover. In practice children have a complete correction with prevention of crises and allowing a normal protein intake(Strauss et al 2006).

In children with type 1 non A glycogen storage disease, liver transplantation corrects the metabolic defect corrects the metabolic defect, although neutropenia persists, albeit often milder. Subsequent treatment with GCSF is effective and appears to be safe following transplantation.

Where the recipient does not have intrinsic liver disease the possibility of using the explant liver for a domino transplant exists. In this procedure the liver removed from the recipient is used to transplant another recipient who would otherwise not be eligible for conventional transplantation. Because of the severity of the defect which would be transmitted to the recipient this is unsuitable for many disorders, including acute porphyria and oxalosis. However organs from patients with MSUD, familial amyloid polyneuropathy and to a lesser extent hypercholesterolaemia, have been used very successfully especially in older recipients (Popescu and Dima 2012).

Cadaveric donation has been the dominant organ source in most programmes with most donors being adults. As a result, most donor organs for children are surgically modified. These are either reduced size or split liver transplants. In the latter the organ is used to benefit two recipients, usually an adult and a child. In all cases the native liver is

removed and the graft placed in the same (orthotopic) position.

Live related liver transplantation (LRLT). The availability of cadaveric liver donation varies widely throughout the world and is the main determinant of the need for LRLT. LRLT has largely utilised left lobe donation from a parent to child, although right lobe adult to adult donation is feasible. Most inherited metabolic diseases are autosomal recessive, hence parents are obligate heterozygotes. This does not seem to affect either the risk to the donor parent or the efficacy of metabolic control in the recipient(Morioka et al 2005). Even in exceptional circumstances a partially affected donor, e.g. a mother with OCT may be used where there is no alternative. In this circumstance the recipient develops the phenotype of the donor(Nagasaka et al 2001). The long-term outcome of LRLT is slightly superior to cadaveric transplantation, but the major advantage is that the transplant is turned into an elective procedure ensuring the recipient is in ideal conditions.

Auxiliary liver transplantation

In auxiliary liver transplantation not all of the recipient liver is removed and the liver graft is additional. This is a reasonable option where the metabolic defect is confined to the liver and where a partial correction is likely to be effective. In practice the use of auxiliary liver transplantation has largely been confined to Crigler-Najjar syndrome and in some forms of urea cycle defects where partial correction effectively changes the phenotype(Rela et al 1999). The major advantage of auxiliary liver transplantation is that the native liver is retained as a "safety net" if the graft fails or also if other options such as gene therapy become available, whereupon immunosuppression could be withdrawn. Unfortunately gene therapy is not likely to be feasible in the medium term for many disorders. The major disadvantage of the procedure is that the surgery is more complex with the need to preferentially divert portal venous blood flow to the graft. In addition the metabolic correction is incomplete and there may be difficulties in recognising rejection using conventional biochemical monitoring. In an individual case the decision on auxiliary transplant is complicated and should be guided by the significance of a partial correction, the likelihood of future successful gene therapy and centre specific experience with the technique.

Hepatocyte transplantation

Hepatocytes can be efficiently isolated from donor livers and transplanted either immediately as fresh cells or thawed following cryopreservation when needed. Transplantation is minimally invasive requiring only infusion into the portal vein using either a percutaneous or surgically placed catheter and can be repeated. Similar levels of immunosuppression compared to whole organ transplantation are necessary.

More than 30 subjects have received hepatocyte transplants for metabolic disease. In general the procedure and immunosuppression have been well tolerated, but the metabolic effect has been modest and usually shortlived. The major role for the first generation of this procedure appears to be in newborn infants with severe forms of urea cycle disorders where it appears to provide some stability and acts as a bridge to subsequent liver transplantation (Hughes et al 2012).

Methods to improve the efficacy of hepatocyte transplantation are needed and these need to be multifaceted. Options include increasing the number of cells transplanted, improving the hepatocyte repopulation rate or using different cell types. Increasing cell numbers will be problematic as the number of organs where cells can be harvested and which are not used for immediate organ transplantation are increasingly rare. In addition, larger cell volumes may not be tolerated due to the risk of acute portal hypertension during the infusion. Efforts to increase hepatocyte repopulation may require a noxious stimulus to the native liver to provide a survival advantage to transplanted cells, hence changing the risk benefit balance. Mature hepatocytes are terminally differentiated cells with limited proliferation potential, hence the use of stem cells, which may retain proliferative potential to repopulate the liver, are very attractive. However these have not yet been proven effective and should only be used in the context of controlled trials. These donor mesenchymal stems will still require immunosuppression (Puppi et al 2012). The ability to develop patient specific induced pleuripotent stem cells, which in theory can be genetically corrected and then transplanted, without the need for immunosuppression, provides an exciting future potential (Yusa et al 2011).

Conflict of interest None.

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