Inherited Metabolic Disorders

16

Nedim Hadzic and Roshni Vara

Key Points

- IMDs are increasingly considered as indications for LT.
- Short-term results are comparable to other elective indications for LT.
- Neurodevelopmental delay usually stabilised, but does not reverse.
- LT, in the majority of IMDs, improves the phenotype rather than correcting completely the disease.

Research Needed in the Field

- Better definition of genotype/phenotype correlations in IMDs.
- Establish which conditions are good candidates for LT.
- Evaluate the medium-to-long-term outcome for LT in IMDs.

Inherited metabolic disorders (IMDs) are relatively rare monogenic conditions, requiring specific lifelong management. They are usually acquired in autosomal recessive manner, exceptions being some forms of urea cycle disorders or glycogen storage diseases, where X-linked inheritance is observed. Paediatric hepatologists encounter IMDs either in early infancy, when they typically present, or later when these patients are considered for liver transplantation (LT). Their initial manifestations may often be similar to clinical features of chronic liver disease (Table 16.1). Consanguinity, previous miscarriages or unexplained early infantile deaths increase the suspicion of an underlying metabolic problem. Of note, they are not frequently associated with prematurity or dysmorphism

Table 16.1 Clinical presentations of inherited metabolic disease

Acute liver failure syndrome (coagulopathy, conjugated jaundice, hepatocellular cytolysis, hypoglycaemia, ascites, oedema)
Galactosaemia
GALD/neonatal haemochromatosis
Mitochondrial cytopathies (*POLG, DGUOK, TRMU, MPV17*)
Tyrosinaemia type I
Hereditary fructose intolerance
GRACILE syndrome
Citrin deficiency
Niemann-Pick type C disease
Cholestatic jaundice (with failure to thrive)
PiZ alpha-1-antitrypsin deficiency
PFIC syndrome
Niemann-Pick type C disease
Inborn errors of bile acid metabolism
Congenital glycosylation disorders
Peroxisomal disorders
Cholesterol biosynthesis defects
Hypoglycaemia (with hepatomegaly/seizures)
Glycogen storage disease (types I and III)
Severe hyperinsulinism
Gluconeogenesis defects
Hepatosplenomegaly
Lysosomal storage disorders
Cystic fibrosis
with Chronic liver disease/cirrhosis:
Cholesterol ester storage disease
Transaldolase deficiency
GSD Type IV
with Fatty liver disease:
Cholesterol ester storage disease
Mitochondrial cytopathies
with Hyperammonaemia:
Urea cycle defects
Fatty acid oxidation defects
Organic acidaemias

N. Hadzic (✉)
Kings College Hospital, London, UK
e-mail: nedim.hadzic@kcl.ac.uk

R. Vara
Paediatric Inherited Metabolic Disease,
Evelina Children's Hospital, London, UK
e-mail: roshni.vara@gstt.nhs.uk

L. D'Antiga (ed.), *Pediatric Hepatology and Liver Transplantation*, https://doi.org/10.1007/978-3-319-96400-3_16

[1]. Clinical symptoms are rather nonspecific and could include lethargy, poor feeding, vomiting, hypoglycaemia with convulsions or abnormal movements, which could often be interpreted as sepsis-related. However, persistently elevated serum lactate in the absence of obvious infection or tissue hypoperfusion should always be taken as a serious pointer to IMD.

History of problems originating during pregnancy could occasionally be noted in some of the IMDs. Examples include Niemann-Pick disease, or long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), which could be associated with foetal hydrops [1]. Babies with GRACILE syndrome (foetal growth retardation, lactic acidosis, failure to thrive, hyperaminoaciduria, very high serum ferritin, liver haemosiderosis and early death) are born with severe intrauterine growth retardation [2]. Dysmorphic features such as microcephaly and facial dysmorphism could be observed in peroxisomal disorders; micrognathia and ambiguous genitalia in Smith-Lemli-Opitz syndrome, or inverted nipples and abnormal fat distribution in carbohydrate glycoprotein deficiency type 1a [1, 4]. Unusual urine odour could suggest some of the organic acidaemias, including maple syrup urine disease (MSUD), while trichorrhexis nodosa could be seen in argininosuccinate lyase deficiency. Physical signs associated with infantile liver disease have been recently reviewed [5].

A diagnostic approach is not simple and includes first-line metabolic investigations such as serum lactate, ammonia, acylcarnitine profile, plasma amino acids and urine organic acids. Mass spectrometry detection of acylcarnitines, following their esterification from carnitine with attached specific metabolites produced secondarily in IMDs, represents a biochemical basis for this valuable screening test [6]. Abnormalities in these tests could offer further direction to more specific biochemical investigations. Some of the blood spot screening tests, such as the ones for medium-chain acyl-coenzyme A deficiency (MCAD), galactosaemia or cystic fibrosis—to name a few—are often included in the national neonatal screening programmes. Nowadays, there is an increasing use of set panels for prolonged neonatal cholestasis ("jaundice chips") where some of the IMDs are increasingly included. Early contact with metabolic specialists is strongly advised as some of the clinical and biochemical features could overlap or may just be secondary to primary liver injury or immature enzymatic systems of a newborn child. Immediate treatment can vary, but it is always prudent to initially remove galactose from the diet, correct hypoglycaemia, attempt improving coagulopathy with vitamin K and cover infectious causes with antibiotics and antivirals until more information is available. It is strongly recommended to store the urine, blood and skin biopsy samples at presentation with suspected metabolic conditions, particularly in clinically unwell children.

Pathophysiological mechanisms leading to the liver impairment in IMDs could be quite diverse. For example, defective energy metabolism is the main problem in mitochondrial cytopathies, fatty acid oxidation (FAO) disorders or congenital lactic acidaemia. Retention of pathological substances in the organelles of the hepatocytes in lysosomal storage conditions, glycogen storage diseases or PiZ alpha-1-antitrypsin deficiency could activate cellular inflammatory responses and lead to their progressive structural damage. Finally, some of the aberrant metabolites could be directly toxic to the liver cells, such as in tyrosinaemia type 1 or in primary bile acid synthesis disorders. Of note, many IMDs will not damage hepatic microarchitecture as enzymatic defect remains at a functional level, and the liver biopsy could appear completely normal, which can be seen in organic acidaemias [7], maple syrup urine disease (MSUD), urea cycle defects or FAO disorders between the symptomatic episodes.

16.1 Inherited Metabolic Disorders Considered for Liver Transplantation

16.1.1 Urea Cycle Disorders

The complete urea cycle is expressed in the liver and is the main pathway for ammonia detoxification. Defects in the urea cycle are inherited in an autosomal recessive manner with the exception of ornithine transcarbamylase (OTC) deficiency, which is X-linked. Deficiencies in the more proximal steps [i.e. *N*-acetyl glutamate synthase (NAGS), carbamyl phosphate synthase 1 (CPS1), OTC and argininosuccinate synthase (ASS)] tend to present in the first few days of life with significant hyperammonaemia, poor feeding, encephalopathy and often coma. The more distal enzymatic steps [argininosuccinate lyase (ASL) and arginase] tend to present later with mild hyperammonaemia and neurological symptoms but can also present with neonatal hyperammonaemia. Urea cycle disorders are diagnosed on plasma amino acid and urine organic acid findings with genetic confirmation and/or enzymology studies. Long-term medical therapy includes a protein-restricted diet, ammonia-lowering medications, essential amino acid supplementation and carbohydrate emergency regimens for "sick days" [8]. There is ongoing risk of hyperammonaemic episodes and neurological injury, particularly in more severe cases, e.g. neonatal male-onset OTC deficiency or severe NAGS or CPS1 deficiency, where LT is often indicated within the first year of life [9, 10]. There are increasing reports of long-term neurological deficit and developmental delay despite medical management. The indication for LT is less clear in ASS and ASL deficiency and reserved for those with frequent metabolic decompensations or development of decompensated

chronic liver injury seen in ASL deficiency [11, 12]. Survival rates following LT in urea cycle defects are excellent, and it should be considered as a management option in selected cases [13].

16.1.2 Classical Maple Syrup Urine Disease (MSUD)

Classical MSUD is an organic acidaemia caused by severe deficiency of branched-chain alpha-ketoacid dehydrogenase complex (BCKDH) resulting in the inability to breakdown leucine, isoleucine and leucine. Leucine is extremely neurotoxic and leads to clinical presentation in the first few days of life with poor feeding, lethargy, encephalopathy, cerebral oedema and seizures. Long-term medical management includes a protein-restricted diet, branched-chain amino acid formula, regular blood spot monitoring and supervised emergency plans. Some newborn screening programmes include MSUD, and early intervention has shown good neurological outcomes with medical management [14]. LT has been shown to be a successful treatment option for classical MSUD and reduces the burden of specialised diet, removes the risk of significant metabolic decompensation and improves quality of life [15]. LT is essentially curative and has been shown to replace sufficient enzyme activity, but there is also a significant extrahepatic expression of BCKDH in the muscle, kidneys and central nervous system. MSUD livers have been successfully used in domino transplantation with normal branched-chain amino acid metabolism subsequently demonstrated in the recipients [16].

16.1.3 Propionic Acidaemia (PA) and Methylmalonic Acidaemia (MMA)

PA and MMA are organic acidaemias caused by enzyme defects in the catabolic pathway of branched-chain amino acids (isoleucine, valine, methionine and threonine), odd chain fatty acids and cholesterol. Propionyl-CoA carboxylase is deficient in PA and encoded by the PCCA and PCCB genes. Classical MMA is due to methylmalonyl-CoA mutase deficiency, and severe cases tend to have little or no activity (mut0). The clinical presentation of severe forms is in the first few days of life with poor feeding, encephalopathy, ketoacidosis, hyperammonaemia and coma. Long-term treatment includes a protein-restricted diet with or without specialised supplements, ammonia-lowering agents, if required, and emergency management plans [17]. There is significant extrahepatic enzyme expression for PA and MMA and considerable multisystem involvement (cardiac, renal, central nervous system, pancreatitis, optic atrophy). Despite maximal medical therapy, neurocognitive outcomes for PA and MMA remain suboptimal [18]. LT has been shown to be successful in some cases, but remains uncertain, particularly in MMA [19, 20]. LT is usually considered in cases with frequent decompensations and severe disease and/or to improve quality of life. Management perioperatively and postoperatively requires a multispecialty team and the availability of metabolic expertise [21, 22]. LT provides only a partial cure in PA and MMA and has been shown to achieve a milder metabolic phenotype with reduction in metabolic decompensations and potentially extrahepatic complications.

16.1.4 Glycogen Storage Disorders (GSD)

Disorders of glycogen metabolism considered for LT encompass type I, III and IV. GSD type Ia is due to deficiency of glucose-6-phosphatase, and GSD type Ib is due to defects in the glucose-6-phosphatase translocase enzyme. GSD type I presents in early infancy with hepatomegaly, hypoglycaemia, lactic acidosis, hyperlipidaemia, hyperuricaemia and neutropenia (type 1b).

GSD type III is due to deficiency of glycogen-branching enzyme and presents in infancy with hepatomegaly, hypoglycaemia, hyperlipidaemia and risk of myopathy and cardiomyopathy in later life. GSD types I and III are also associated with the development of hepatic adenoma in later life. The medical treatment is avoidance of fasting and correction of hypoglycaemia and lactic acidosis with a closely supervised metabolic diet [23, 24]. GSD type IV is rare with variable phenotype and is due to glycogen-debranching enzyme deficiency, which results in an abnormal glycogen (amylopectin), leading to liver fibrosis, cirrhosis, cardiomyopathy and myopathy in some. The progressive hepatic form tends to result in decompensated liver requiring LT before 5 years, and the nonprogressive form results in stable liver disease, requiring surveillance [25]. Medical treatment for GSD types I and III is successful; however LT has been reported in the presence of a poor metabolic control to improve quality of life and when hepatocellular neoplasms could develop. Neutropenia and hyperuricaemia may persist in GSD 1a following LT [26].

16.1.5 Mitochondrial Disease

Mitochondria are ubiquitous in cells and hence their disorders can present at any age with any symptom. Oxidative phosphorylation and generation of adenosine triphosphate via the respiratory chain complex, fatty acid oxidation, the urea cycle and other pathways within the mitochondria can be affected. Primary mitochondrial hepatopathies are inherited disorders, usually nuclear DNA defects, which affect the structure or function of mitochondria. The mitochondrial

DNA (mtDNA) depletion syndrome, which often leads to liver failure and neurologic abnormalities, is caused by a nuclear gene defects that control mtDNA replication or stability. Hepatic presentations of mitochondrial disease with acute liver failure, recurrent acute liver failure, fatty liver disease and chronic liver disease are increasingly recognised with the emergence of rapid genetic testing. The hepatocerebral form of mitochondrial DNA depletion syndrome is usually due to mutations in *POLG, DGUOK, MPV17, SUCLG1 and Twinkle* genes. Biochemical investigations such as plasma lactate, plasma amino acids, urine organic acids, acylcarnitines, CSF lactate and MRI brain scan can be helpful but may not be diagnostic. Muscle biopsy is often contraindicated in the acute situation due to coagulopathy. LT in mitochondrial disease is a difficult decision, particularly if the diagnosis cannot be confirmed promptly. LT remains controversial, and it is imperative to attempt to make a genetic diagnosis and exclude extrahepatic involvement when considering this option [27, 28].

16.2 Management

Basic management principles for IMDs include (a) long-term specific dietary restrictions to minimise the traffic through defective pathway and the accumulation of toxic metabolites, (b) the use of cofactors to enhance the residual activity of residual enzyme, (c) supplementation of downstream products beyond the metabolic defect, (d) preventing catabolism with emergency regimens in specific conditions and (e) disposal of toxic metabolites, where possible. Therapeutic improvements in different IMDs are variable, but unfortunately frequently result only in a limited overall biochemical control and medical stabilisation with sometimes suboptimal neurocognitive outcomes despite medical therapy.

The development of hepatocellular carcinoma (HCC) is a rare but well-recognised complication of some IMDs, including tyrosinaemia type 1, bile salt export pump (BSEP) deficiency, mitochondrial cytopathies and PiZ alpha-1-antitrypsin deficiency. Adenomas often develop in glycogen storage disease types I and III, but usually not before the second or third decade of life. They also may progress to HCC. Mechanisms responsible for the neoplastic proliferation are not completely understood, but are likely to be multifactorial, albeit driven by the abnormal metabolites. Therefore, HCC surveillance with regular liver ultrasonography and serum alpha-fetoprotein measurement is mandatory in the majority of IMDs.

It is becoming increasingly clear that many children with IMDs, despite medical treatment, will continue to require hospital admission due to metabolic decompensations and suboptimal chronic metabolic control, resulting in missed milestones, developmental delay, social and learning difficulties and poor education [6, 17]. This disappointing scenario, now confirmed after decades of expert follow-up for IMDs, has prompted increasing consideration for the liver replacement, where effective provision of a normal enzymatic supply could potentially be achieved [10].

16.3 Inherited Metabolic Disorders and Liver Transplantation

Liver transplantation (LT) is now the widely established mode of clinical management for many cholestatic, anatomical, neoplastic and toxic conditions. The standardisation of surgical methods, the introduction of tailor-made immune suppression and effective anti-infectious regimes have reduced mortality risks for elective indications to less than 5% in most of the large specialist centres [29]. LT has therefore emerged as one of the management options for IMDs due to ongoing issues with their conventional treatment, including very restricted metabolic diets, lifelong use of potentially toxic medications, frequent requirements for hospital admissions in metabolic crises and, most importantly, unsatisfactory neurological and intellectual outcome medium term [6, 30]. Worldwide, IMDs currently represent approximately 15–25% of the primary indications for LT [9, 31, 32].

Selection for LT is always a complex undertaking, but in this particular setting, it is even more challenging as risks of this complex surgico-medical intervention need to be carefully counterbalanced by potential benefits of the effective metabolic correction. This can only be achieved by a close collaboration between metabolic physicians and LT team during each phase of the process. Due to their relative rarity, clinical experiences with particular IMDs will never be extensive in any single centre. Table 16.2 is an attempt to summarise present clinical indications for LT among IMDs, but it is by no means definite (Table 16.2).

The benefits of LT depend on the provision of the defective enzyme provided by the liver graft cells and re-establishment of the physiological metabolic pathway. This reparatory process could be difficult to anticipate and is variably effective, depending on the biology of the underlying IMD. In addition, the clinical manifestations could be diverse even within the same condition (e.g. infantile vs. juvenile types) or even within the same family (e.g. Wilson disease or PiZ alpha-1-antitrypsin deficiency). Another unsolved question is about the quantity of missing enzyme required to achieve a clinical modification of the phenotype, which is known for only a handful of IMDs. This could be a relevant clinical point if the liver graft function becomes suboptimal for whatever postoperative complication, but also during donor selection process. Living-related donor

Table 16.2 Metabolic conditions of childhood potentially treatable by liver transplantation

Curable by liver transplantation
Wilson disease
Alpha-1-antitrypsin PiZ deficiency
Tyrosinaemia type 1
Bile salt export pump (BSEP) deficiency
Multiple drug resistance 3 (MDR3) deficiency
Double domain-containing protein 2 (DCDC2) deficiency
Urea cycle disorders
Ornithine transcarbamylase (OTC) deficiency
Carbamoyl phosphate synthetase 1 (CPS1) deficiency
Citrullinaemia
Argininosuccinate lyase (ASL) deficiency
Argininaemia
Familial hypercholesterolaemia
Organic acidaemias
Maple syrup urine disease (MSUD)
Coagulation disorders
Haemophilia A and B
Factor VII deficiency
Protein C and S deficiencies
Acute intermittent porphyria
Complement factor H and I deficiency
Afibrinogenaemia
Hereditary haemochromatosis
Partially treated by liver transplantation
FIC-1 disease
TJP2 deficiency
Organic acidaemias
Propionic acidaemia
Methylmalonic acidaemia
Cystic fibrosis
Glycogen disease type III and IV
Familial amyloidosis
Experimental
Mitochondrial hepatopathies
Mitochondrial DNA depletion (POLG1, MPV17, DGUOK)
Erythropoietic protoporphyria
Cholesterol-esterase storage disease
Gaucher disease
Phenylketonuria
Citrin deficiency
Relative contraindications
Niemann-Pick type C disease
Peroxisomal disorders
Alpers syndrome

options, involving typically one of the parents, are increasingly exploited in paediatric liver centres and contribute to reducing waiting times and ameliorating chronic donor shortages. In IMDs, living donation is less desirable as parents are expected to be phenotypically unaffected carriers. However, effects of the major surgery on their metabolic control and long-term complications and viability of the heterozygous graft are generally incompletely understood [33, 34]. In OTC deficiency, inherited in an X-linked manner, it is preferable to investigate the father as a prospective living donor, as the carrier mothers could have a different enzymatic expression, and formal assessment to measure the levels in the liver tissue may be necessary. Large experience from Japan, where the living liver donation is predominant, is overall encouraging [35], but many other centres still prefer avoiding obligate carriers as donors for IMD indications and obtain the organs from unrelated anonymous sources. However, routine LT criteria for conventional indications in paediatric hepatology (coagulopathy, serum bilirubin, albumin, platelet count, etc.) usually do not apply to IMDs, and transplant centres tend to develop their own internal policies for these conditions. These scoring tasks are not simple as they must account for different biology of distinct IMDs, but also their increasing referrals for LT consideration, which should not jeopardise expected standard waiting times for the routine life-threatening transplant indications in other children.

One potential attractive option in LT for IMDs is using the auxiliary grafting, where only a part of the native liver is replaced during the operation, providing the missing enzymatic supply [36]. The remaining native liver could still represent a reliable backup option should the graft function becomes seriously deranged for whatever reason during follow-up. Furthermore, auxiliary LT leaves a possibility of genetic manipulation or genetic material transfer open for the future. Auxiliary LT, in children usually with the left segmental graft, is more technically challenging but should be considered in conditions where extrahepatic expression of the missing enzyme is limited, requirements for correction are known, and the clinical effects are easily monitored (e.g. serum bilirubin in Crigler-Najjar syndrome type 1, or ammonia, ketones and metabolic acidosis in organic acidaemias). Preferential surgical redistribution of the portal flow by partial banding between the auxiliary and native liver may be required in order to increase the blood supply and improve desired enzymatic activity [37]. Overall, elective auxiliary LT should be considered in the presence of sufficient local surgical expertise for indications where gene transfer therapy will not be imminently available.

On a positive side, patients with IMDs will only exceptionally have evidence of chronic liver disease, portal hypertension or previous abdominal surgeries, which could make LT technically more straightforward [29]. However, some of the previous long-term dietary restrictions, for example, in protein intake, may affect postoperative healing process and recovery. It is also possible that some of the IMDs may render children procoagulant [38] or having mild immune deficiency (like in propionic acid-

aemia) [39]. If the explanted liver or its part is histopathologically unaffected, it could be potentially considered for domino grafting in patients affected by unrelated conditions [40, 41]. This concept has been well-documented in LT for MSUD, where the missing branched-chain amino acid enzyme from the explanted liver graft was counterbalanced by the normal extrahepatic metabolic pathways of the domino recipient [42].

16.4 Perioperative Management

Children with IMDs were noted to be prone to more significant metabolic derangements during the surgery. One study has described higher levels of oxidative stress, transforming growth factor-β1and complement activity during LT for IMDs in comparison to children with biliary atresia [43]. In preparation for LT, many centres try to minimise preoperative fasting, ensure steady intravenous supply of a glucose infusion rate of at least 6–8 mg/kg/min (to avoid hypoglycaemia and catabolic state) and strictly control fluid and electrolyte balance [42, 44]. Administering short-term parenteral nutrition may occasionally be necessary. From experience with levels of the branched-chain amino acids in MSUD, the metabolic correction can be achieved within 6 h after LT [42, 44], but strict observation for several more postoperative days—until normal enteral intake is established—appears prudent.

If LT genuinely represents a good long-term management option for some IMDs, then the timing of this intervention becomes critically important. It is conceivable that earlier LT could reduce the risk of neurological and developmental damage in children who remain at risk due to brittle clinical course of their underlying IMDs. After the first 3 months of life, surgical issues become less challenging, while immunological aspects could actually be favourable for an early LT. Of note, it has also been hypothesised that rapid growth and development in the first year of life, with increased utilisation of nitrogen, could reduce retention of potentially toxic compounds such as ammonia in urea cycle disorders and presumably protect from detrimental neurodevelopmental effects until the growth relatively slows down after 2 or 3 years of age [10]. This "honeymoon" period should then offer an optimal opportunity window for the LT. In any case, there are increasing trends of working up the infants with IMDs for the surgery in the first year of life to minimise the impact of the suboptimal metabolic control on the developing brain of young children. However, given the overall rarity of IMDs, phenotypic differences, lack of reliable markers of metabolic control and difficulties in consistent neurodevelopmental assessment and follow-up, each decision about benefits/risks of LT must be carefully balanced and strictly individualised. In that context, comprehensive family education and the early use of elective accelerated immunisation schedules are very important. Novel methods such as hepatocyte transplantation may offer some palliative measures of metabolic control ("bridging") until the small neonate or young infant becomes physically fit for LT as a definite corrective intervention. At the present time, medium-term viability of the cell transplantation has not been yet established, but attempts of its expansion are ongoing.

16.5 Management After Liver Transplantation

There is emerging evidence that in patients with IMDs, a good graft function after LT provides a stable clinical phenotype with no metabolic crises and a much improved quality of life [19, 45]. Reported 5- and 10-year patient and graft survival are around 90 and 80%, respectively, with ever-improving trends [29, 32]. The effects of successful LT to neurological, cognitive and intellectual aspects are much more difficult to ascertain due to individual differences and the lack of consistent psychometric and neurodevelopmental quantitative monitoring [19, 45].

Strict dietary restrictions are usually completely removed after LT in disorders where the defect is corrected, e.g. urea cycle defects; however, some restriction may be required in organic acidaemias where the correction is incomplete. Some children, who had been showing aversion to certain food, for example, protein, may start showing renewed interest after the surgery, resulting in improved growth and development. There is no evidence whether the dietary restrictions should not be lifted in living-related LT or where graft function may have been suboptimal.

It is unclear yet whether the effective LT arrests development of all extrahepatic complications, such as cardiac, renal or ophthalmic. In propionic acidaemia, there is some evidence that hypertrophic cardiomyopathy could be reverted following effective LT [46]. Some children post LT for tyrosinaemia type 1 continue excreting succinylacetone in urine with low normal activity of the enzyme porphobilinogen (PBG) synthase, which could indicate the ongoing activity of the aberrant tyrosinaemia pathway [47]. It is therefore arguable whether there are potential benefits of using metabolic modifier nitisinone after LT in order to completely abolish the production of succinylacetone and minimise long-term renal toxicity due to both the original disease and anti-rejection therapy with calcineurin inhibitors. There is no present consensus on that, but further research into whether some forms of adjunct metabolic management, particularly for IMDs with known extrahepatic features, are still required.

In conclusion, LT offers a viable management option for many IMDs. With careful selection, benefits often outweigh the long-term risks associated with LT. After the surgery the clinical phenotype becomes stable with only exceptional occurrence of metabolic derangements or life-threatening metabolic crises. The standard measures of quality of life for the child and family usually dramatically improve. However, one has to offer realistic expectations about the neurocognitive outcome, which usually does not deteriorate, but also does not get better with the established metabolic control. Pre-existing neurological changes usually do not revert. Given the increasing confidence and acceptable safety profile of elective LT, the overall intuitive approach is to consider this procedure much earlier in the infancy. The role of auxiliary and living-related LT is not optimally defined and may well need to be individualised for different conditions. Clinical indications for LT in IMDs will continue to change, dependent on the further success of transplantation options, including stem and mesenchymal cell transfer techniques, better understanding of natural history and long-term complications of individual IMDs, the general impact of the metabolic defect on neurodevelopment and the quality of life for the child and the family and whether any new superior therapeutic modalities will become available in the foreseeable future.

References

1. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. Semin Neonatol. 2002;7:3–15.
2. Fellman V, Rapola J, Pihko H, et al. Iron-overload disease in infants involving fetal growth retardation, lactic acidosis, liver haemosiderosis, and amino aciduria. Lancet. 1998;351:490–3.
3. Jaeken J, Matthijs G, Saudubray JM, et al. Phosphomannomutase isomerase deficiency: a carbohydrate-deficient glycoprotein syndrome with hepatic-intestinal presentation. Am J Hum Genet. 1998;62:1535–9.
4. Hadzic N, Verkade HJ. The changing spectrum of neonatal hepatitis. J Pediatr Gastroenterol Nutr. 2016;63:316–9.
5. Santra S, Hendriksz C. How to use acylcarnitine profiles to help diagnose inborn errors of metabolism. Arch Dis Child Educ Pract Ed. 2010;95:151–6. https://doi.org/10.1136/adc.2009.174342.2010.
6. Oishi K, Arnon R, Wasserstein MP, Diaz GA. Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, perioperative management. Pediatr Transplant. 2016;20:756–69. https://doi.org/10.1111/petr.12741.
7. Imbard A, Garcia Segarra N, Tardieu M, Broué P, Bouchereau J, Pichard S, de Baulny HO, Slama A, Mussini C, Touati G, Danjoux M, Gaignard P, Vogel H, Labarthe F, Schiff M, Benoist JF. Long-term liver disease in methylmalonic and propionic acidemias. Mol Genet Metab. 2018;123(4):433–40.
8. Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, Karall D, Martinelli D, Crespo PS, Santer R, Servais A, Valayannopoulos V, Lindner M, Rubio V, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;7:32.
9. Yu L, Rayhill SC, Hsu EK, Landis CS. Liver transplantation for urea cycle disorders: analysis of the united network for organ sharing database. Transplant Proc. 2015;47(8):2413–8.
10. Ah Mew N, Krivitzky L, McCarter R, Batshaw M, Tuchman M. Clinical outcomes of neonatal onset proximal versus distal urea cycle disorders do not differ. J Pediatr. 2013;162:324–9.e1. https://doi.org/10.1016/j.jpeds.2012.06.065.
11. Yankol Y, Mecit N, Kanmaz T, Acarli K, Kalayoglu M. Argininosuccinic aciduria—a rare indication for liver transplant: report of two cases. Exp Clin Transplant. 2017;15(5):581–4.
12. Robberecht E, Maesen S, Jonckheere A, Van Biervliet S, Carton D. Successful liver transplantation for argininosuccinate lyase deficiency (ASLD). J Inherit Metab Dis. 2006;29(1):184–5.
13. Kido J, Matsumoto S, Momosaki K, Sakamoto R, Mitsubuchi H, Endo F, Nakamura K. Liver transplantation may prevent neurodevelopmental deterioration in high-risk patients with urea cycle disorders. Pediatr Transplant. 2017;21(6).
14. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002;109(6):999–1008.
15. Díaz VM, Camarena C, de la Vega Á, Martínez-Pardo M, Díaz C, López M, Hernández F, Andrés A, Jara P. Liver transplantation for classical maple syrup urine disease: long-term follow-up. J Pediatr Gastroenterol Nutr. 2014;59(5):636–9.
16. Celik N, Squires RH, Vockley J, Sindhi R, Mazariegos G. Liver transplantation for maple syrup urine disease: a global domino effect. Pediatr Transplant. 2016;20(3):350–1.
17. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: clinical management update. Curr Opin Pediatr. 2016;28:682–93.
18. Kölker S, Valayannopoulos V, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, Zeman J, Dionisi-Vici C, Barić I, Karall D, Arnoux JB, Avram P, Baumgartner MR, Blasco-Alonso J, Boy SP, Rasmussen MB, Burgard P, Chabrol B, Chakrapani A, Chapman K, Cortès I Saladelafont E, Couce ML, de Meirleir L, Dobbelaere D, Furlan F, Gleich F, González MJ, Gradowska W, Grünewald S, Honzik T, Hörster F, Ioannou H, Jalan A, Häberle J, Haege G, Langereis E, de Lonlay P, Martinelli D, Matsumoto S, Mühlhausen C, Murphy E, de Baulny HO, Ortez C, Pedrón CC, Pintos-Morell G, Pena-Quintana L, Ramadža DP, Rodrigues E, Scholl-Bürgi S, Sokal E, Summar ML, Thompson N, Vara R, Pinera IV, Walter JH, Williams M, Lund AM, Garcia-Cazorla A. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis. 2015;38(6):1059–74.
19. Vara R, Turner C, Mundy H, Heaton ND, Rela M, Mieli-Vergani G, Champion M, Hadzic N. Liver transplantation for propionic acidaemia in children. Liver Transpl. 2011;17:661–7.
20. Niemi AK, Kim IK, Krueger CE, Cowan TM, Baugh N, Farrell R, Bonham CA, Concepcion W, Esquivel CO, Enns GM. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. J Pediatr. 2015;166(6):1455–61.
21. Rajakumar A, Kaliamoorthy I, Reddy MS, Rela M. Anaesthetic considerations for liver transplantation in propionic acidemia. Indian J Anaesth. 2016;60(1):50–4.
22. Sloan JL, Manoli I, Venditti CP. Liver or combined liver-kidney transplantation for patients with isolated methylmalonic acidemia: who and when? J Pediatr. 2015;166(6):1346–50.
23. Weinstein DA, Steuerwald U, De Souza CFM, Derks TGJ. Inborn errors of metabolism with hypoglycemia: glycogen storage diseases and inherited disorders of gluconeogenesis. Pediatr Clin North Am. 2018;65(2):247–65.
24. Bhattacharya K. Investigation and management of the hepatic glycogen storage diseases. Transl Pediatr. 2015;4(3):240–8.
25. Szymańska E, Szymańska S, Truszkowska G, Ciara E, Pronicki M, Shin YS, Podskarbi T, Kępka A, Śpiewak M, Płoski R, Bilińska ZT, Rokicki D. Variable clinical presentation of glycogen storage

disease type IV: from severe hepatosplenomegaly to cardiac insufficiency. Some discrepancies in genetic and biochemical abnormalities. Arch Med Sci. 2018;14(1):237–47.
26. Davis MK, Weinstein DA. Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure. Pediatr Transplant. 2008;12(2):137–45.
27. De Greef E, Christodoulou J, Alexander IE, Shun A, O'Loughlin EV, Thorburn DR, Jermyn V, Stormon MO. Mitochondrial respiratory chain hepatopathies: role of liver transplantation. A case series of five patients. JIMD Rep. 2012;4:5–11.
28. Dubern B, Broue P, Dubuisson C, Cormier-Daire V, Habes D, Chardot C, Devictor D, Munnich A, Bernard O. Orthotopic liver transplantation for mitochondrial respiratory chain disorders: a study of 5 children. Transplantation. 2001;71(5):633–7.
29. Mazariegos G, Shneider B, Burton B, Fox IJ, Hadzic N, Kishnani P, Morton DH, McIntire S, Sokol RJ, Summar M, White D, Chavanon V, Vockley J. Liver transplantation for pediatric metabolic disease. Mol Genet Metab. 2014;111:418–27. https://doi.org/10.1016/j.ymgme.
30. McKiernan PJ. Liver transplantation and cell therapies for inborn errors of metabolism. J Inherit Metab Dis. 2013;36:675–80. https://doi.org/10.1007/s10545-012-9581-z.
31. Fagiuoli S, Daina E, D'Antiga L, Coledan M, Remuzzi G. Monogenic diseases that can be cured by liver transplantation. J Hepatol. 2013;59:595–612.
32. Arnon R, Kerkar N, Davis MK, Anand R, Yin W, González-Peralta RP, SPLIT Research Group. Liver transplantation in children with metabolic diseases: the studies of pediatric liver transplantation experience. Pediatr Transplant. 2010;14:796–805. https://doi.org/10.1111/j.1399-3046.2010.01339.x.
33. Rahayatri TH, Uchida H, Sasaki K, et al. Hyperammonemia in ornithine transcarbamylase-deficient recipients following living donor liver transplantation from heterozygous carrier donors. Pediatr Transplant. 2017;21:e12848. https://doi.org/10.1111/petr.12848.
34. Feier F, Schwartz IV, Benkert AR, Seda Neto J, Miura I, Chapchap P, da Fonseca EA, Vieira S, Zanotelli ML, Pinto e Vairo F, Camelo JS Jr, Margutti AV, Mazariegos GV, Puffenberger EG, Strauss KA. Living related versus deceased donor liver transplantation for maple syrup urine disease. Mol Genet Metab. 2016;117:336–43. https://doi.org/10.1016/j.ymgme.2016.01.005. Epub 2016 Jan 12.
35. Kasahara M, Sakamoto S, Horikawa R, et al. Living donor liver transplantation for pediatric patients with metabolic disorders: the Japanese multicenter registry. Pediatr Transplant. 2014;18:6–15.
36. Reddy MS, Rajalingam R, Rela M. Revisiting APOLT for metabolic liver disease: a new look at an old idea. Transplantation. 2017;101:260–6. https://doi.org/10.1097/TP.0000000000001472.
37. Rela M, Bharathan A, Palaniappan K, Cherian PT, Reddy MS. Portal flow modulation in auxiliary partial orthotopic liver transplantation. Pediatr Transplant. 2015;19:255–60. https://doi.org/10.1111/petr.12436.
38. Dowman JK, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, Newsome PN, UK Liver Selection and Allocation Working Party. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transpl. 2012;18:195–200. https://doi.org/10.1002/lt.22345.
39. Raby RB, Ward JC, Herrod HG. Propionic acidaemia and immunodeficiency. J Inherit Metab Dis. 1994;17:250–1.
40. Chen CY, Liu C, Lin NC, Tsai HL, Loong CC, Hsia CY. Exchange of partial liver transplantation between children with different non-cirrhotic metabolic liver diseases: how do we arrive there? Ann Transplant. 2016;21:525–30.
41. Govil S, Shanmugam NP, Reddy MS, Narasimhan G, Rela M. A metabolic chimera: two defective genotypes make a normal phenotype. Liver Transpl. 2015;21:1453–4. https://doi.org/10.1002/lt.24202.
42. Mazariegos GV, Morton DH, Sindhi R, Soltys K, Nayyar N, Bond G, Shellmer D, Shneider B, Vockley J, Strauss KA. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. J Pediatr. 2012;160:116–21.e1. https://doi.org/10.1016/j.jpeds.2011.06.033.
43. Hussein MH, Hashimoto T, Suzuki T, Daoud GA, Goto T, Nakajima Y, Kato T, Hibi M, Tomishige H, Hara F, Kato S, Kakita H, Kamei M, Ito T, Kato I, Sugioka A, Togari H. Children undergoing liver transplantation for treatment of inherited metabolic diseases are prone to higher oxidative stress, complement activity and transforming growth factor-β1. Ann Transplant. 2013;18:63–8. https://doi.org/10.12659/AOT.883820.
44. Strauss KA, Mazariegos GV, Sindhi R, Squires R, Finegold DN, Vockley G, Robinson DL, Hendrickson C, Virji M, Cropcho L, Puffenberger EG, McGhee W, Seward LM, Morton DH. Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant. 2006;6:557–64.
45. Shellmer DA, DeVito Dabbs A, Dew MA, Noll RB, Feldman H, Strauss KA, Morton DH, Vockley J, Mazariegos GV. Cognitive and adaptive functioning after liver transplantation for maple syrup urine disease: a case series. Pediatr Transplant. 2011;15:58–64. https://doi.org/10.1111/j.1399-3046.2010.01411.x.
46. Romano S, Valayannopoulos V, Touati G, Jais JP, Rabier D, de Keyzer Y, Bonnet D, de Lonlay P. Cardiomyopathies in propionic aciduria are reversible after liver transplantation. J Pediatr. 2010;156:128–34. https://doi.org/10.1016/j.jpeds.2009.07.002.
47. Bartlett DC, Preece MA, Holme E, Lloyd C, Newsome PN, McKiernan PJ. Plasma succinylacetone is persistently raised after liver transplantation in tyrosinaemia type 1. J Inherit Metab Dis. 2013;36:15–20. https://doi.org/10.1007/s10545-012-9482-1. Epub 2012 Mar 29.