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Recent advances in liver transplantation for metabolic disease

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Abstract The indications and outcomes of liver transplantation for metabolic disease have been reviewed recently and this short review concentrates on recent developments and advances. Recently recognized metabolic causes of acute liver failure are reviewed and their implications for transplantation discussed. Newly described indications for liver transplantation in systemic metabolic diseases are described and an update is given on the role of auxiliary and domino liver transplantation.

Metabolic liver disease continues to be an important indication for liver transplantation accounting for approximately 20% of cases in childhood. Long-term outcomes continue to be excellent with >95% 10 year survival in some disorders combined with lifelong correction of the metabolic defect(Mazariegos et al 2014). With such outcomes liver transplantation is being increasingly utilized to improve quality of life and to prevent neurological damage in conditions such as urea cycle disorders and Maple syrup urine disease where there is no structural liver disease. Reflecting these changes, in some specialized centres metabolic disease accounts for more than one third of the indications for transplant (Mazariegos et al 2014).

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Liver transplant in acute liver failure

Acute liver failure is a medical emergency with a multiplicity of causes which has a poor prognosis without liver transplantation (Lee et al 2005). Management is highly time sensitive and should include a rapid diagnostic survey to recognize treatable, reversible disorders where transplantation might be avoided and untreatable disorders where transplantation may be contraindicated. For most cases with severe liver failure, liver transplantation remains the definitive treatment. Recently some new metabolic causes of recurrent acute liver failure have been recognized. Establishing a specific diagnosis may allow preemptive emergency management of acute episodes which may in turn avoid the need for acute transplantation. Alternatively, the natural history may make elective transplantation the best option.

Wolcott-rallison syndrome

This rare disease is due to mutations in *EIF2AK3* and presents with infantile diabetes and skeletal dysplasia. Up to 80% develop recurrent liver failure (Habeb et al 2012). Most will recover from individual episodes with supportive care, especially where the diagnosis is established. Despite this the cumulative mortality remains high, so elective transplantation may be a reasonable consideration. Liver transplantation appears to provide complete protection against recurrent episodes and has been successfully combined with pancreas transplantation in some cases (Tzakis et al 2015; Rivera et al 2016). It is important to be aware of the risk of symptomatic atlanto-axial instability causing spinal compression when planning anesthesia (Dias et al 2016).

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Neuroblastoma amplified sequence (NBAS) deficiency

Recurrent acute liver failure due to mutations in *NBAS,* which encodes a protein involved in transport between endoplasmic reticulum and Golgi apparatus, has been recently described (Haack et al 2015). Children present with acute episodes of high transaminases, severe coagulopathy and encephalopathy during febrile illnesses, starting in infancy. While the initial episode may be life threatening, supportive treatment appears effective. This comprises aggressive antipyresis, coagulation support and intralipid infusion. There is complete recovery between episodes, the frequency of which diminish by adulthood.

Some children have undergone transplant during an acute episode, usually prior to a specific diagnosis being established. This seems to be successful in abolishing the risk of recurrent episodes (Staufner et al 2016). Where the diagnosis has been established preemptive supportive treatment is usually sufficient, but transplantation may be an option where episodes are particularly frequent or severe.

Valproate associated acute liver failure (VPA-ALF)

This devastating complication of VPA treatment occurs in approximately 1/40,000 subjects and is most common in young children. It is usually caused by mutations in *POLG*, which encodes DNA polymerase gamma. Where liver transplantation has been undertaken in affected children the outcomes have been devastating with children eventually succumbing to a progressive neurological disorder and intractable seizures (Thomson et al 2000; Mindikoglu et al 2011). As a result VPA-ALF has been considered an absolute contraindication to liver transplantation.

More recent observations have highlighted the complexity of this disorder. Firstly, some children with VPA–ALF may show spontaneous recovery with supportive treatment incorporating N-acetylcysteine and carnitine (McFarland et al 2008). In addition, it appears that the disorder may not be so severe where the first presentation is as an adult. In affected adults transplantation has had an altogether better outcome (Hynynen et al 2014), probably reflecting that age at presentation is a proxy of the severity of the defect.

So while VPA–ALF remains an absolute contraindication to liver transplantation in childhood it is not necessarily an indication to withdraw treatment. In selected adults with VPA–ALF who do not have signs of progressive disease, liver transplantation may be a successful option (McKiernan 2014).

Liver transplantation as an enzyme replacement strategy

With increasing confidence in the outcome of liver transplantation it can be considered in a wider range of metabolic disorders where there is no structural liver disease. Improved understanding of the natural history of some progressive systemic metabolic diseases may suggest a role for early liver transplantation, particularly where effective hepatic enzyme activity may influence extrahepatic metabolism (Table 1).

Ethylmalonic encephalopathy

This disorder is due to deficiency of the mitochondrial enzyme sulphur dioxygenase, which results in the accumulation of highly toxic hydrogen sulphide and its metabolite thiosulfate. These cause secondary mitochondrial dysfunction with lactic acidosis and a severe vasculopathy. This in turn leads to recurrent cerebral infarction with seizures and severe psychomotor delay. The major source of hydrogen sulphide is from gut flora absorbed via the portal vein which can be decreased with antibiotic treatment. Despite such treatment most affected children die before age 10 years. Liver transplantation seems an appropriate option as it should be able to metabolize intestinally produced hydrogen sulphide and liver specific gene therapy significantly ameliorated the disease in an animal model (Dionisi-Vici et al 2016).

In a single case report, living related transplantation aged 7 months had a dramatic biochemical defect. There was a rapid normalization of thiosulfate combined with a significant improvement in plasma lactate and urinary ethylmalonate levels. After 1 year follow-up she is still globally delayed but showing significant developmental catch-up and no new brain MRI lesions have developed (Dionisi-Vici et al 2016).

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

MNGIE is a fatal disease caused by thymidine phosphorylase deficiency which results in toxic accumulation of thymidine and deoxyuridine with secondary mitochondrial DNA depletion. The clinical phenotype encompasses severe gastrointestinal (GI) and neurological dysfunction. The GI involvement usually consists of chronic intestinal pseudo obstruction often requiring parenteral nutrition. Neurological involvement is more variable but may include ptosis, ophthalmoparesis, peripheral neuropathy and myopathy. Those most severely affected present by the second decade of life and rarely survive beyond middle-age (Boschetti et al 2014). Hematopoietic stem cell transplantation has been shown to prevent disease progression and in long term survivors to allow some functional recovery (Halter et al 2015). However, stem cell treatment carried a high mortality and as thymidine phosphorylase is present in the liver, liver transplantation has been explored.

In a single case report cadaveric liver transplantation was undertaken in a severely affected 25-year-old male who was immobile, severely undernourished and parenteral nutrition dependent (De Giorgio et al 2016). Transplantation had a

Table 1 Novel indications for liver transplantation in metabolic disease

Metabolic disorder	Outcome of transplantation	Clinical recommendations
Ethylmalonic encephalopathy	In a single case there was biochemical correction and subsequent developmental catch-up	Liver transplantation in infancy would appear to offer the best chance of high-quality survival.
S-adenosylhomocysteine hydrolase deficiency	Single case showed improved liver function and apparent developmental catch-up.	
Mitochondrial neurogastrointestinal encephalomyopathy	Stem cell transplantation appears affecting effective but high risk. A single case of liver transplantation showed biochemical improvement and did function recovery.	Liver transplantation should be explored in young adults prior to the onset of parenteral nutrition dependency in those who are not suitable for stem cell transplantation.
Infantile Refsum disease	Liver transplantation shows biochemical improvement but no objective clinical progress.	Liver transplantation does not appear justified at present.

rapid biochemical defect with normalization of plasma thymidine levels. At one year post transplant he was able to walk and his oral intake had improved, albeit he remained dependent on parenteral nutrition. Repeat muscle biopsy showed a trend towards improved mitochondrial DNA copy numbers and brain MRI showed reduced cerebral lactate.

S-adenosylhomocysteine hydrolase deficiency (SAHHD)

Methylgroup donation is crucial to a wide range of cellular processes and is concentrated in the liver but present in all tissues. S-adenosylmethionine (SAM) acts as the universal methyl donor, producing S-adenosylhomocysteine (SAH). This is in turn metabolized to homocysteine by SAHH. SAHHD results in an abnormal SAM/SAH ratio which inhibits transmethylation reactions throughout the body. Clinically this presents in infancy with a multisystemic disorder including microcephaly, developmental delay, growth failure and coagulopathy.

In a single case report liver transplantation resulted in resolution of the coagulopathy, a significant increase in hepatic methylation products and improvement of the SAM/SAH ratio (Strauss et al 2015). This was accompanied by accelerated developmental progress, increased head growth and an improvement in brain MRI appearance. This provided strong indirect evidence that normalization of the circulating SAM/SAH ratio due to the liver correction in turn facilitated cerebral methyltransferase activity. This represents a novel way to cross the blood-brain barrier by using liver transplantation to impact on cerebral intracellular processes.

Infantile Refsum disease (IRD)

Although this is the mildest phenotype of the peroxisome biogenesis disorders it is a devastating disease with clinical features including retinitis pigmentosa, sensorineural deafness, severe neurodevelopmental delay and chronic liver disease. Affected children may survive into the second decade. The peroxisomal defect is systemic and is characterized by elevated very long chain fatty acid, plasminogen and phytanic acid levels.

There are now two case reports of living related liver transplantation for infantile Refsum disease, both undertaken in the first year of life (Van Maldergem et al 2005; Matsunami et al 2016). This appears to have a significant metabolic effect with normalization of phytanic acid levels and improvement in very long chain fatty acid levels. There was an impression of stabilization in the children's neurological status compared to other affected family members. However, there was no objective sustained neurological or ophthalmic improvement (Matsunami et al 2016).

Implications for clinical practice

These complex clinical decisions raise considerable practical and ethical difficulties. Where the outcome of transplantation is uncertain, it is best practice that such decisions are submitted to an institutional review board or similar mechanism. Prioritization of such cases in the era of severe organ shortage will always be problematic and this is reflected in the frequent use of living related transplantation. Another factor to consider is that where the primary aim is to prevent neurological deterioration, transplantation should be undertaken early. This in turn emphasizes the importance of early diagnosis and in many cases such treatment may only be practical where universal newborn screening is available or where an affected sibling is detected at or before birth.

With current knowledge and given the appalling natural history, early liver transplant for infants with Ethylmalonic encephalopathy and SAHHD appears a very reasonable approach while we await more outcome data. For MNGIE liver transplant could be explored as an option in young adults prior to the onset of parenteral nutrition dependency in those who do not have suitable stem cell donors. For infantile Refsum disease the reported experience to date does not suggest that liver transplantation is a useful option. When transplant is undertaken for such unproven indications it is important that a structured follow-up protocol is agreed and adhered to.

Given these are rare diseases, this will require significant collaboration between centres and it is important that the results and outcomes are widely disseminated.

Domino and auxiliary liver transplant

Where the underlying defect does not cause intrinsic liver disease the possibility of using the explanted liver as a domino transplant exists. Here, the explanted liver is used to transplant another recipient with the expectation that the disease will not be clinically expressed, or if it is expressed that it could be easily managed. A significant advantage of the domino procedure is that the donor is hemodynamically stable, short graft ischemia times can be achieved and it expands the overall donor organ pool. However, the need to use the domino organ immediately after the original transplant introduces logistical difficulties. As a result, this is better undertaken in high volume, well resourced centres where parallel operating is feasible (Celik et al 2016). The commonest indication for domino transplant has been from donors with familial amyloid polyneuropathy. Although recipients express this disease it takes many years to become clinically relevant and this does not impact on overall survival when used for older recipients (Popescu and Dima 2012). The major pediatric experience has been with organs from patients with MSUD which have been used successfully in a range of pediatric disorder, including other metabolic defects. There have been no untoward recipient metabolic consequence after prolonged follow-up of up to 10 years (Celik et al 2016). Domino organs from patients with familial hypercholesterolemia, methylmalonic acidemia and propionic acidemia have also been used successfully (Khanna et al 2016). However, organs from patients with acute porphyria and oxalosis rapidly produce severe disease in the recipient and should not be utilized (Popescu and Dima 2012).

In auxiliary liver transplantation not all of the recipient liver is removed and a partial donor graft is placed orthotopically. This is only recommended where the defect does not cause liver disease and where a partial correction is likely to be effective. The major advantage of auxiliary liver transplantation is that the native liver is retained as a "safety net" if the graft fails or if gene therapy become available, whereupon immunosuppression could be withdrawn. The major disadvantage of the procedure is that the surgical technique is highly complex with the need to preferentially divert portal venous blood flow to the graft by native portal vein banding. In experienced hands this can be very effective and longterm stable graft function can be achieved (Rela et al 2015). As a result auxiliary liver transplantation has not been widely adopted and has largely been confined to Crigler-Najjar syndrome and highly selected cases of urea cycle defects or propionic acidemia (Rela et al 1999).

The potential of auxiliary transplant has been boosted by the concept of the "domino auxiliary". In this technique the auxiliary transplant comes from a domino procedure. In the first reported case the explanted left lobe of a child with propionic acidemia undergoing elective transplant was implanted as an auxiliary in a child with Crigler-Najjar syndrome type I with complete correction of the metabolic defect (Govil et al 2015). This raises the possibility of the elective transfer of left lobes between patients with differing metabolic diseases, without impacting on the cadaveric donor pool.

The domino concept has also been applied to hepatocyte transplant where cells from the explanted liver of a patient with glycogen storage disease type I non-a were infused in a patient with severe phenylketonuria (Stephenne et al 2012). This resulted in an improvement in metabolic control which unfortunately was not sustained. This has been the experience with most trials of hepatocyte transplantation to date. New techniques to improve the efficiency of liver cell transplantation are necessary before this becomes clinically viable (Puppi et al 2012).

Compliance with ethical standards

Competing interests Dr. McKiernan has previously undertaken consultancy for Alexion and SOBI AB. Dr. McKiernan has been paid for participating in advisory boards on behalf of Audentes Therapeutics and Horizon Pharma.

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