Paediatric liver transplantation for metabolic disorders. Part 2: Metabolic disorders with liver lesions

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Summary
Liver based metabolic disorders account for 10 to 15% of the indications for paediatric liver transplantation. In the last three decades, important progress has been made in the understanding of these diseases, and new therapies have emerged. Concomitantly, medical and surgical innovations have lead to improved results of paediatric liver transplantation, patient survival nowadays exceeding 80% 10 year after surgery with close to normal quality of life in most survivors. This review is a practical update on medical therapy, indications and results of liver transplantation, and potential future therapies, for the main liver based metabolic disorders in which paediatric liver transplantation may be considered. Part 1 focuses on metabolic based liver disorders without liver lesions, and part 2 on metabolic liver diseases with liver lesions.

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Wilson’s disease

Wilson’s disease (WD) is an autosomal recessive disorder of copper metabolism with a prevalence of 1 in 30,000 in the general population [1]. WD results from mutations of the gene ATP7B located on chromosome 13, coding for the transmembrane ATP7B transporter, which is involved in the trans Golgi transport of Copper, incorporation of copper into the plasma protein caeruloplasmin, and excretion of excessive copper into bile [2]. About 300 mutations of the ATP7B gene have been identified. Accumulation of copper in the hepatocytes leads to gradual liver destruction, then diffusion into blood, and later, accumulation in other organs. Hepatic, neuropsychiatric, haematological and renal lesions develop secondary to high copper levels in the plasma and in the tissues where it accumulates.

Natural history and medical therapy

WD has three major hepatic presentations [3]: (1) Acute form: fulminant hepatic failure, hemolysis and renal failure; (2) Subacute hepatitis; (3) Chronic hepatitis with liver
Alpha-1-Antitrypsin (AAAT) is the most common protease inhibitor in human plasma. The gene that encodes the protein is located on chromosome 14. This glycoprotein is synthesized in the liver and protects the lung alveolar tissues from destruction by the proteolytic attacks of neutrophil elastase. AAAT deficiency is a common autosomal recessive condition (estimated incidence: 1:2500 in Europe and 1:5000 in the USA) [16]. Numerous mutations are possible, leading to various phenotypes of the protein, the most frequent in Europe being the Z and S mutations. Liver disease develops in some children with the homozygous PiZZ mutation, resulting from accumulation of loop sheet polymers of mutated protein which are retained in the liver. Lungs disease occurs mainly in PiZZ and PiSZ phenotypes, and is related to low plasma levels causing lack of anti-inflammatory activity of AAT in the alveoli [17-19]. AAAT deficiency is the most common genetic cause of liver disease during childhood, and is the most common metabolic indication for liver transplantation in children [20].

Natural history and medical therapy

Ten to 25% of children with the PiZZ phenotype present with neonatal cholestasis which usually resolves before the age of 6 months [21]. Subsequent progression is variable and approximately 20-30% develop progressive liver disease in childhood [22,23]. Persistence of jaundice beyond the sixth month of age, paucity of bile ducts, early development of fibrosis and portal hypertension are signs of poor prognosis [24]. However, 10% of AAAT children with liver cirrhosis have no history of neonatal cholestasis, and may present with chronic liver disease for the first time during childhood or early adulthood. An increased risk of hepatocellular carcinoma has been reported in adults [25] and even in children [26]. Respiratory manifestations appear later in life, usually in middle age.

Good supportive and nutritional care is important. Ursodeoxycholic acid may improve liver tests and clinical status in some children with mild to moderate liver disease, but has little effect in severe forms of the disease [27]. Prevention of lung disease includes avoiding cigarette smoking, flu and pneumococcal vaccinations. Augmentation therapy by weekly IV injections of AAT may delay the progression of lung disease [28].

Results of transplantation

Replacement of the cirrhotic liver results in acquisition of the donor phenotype, a rise in serum levels of AAAT and significant improvement in the quality of life [29]. Since the first report of successful liver transplantation for AAAT deficiency associated liver disease [30], results have steadily improved and current survival exceeds 80% in adults and 90% in children [31,32].

Indications for transplantation

Early LT may be necessary before the age of two years due to rapid deterioration of liver function, however in most cases LT is indicated in late childhood due to reappearance of jaundice or due to complications of cirrhosis [33].
Tyrosinemia

Tyrosinemia type 1 (TT1) is a metabolic disorder characterized by deficiency of the enzyme fumarylacetoacetase (FAA), which is the terminal enzyme in tyrosine and phenylalanine degradation. This result in the formation of several toxic intermediate metabolites, including succinylacetone which is pathognomonic [37]. TT1 is an autosomal recessive disorder, the gene of FAA is located on chromosome 15. TT1 incidence is estimated to be 1/100,000 to 1/120,000 [38], but is higher in Scandinavia and Quebec, where it reaches 1/1850 live births in the region of Saguenay—Lac Saint-Jean [39].

Natural history and medical therapy

Tyrosinemia has two clinical presentations: (1) Acute form: Neonatal liver dysfunction or decompensated cirrhosis at the third or fourth month of life with coagulopathy, encephalopathy and death during the first year of life. (2) Chronic form: failure to thrive, hepatosplenomegaly, cardiomyopathy, porphyria-like syndrome, Fanconi-like tubular dysfunction, rickets and renal failure. The risk of developing hepatocarcinoma (HCC) is very high in this group of patients and diagnosis cannot rely on alphafetoprotein (AFP) levels which is very elevated due to tyrosinemia itself [40]. The diagnosis of tyrosinemia is based on detection of urinary succinylacetone, whereas confirmation relies on detection of two pathogenic mutations or measuring FAA activity in fibroblasts or lymphocytes.

The natural history of the disease has been transformed by the introduction of (2-(2-nitro-trifluoromethyl)benzoyl)-1,3-cyclohexenedione) NTBC (Nitisinone) [41], which blocks the formation of toxic metabolites. With phenyl alanine- and tyrosine-restricted diet and NTBC, a complete control of porphyria-like crisis, an improvement of nutritional status, kidney and liver function is achieved [42,43]. However, significant liver disease may predate NTBC therapy [42,44]. Early treatment (before the age of 2 years) reduces, but does not abolish the risk of HCC [44], probably because NTBC fails to normalise gene expression, as demonstrated in the mouse model of TT1 [45].

Liver transplantation in tyrosinemia does not fully correct the metabolic abnormalities, as excretion of succinylacetone by the affected kidneys persists, but the clinical significance of this is unclear. Prior to the introduction of NTBC, renal dysfunction was common at the time of transplant, with the risk of further deterioration [46–48], and combined liver-kidney transplantation has been recommended in patients with GFR lower than 40 ml/min/1.73 m² [40]. This is however, an unlikely scenario in current practice as NTBC protects against renal dysfunction [40,49,50]. Patient survival after liver transplantation is greater than 85% [40,49], with normal liver function, normal growth, and no recurrence of neurological crises on a normal diet. Since heterozygous parents are unaffected, they can be live liver graft donors [9].

Future therapies

Several approaches to medical treatment of AAT are possible [34]. Deficient AAT can be replaced using recombinant AAT. This replacement therapy (usually by inhalation) may slow down the progress of lung disease, but does not prevent the accumulation of abnormal AAT in the hepatocytes of patients with liver disease. Similarly, gene therapy can achieve production of normal AAT (easy routes of administration being nebulisation or intramuscular injection), but whether liver directed gene therapy could prevent the development of liver disease in PiZZ patients remains uncertain [35]. The same limitation might apply to stem cell therapy, although encouraging results have been obtained in animal models [36]. Therapies to prevent polymerization and/or to promote secretion of AAT by the hepatocyte are being studied.

Indications of liver transplantation

NTBC and dietary treatment is currently the first line treatment in patients with TT1. The current indications of LT include: (1) acute liver failure not responding to NTBC (no improvement of coagulopathy or progressive jaundice after 1 week of treatment) [43], (2) Severe dysplasia or localised HCC: the decision is relatively easy in case of appearance of a new nodule and/or rebound of AFP under NTBC, but is less clear in patients with an already nodular liver at diagnosis. Some teams consider a nodular liver as an indication for early LT, due to the high risk of severe dysplasia or HHC, even if they have not been demonstrated yet in the patient [51]. The other option is close monitoring of the nodules and AFP [43,44], but delaying LT may increase the risk of recurrent HCC after surgery [49,52]. The age threshold of 2 years when NTBC was started is often used to differentiate children with low or high risk of malignancy, but HHC has been reported in children less than 2 years [52], and rebound of AFP and/or development of cirrhosis have been reported under NTBC even in patients treated before the age of 6 months [44]; (3) Rarely, LT may be indicated due to poor quality of life related to dietary restriction under NTBC.

Future therapies

FAA deficient mouse is an interesting model for hepatocyte transplantation and gene therapy, since normal hepatocytes (wild type or genetically corrected) can metabolise the toxic metabolites produced by diseased cells, and therefore have a selective growth advantage [53]. Prolonged survival of FAA deficient mice have been achieved by hepatocyte allotransplantation, in vivo and ex vivo gene therapy, as well as bone marrow transplantation, due to cell fusion of bone marrow derived cells with mature hepatocytes [54,55]. However, even if liver repopulation with corrected cells allowed prolonged survival of the animals, a high incidence of HCC was observed in the survivors, suggesting that 100% correction or replacement of diseased cells might be necessary to prevent malignancy [56,57].
Neonatal haemochromatosis

Neonatal haemochromatosis (NNH) is defined as severe neonatal liver disease in association with extrahepatic siderosis in a distribution similar to that seen in hereditary haemochromatosis. Hepatocytes often show siderosis, while Kupfer cells are spared [58]. NNH has classically been classified as a metabolic liver disease, but recent evidence suggests it is an alloimmune hepatitis [59]. NNH shows non-Mendelian inheritance: NNH is extremely rare in first pregnancies, and once one affected child was born, the risk of recurrence in subsequent pregnancies is 80 to 90%. Although no maternal alloantibody has been identified so far, there is a strong suspicion that in most cases of NNH, foetal liver damage is caused by a maternal alloantibody directed against an unknown foetal liver antigen, and that iron deposition is secondary to hepatocyte dysfunction, maybe via dysregulation of foetal hepcidin/placental ferroportin pathway producing foetal iron overload [59]. This alloimmune hypothesis is supported by the high risk of recurrence of NNH in future pregnancies, and by the efficacy of maternal IV immunoglobulins therapy in preventing these recurrences [60]. Other mechanisms might account for the rare non-recurrent cases [61].

Natural history and medical therapy

NNH is a rare condition but the most common cause of acute liver failure and LT in the neonatal period [62]. All infants present with acute liver failure with both intrahepatic and extrahepatic siderosis, which affects the parenchyma of the liver, pancreas, oral mucosa, and thyroid among other sites, but spares the reticuloendothelial system [63]. Diagnosis is based by demonstrating extrahepatic siderosis in salivary gland biopsy (lip) or by magnetic resonance imaging [64]. Apart from rare cases of spontaneous recovery with supportive care, untreated NNH is usually fatal within days. The efficacy of medical therapy including an antioxidant and iron chelating cocktail (Desferioxamine, N-Acetylcycteine, Selenium, Vitamin E, Prostaglandin E1) is controversial [61], but appears to have some effect in milder cases, particularly if started early [63,64]. Exchange transfusions have been reported to be successful in NNH [65]. Patients who recover from neonatal liver failure progressively clear the systemic iron overload.

Results of liver transplantation

LT is the only effective treatment in severe cases. Survival rates after neonatal LT for acute liver failure are nowadays up to 80% [66]. NNH does not recur in the liver graft, and systemic iron overload progressively clears as for non-transplanted patients who recover [61]. Normal neurological development and good quality of life are obtained in most patients [61,66].

Indications for liver transplantation

All but the mildest cases should be listed for transplantation at diagnosis while continuing the antioxidant cocktail as suitable donor organs are scarce in this age group. If there is response to treatment within 48—72 hours, the need for transplantation should be reassessed [63].

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease with an incidence of 1:2400 to 1:3400 live births in Caucasians [67]. CF is caused by mutations of a gene located on chromosome 7 coding for a large membrane protein called cystic fibrosis transmembrane conductance regulator (CFTR) that functions as an ion transporter (especially chloride and bicarbonate), as well as a regulator of other transporters and cellular functions [68—70]. In the normal liver, CFTR is expressed on the apical (intraluminal) membrane of cholangiocytes, but not in hepatocytes or other liver cells [71], and plays a role in bile formation and alkalisation through the regulation of chloride, bicarbonate and water transport. CFTR also regulates other permeability pathways involved in bile formation. The pathogenesis of liver injury is not completely understood: it may be partly the consequence of the systemic disease and malnutrition, and partly directly due to the genetic defect in the liver, the main suspected mechanisms being thickened secretions resulting in bile duct plugging and cholestasis, or direct cholangiocyte injury, especially when the mutation (like the most common ΔF508) leads to a misfolded CFTR protein [72].

Natural history and medical therapy

The clinical course of CF has changed as the management of CF lung disease improves, allowing survival of most patients till adulthood, hence revealing dysfunction in other organs. Liver disease has become the second commonest cause of mortality in CF patients [73], and may have various manifestations: (1) neonatal cholestasis [74], which may be difficult to distinguish from biliary atresia. The cholangiogram shows a normal biliary tree, with often a small gallbladder, and may be therapeutic by flushing any inspissated bile; (2) steatosis, whose aetiology is unknown, but may be triggered by malnutrition and/or deficiencies in trace elements or minerals; (3) biliary tract disease may have various presentations: a small gallbladder is present in 20—30% of cases [75]; Gallstones (1—10% of cases), which are mainly constituted by calcium bilirubinate, and cannot be dissolved by ursodeoxycholic acid (UDCA) therapy; Common bile duct stenosis (1% of cases) and sclerosing cholangitis (< 1%) [76]; (4) focal biliary cirrhosis and multilobular cirrhosis, which is found in about 20% of adult patients [73,77]; (5) malignancy is rare: HCC [78] cholangiocarcinoma [79]; (6) congestive liver disease secondary to elevated right heart pressures as a complication of lung disease; (7) asymptomatic elevation of liver enzymes [70], and/or histological changes, which can be found despite little biochemical or physical examination evidence of disease [80].

The medical management of CF liver disease first relies on the appropriate treatment of the systemic disease, especially lung disease and pancreatic insufficiency, and nutritional management, including replacement therapy of minerals, trace elements, and vitamins. This management necessitates a multidisciplinary approach. UDCA improves
liver function tests in children with CF liver disease [81,82], the ultrasonic (US) appearance of the liver [83], and may improve liver histology [84], and therefore is widely used in patients with CF liver disease [85]. However, it remains uncertain that UDCA can alter the long-term evolution of liver disease [86].

Regarding portal hypertension, the whole panoply of available therapies can be considered, but β-blockers are usually not recommended since they may cause bronchospasm. Endoscopic sclerosis or variceal banding, transjugular porto systemic shunts (TIPS), may be used to prevent or treat gastrointestinal bleeding. In children with compensated cirrhosis and moderate lung disease, surgical portosystemic shunts can efficiently prevent bleeding and postpone for many years the need for transplantation [87]. These patients should be closely monitored for pulmonary hypertension, whose progress may be accelerated due to increased portosystemic shunting.

**Results of liver transplantation**

One-year survival of liver transplanted CF patients is above 90%, comparable to other groups of children [88—90]. With adequate perioperative management, chest infections or other postoperative complications (distal intestinal obstruction syndrome [DIOS]) can be prevented. Lung function generally improves after LT in patients with CF, due to improved nutritional status, removal of ascites, improved diaphragmatic function, and possibly due to a beneficial effect of immunosuppression on lung disease. Successful multiorgan transplantations such as lung-liver, double lung and liver, heart-lung liver, [91—93] have been reported with 85% patient survival at 1 year. However, long-term outcomes of lung transplantation remain a concern, median post transplantation survival being less than 5 years mostly due to bronchiolitis obliterans [94,95]. Moreover, the limited organ pool may result in a greater waiting time for a triple procedure than for a single liver, increasing the risk of death while waiting for a graft [96].

**Indications of liver transplantation**

LT in patients with CF liver disease is mainly indicated for cirrhosis with liver failure. In a multicentric report of current practice for LT in patients with advanced CF-related liver disease in Europe, liver failure accounted for 2/3 of the indications and was defined by the presence of at least two of the following criteria: albumin level < 30 g/L, prolonged prothrombin time > 3 s over normal, increasing bilirubin level > 50 μmol/L, or the development of ascites. Other main indications for LT were hypersplenism (16%) gastro-intestinal bleeding (12%) and malnutrition (8%). LT should be planned before severe worsening of respiratory function (forced expiratory volume at 1 s > 50%) [89].

**Future therapies**

Several therapies are being studied for prevention or treatment of CF liver disease [86,97]: gene therapy targeting biliary epithelial cells, pharmacologic treatments to correct CFTR protein structure and improve its functionality, stimulation of alternate transmembrane channels to bypass the CFTR defect, development of new medications such as choleretic agents, antioxidants or antifibrotic agents.

**Glycogen storage diseases**

Glycogen storage diseases (GSD) are group of autosomal recessive metabolic disorders, characterized by accumulation of an abnormal amount or type of glycogen, with an incidence of 1:50,000 live births. Several enzymes of glycogen metabolism may be involved, resulting in 12 recognised types of GSD, seven of which have an enzymatic defect in the liver. Liver transplantation has been performed in GSD types Ia, Ib, III and IV, and may be indicated for: (1) correction of liver metabolic disease, when medical therapy either cannot control the disease (hypoglycemia, poor growth), or severely impairs quality of life; (2) cirrhosis and its complications; (3) liver tumours: adenoma, dysplasia, HCC. Liver transplantation for GSD will not be developed here since it has been extensively reviewed in a recent issue of Pediatric Transplantation [98].

**Disorders of mitochondrial energy metabolism (respiratory chain defects)**

Disorders of mitochondrial energy metabolism constitute a group of diseases secondary to dysfunction of the respiratory chain (RC) resulting in cellular ATP deficiency, increased production of reactive oxygen species and other toxic metabolites, and cell death [99,100]. The RC is formed of five protein complexes each consisting of several polypeptides subunits, most of which are encoded by nuclear DNA, and a few by mitochondrial DNA (complexes I, III, IV, V). Disorders of mitochondrial energy metabolism can result from mutations of nuclear or mitochondrial DNA, and therefore have several modes of inheritance (autosomal recessive, autosomal dominant or maternal). Each mitochondrion contains 2—10 copies of the mitochondrial genome, and usually all mitochondrial DNA (mtDNA) is identical (homoplasmy). When a mutation of mtDNA occurs, normal and mutant mtDNA can coexist in a single cell (heteroplasmy), whose phenotype is determined by the proportion of abnormal mtDNA. During cell division, mitochondria are randomly partitioned into daughter cells, resulting in heterogeneous levels of mutated mtDNA, and subsequent mitochondrial dysfunction, in various organs and tissues. This explains why the disease phenotype may change with age. Mitochondrial DNA depends on nuclear encoded genes for its enzymes of replication, transcription, translation and repair: mutations of these nuclear genes result in generalised depletion of mitochondrial DNA [99,100].

RC defects can affect any organ or tissue, at any age [101]. However, tissues with high-energy requirements (brain, muscle, liver) are more commonly affected. Unexplained association of neuromuscular symptoms in patients with acute or chronic liver disease is the most common presentation suggesting mitochondrial hepatopathy [102]. Although the true prevalence of mitochondrial disorders is difficult to evaluate due to high variability of clinical presentation and genetic inheritance, it has been estimated at
1/8500 in the general population [103]. Three main entities are related to RC defects and liver disease: deficiencies of RC enzymes, mitochondrial DNA depletion syndrome, and Alper’s syndrome.

Deficiencies of RC enzymes

The most common isolated defects involve complexes IV or I. A history of consanguinity is often present, suggesting a nuclear gene mutation. Combined defects are usually part of a mitochondrial DNA depletion syndrome [104].

Natural history and results of medical therapy

A frequent feature is the increasing number of organs involved in the course of the disease [101]: central nervous system, muscle, kidneys, liver. The hepatic involvement may present as isolated hepatomegaly, neonatal cholestasis or acute liver failure. Two forms of liver failure are distinguished [105]: neonatal liver failure (before one week) with a rapidly fatal course, and frequently includes severe hypotonia and myoclonic epilepsy [106]; delayed onset liver failure in infancy and early childhood (most commonly from 2 to 18 months) with a milder clinical course, inconstant neurological involvement, and unpredictable outcome, spontaneous recovery being rare but possible [107]. Medical therapy is mainly supportive as no medical treatment has proven efficacy [108].

Mitochondrial DNA depletion syndrome (MDS)

MDS result from mutations of nuclear genes regulating mitochondrial DNA replication, and lead to depletion of mtDNA. MDS have an autosomal recessive inheritance [37]. Two clinical phenotypes of MDS have been distinguished: myopathic [109] and hepatocerebral forms. However, the two phenotypes may be observed in the same family, with variable liver and muscle involvement between individuals [110].

Natural history of the disease

Infants with the hepatocerebral form of MDS present in the first weeks or months of life with liver failure, neurologic abnormalities, hypoglycemia and lactic acidosis, as well as gastroesophageal reflux, failure to thrive, and developmental delay. Death usually occurs before 1 year of age [111,112].

Alper’s syndrome

Alper’s syndrome is a particular form of MDS characterised by degenerative brain and liver disease, which may be precipitated by valproate therapy. Alper’s syndrome is often due to mutations of the nuclear gene coding for mitochondrial DNA polymerase γ subunit (POLG) [113].

Natural history of the disease

In most patients, liver disease is preceded by neurological symptoms including hypotonia, ataxia, and seizures, which are classically focal and refractory, as well as feeding difficulties and failure to thrive. Liver dysfunction may be discovered by blood tests done for monitoring of anticonvulsant therapy. Liver failure appears in infancy or childhood, and may rarely occur before neurological symptoms. Death usually results from liver failure [114,115].

Diagnosis of RC defects

The diagnosis of RC disorders is based on metabolic findings (high lactate and lactate/pyruvate ratio in plasma, and cerebrospinal fluid), histology of muscle (steatosis, ragged red fibers on Gomori stain) and liver (steatosis, necrosis, cholestasis, fibrosis and cirrhosis), electron microscopy (abnormal mitochondrial structure), histochemistry, immunocytochemistry, direct measurement of enzyme activity, and increasingly by mutation detection. The genetic characterisation of the primary defect (nuclear or mitochondrial) is needed to inform genetic counselling. The presence of muscle anomalies usually correlates with neurological involvement.

On the contrary, normal muscle investigations do not exclude neurological involvement: for instance in Alper’s syndrome, the muscle biopsy is usually normal at presentation and lactic acidosis is infrequent. The diagnosis can be suspected on clinical presentation, abnormalities of visual evoked potentials and brain MRI, and suggestive EEG findings. Genetic analysis is useful to confirm the diagnosis, but is rarely available in time when the acute decision to proceed with LT has to be taken in a child with acute liver failure.

Results of liver transplantation

In a multicentric study, Sokal et al. reported 11 patients transplanted for RC defects: five of them were alive and well at last follow-up (range 5 months to 8 years), six died including three after neurological deterioration post-LT [116]. Some of the same children have been reported in previous or later monocentric studies [105,117,118]. If the disease is confined to the liver, favourable outcome is possible, although available reports still have only limited follow-up. Exclusion of extrahepatic involvement is difficult, especially in the context of acute liver failure: lactate and lactate/pyruvate ratio in cerebrospinal fluid are difficult to interpret in the context of acute liver failure; normal muscle biopsy or brain MRI does not exclude neurological involvement [117]. A pre-transplantation comprehensive assessment of extrahepatic disease is recommended, however post transplantation neurological deterioration is possible even if this work-up was completely normal [99].

In Alper’s syndrome, progression of the neurological disease is inevitable after LT and leads to death [113,119,120].
Indication of liver transplantation

Since liver disease may stabilize or even regress in some patients, LT for RC defects is considered only in patients with life threatening liver failure. Due to its constant poor neurological outcome, Alper’s syndrome or valproate associated liver failure are formal contra-indications to LT. In the other RC defects, absence of extrahepatic involvement is usually considered as a pre-requisite to LT. However, even if no extrahepatic disease has been demonstrated prior to transplantation, involvement of other organs after LT remains a possibility of which the family should be informed.

Conflict of interest statement

Nothing declared.

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