Liver Transplantation for Monogenic Metabolic Diseases Involving the Kidney

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Abstract

Several metabolic monogenic diseases may be cured by liver transplantation alone (LTA) or by combined liver–kidney transplantation (CLKT) when the metabolic disease has caused end-stage renal disease. Liver transplantation may be regarded as a substitute for an injured liver or as supplying a tissue that may replace a mutant protein. Two groups of diseases should be distinguished. In the first group, the kidney tissue may be severely damaged while the liver tissue is almost normal. In this group, renal transplantation is recommended according to the degree of renal damage and liver transplantation is essential as a genetic therapy for correcting the metabolic disorder. In the second group, the liver parenchymal damage is severe. In this group, liver transplantation is essential to avoid liver failure. LTA may also avoid the progression of the renal disease; otherwise a CLKT is needed. In this review, we describe monogenic metabolic diseases involving the kidney that may have beneficial effects from LTA or CLKT. We also highlight the limitations of such procedures and the choice of alternative medical conservative treatments.

Keywords: atypical hemolytic uremic syndrome; glycogen storage disease; monogenic metabolic diseases; organic acidurias; primary hyperoxaluria

Introduction

Monogenic metabolic diseases involving the kidney are relatively rare and primarily found in children. In these diseases, genes encoding enzymes that allow the regulation of complex metabolic pathways, or circulating proteins mainly produced by the liver, are involved. In some diseases, the liver itself is affected along with other organs. Conversely, in some cases, the liver is free from significant parenchymal damage, but other organs, for example, the kidneys, may be severely injured. Tables 1 and 2 give a summary of these monogenic metabolic diseases (1, 2). In addition to the diseases shown in the tables, other monogenic metabolic diseases do exist with possible involvement of the kidneys and the liver. Alagille syndrome, Wilson’s disease, and hemochromatosis are a few examples. For this review, the diseases listed in Tables 1 and 2 were selected because they are more frequent with severe renal involvement and may be cured either by liver transplantation alone (LTA) or by combined liver–kidney transplantation (CLKT). For some diseases, an enzyme replacement therapy (ERT) is a possible option; however, ERT is
Table 1. Monogenic metabolic diseases caused by the liver that affect the kidney or both liver and kidney

<table>
<thead>
<tr>
<th>Diseases affecting the kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Primary hyperoxaluria types I and II</td>
</tr>
<tr>
<td>- Atypical hemolytic uremic syndrome</td>
</tr>
<tr>
<td>- Methylmalonic acidosis</td>
</tr>
<tr>
<td>- Transthyretin amyloidosis</td>
</tr>
<tr>
<td>Diseases affecting kidney and liver</td>
</tr>
<tr>
<td>- Glycogen storage disease</td>
</tr>
<tr>
<td>- Tyrosinemia type I</td>
</tr>
<tr>
<td>- α1-antitrypsin deficiency</td>
</tr>
</tbody>
</table>

not always available and is extremely expensive (3). A different approach could be gene therapy but its application encounters technical difficulties and to date is not a real option (4). When an alternative medical and conservative therapy is not available, organ transplantation may represent the only alternative therapy. Whether LTA or liver after kidney, or CLKT is the preferred strategy depends on kidney function or the availability of organs.

Due to the fact that these diseases are rare, epidemiological data come from national or international registries. According to the European Liver Transplant Registry (ELTR), between 1968 and 2010, orthotopic liver transplantation (OLT) for monogenic metabolic diseases was performed in 5.4% of adults, and in 17.3% of pediatric population (1). In the latter group, the predominant disorder was alpha 1 antitrypsin deficiency (AATD) (16%), followed by tyrosinemia (7%), primary hyperoxaluria (PH1) (7%), and glycogen storage disease (GSD) (4%). According to the United Network for Organ Sharing (UNOS) data (5), from 1996 to 2006, PH1 was the most predominant disorder (20.8%) with few patients transplanted because of atypical hemolytic uremic syndrome (aHUS) (0.8%) or AATD (0.8%). In these data, a large number of liver transplantation is reported without clarifying the original disease (33.6%). A review performed in 2013 (6), which included only CLKT in children, showed that PH1 prevailed with 72%, followed by aHUS (1%), organicacidurias (1%), and AATD (0.5%). Finally, according to the Japanese multicenter registry for living donor liver transplantation (LDLT) for pediatric patients with metabolic disorders, the first cause of LDLT is methylmalonic aciduria (10.3%), followed by GSD (7.7%), tyrosinemia (6.7%), and PH1 (4.6%) (7).

These registries report discordant data. The causes may be multifactorial: geographic and ethnic disparities, and LDLT data versus OLT versus CLKT data. Additionally, an important role may have been exerted by various considerations given to alternative treatments and different periods for collecting the data. Finally, the lack of OLT or CLKT for aHUS in registries such as the UNOS and ELTR, even during periods when eculizumab was not available, means a different therapeutic approach to the disease. The efforts of the Organ Procurement and Transplantation Network (OPTN) to realize guidelines for CLKT document the aforementioned concerns (8). At the meeting held in 2012 at the University of South California (8), the authors highlighted several previous consensus and tried to develop recommendations for the selection of candidates for CLKT (9, 10), but these recommendations have not yet become OPTN policy. In a recent review, Bacchetta et al. (11) pointed out that the experience of CLKT is limited and that some issues such as the respective place of a combined versus sequential liver kidney transplantation or the role of alternative therapies remain unanswered. According to the authors, the following key points should be highlighted:

- CLKT has encouraging results, provided that highly trained multidisciplinary teams are involved.
- The first issue is the safety of the procedure, principally in smaller children or in severely sick patients.
- Specific managements after CLKT or LTA are needed to avoid the recurrence of diseases such as PH1 and aHUS.
- The timing of CLKT, whether to perform a combined or sequential transplantation.

In this review, we describe monogenic metabolic diseases involving the kidney that may have beneficial effects from LTA or CLKT. We also highlight the limitations of such procedures and the choice of alternative medical conservative treatments. A literature search was performed in Web of Science, PubMed, EMBASE, Scopus, and directory of open access journals (DOAJ). The search was performed using the following key words: kidney–liver transplantation monogenic diseases, hyperoxaluria, aHUS, organic acidurias, GSD, tyrosinemia, and alpha-1-antitrypsin deficiency (AATD).

Metabolic monogenic diseases affecting mainly the kidney

Primary hyperoxaluria

The autosomal recessive inherited primary hyperoxaluria types I, II, and III are caused by defects in glyoxylate metabolism that lead to the endogenous overproduction of oxalate (12). PH1 is the most severe form of the disease and is present in approximately 80% of patients included in the two international registries (13, 14). It is an autosomal recessive liver disease caused by deficiency or loss of activity of peroxisomal alanine glyoxylate aminotransferase (AGXT) (Table 3). This results in an overproduction of oxalate and glycolate (15, 16), with oxalate deposition in several organs and tissues including the kidney. PH2 is caused by deficiencies of the glyoxylate reductase/hydroxypropionate reductase (GRHPR) enzyme. GRHPR is ubiquitous, but its expression is higher in the liver (17). The clinical expression is less severe although patients may be affected by severe urolithiasis with end-stage renal disease (ESRD) (18). PH3 has only recently been described (19).
It is caused by loss of function of the mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA) enzyme. PH3 does not appear to progress to ESRD (20). Table 3 reports the incidence percentage of PH according to Hoppe et al. (21). It should be highlighted that the percentage of PH2 and PH3 may be slightly higher. Indeed, PH2 may be undiagnosed because of the less severe clinical course.

The conservative treatment of PH1 has several limitations. Patients should intake high quantities of fluids (22). In addition to fluid intake, patients are recommended to take alkaline citrate or orthophosphate to increase urinary pH and urinary citrate excretion (23). In one-third of the patients, supraphysiological dosages of pyridoxine may reduce the oxalate excretion (23). It has been documented that patients with a homozygous c.508G>A mutation of the AGXT gene experience a better response from pyridoxine therapy (24). Oxalate-degrading bacteria usually colonize the intestinal tract. Oxalobacter-driven activation of the intestinal transporter results in an increased oxalate elimination with feces, and a decrease of plasma oxalate (25). Peritoneal dialysis and hemodialysis are relatively ineffective in removing oxalate (26).

### Table 2. Diseases involving the kidney amenable to LTA or CLKT as surgical therapy

<table>
<thead>
<tr>
<th>Disorder, type, and acronym</th>
<th>Gene symbol</th>
<th>Inheritance</th>
<th>Mechanism of disease</th>
<th>Deficient enzyme</th>
<th>Liver features</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperoxaluria type I</td>
<td>AGXT</td>
<td>AR</td>
<td>Calcium oxalate accumulation in tissues</td>
<td>Alanine-glyoxylate-aminotransferase</td>
<td>Normal liver</td>
<td>Nephrolithiasis; renal failure</td>
</tr>
<tr>
<td>Atypical hemolytic uremic syndrome (aHUS1)</td>
<td>CFH</td>
<td>AR, AD</td>
<td>Thrombotic microangiopathy, complement activation</td>
<td>Complement factor H</td>
<td>Normal liver</td>
<td>Acute renal failure; hypertension</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MUT</td>
<td>AR</td>
<td>Disorder of methylmalonate and cobalamin leading to methylmalonyl-CoA accumulation</td>
<td>Methylmalonyl-CoA mutase</td>
<td>Normal liver</td>
<td>Toxic encephalopathy; acidosis; renal failure</td>
</tr>
<tr>
<td>TTR familial amyloid polyneuropathy (TTR1-FAP)</td>
<td>TTR</td>
<td>AD</td>
<td>Deposit of insoluble protein fibrils in the extracellular matrix</td>
<td>Transthyretin</td>
<td>Normal liver</td>
<td>Polyneuropathy; cardiomyopathy; renal failure</td>
</tr>
<tr>
<td>Glycogen storage disease type Ia</td>
<td>G6Pase</td>
<td>AR</td>
<td>Abnormal accumulation of glycogen in the tissues</td>
<td>Glucose-6-phosphatase</td>
<td>Glycogen in the liver; Adenomas HCC</td>
<td>Hepatomegaly; Nephromegaly; Growth retardation</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
<td>FAH</td>
<td>AR</td>
<td>Lack of tyrosine degradation</td>
<td>Fumaryl-acetoacetate hydrolase (FAH)</td>
<td>Liver failure; HCC</td>
<td>Secondary renal tubular dysfunction</td>
</tr>
<tr>
<td>α-1 antitrypsin deficiency (AATD)</td>
<td>PI</td>
<td>AR</td>
<td>Lack of inhibitory action against neutrophil elastase</td>
<td>Protease inhibitor</td>
<td>Cirrhosis HCC</td>
<td>Emphysema; glomerulonephritis</td>
</tr>
</tbody>
</table>

AATD, α-1antitrypsin deficiency; AD, Autosomal dominant; AGXT, Alanine-glyoxylate aminotransferase; AR, Autosomal recessive; CFH, Complement factor H; G6Pase, Glucose-6-Phosphatase; FAH, Fumaryl-acetoacetate hydrolase; MMA, Methylmalonic academia; MUT, Methylmalonyl-CoA mutase; PI, Protease inhibitor; TTR, Transthyretin; TTR1-FAP, Transthyretin-type familial acidosis polyneuropathy.
The best transplantation strategy for a patient affected by PH1 has been a matter of discussion. Preemptive LTA is the best strategy for patients before the occurrence of ESRD, and to prevent systemic oxalosis (27). LTA is the best strategy for patients with glomerular filtration rate (GFR) higher than 40 mL/min/1.73 m² (28). CLKT is the preferred option when GFR is below 40 mL/min/1.73 m² (29). The transplant outcome is optimal in CLKT according to the International Primary Hyperoxaluria Registry (30) and the recently published French experience (31), which concludes that CLKT for PH1 provides better kidney graft survival, less rejection rate, and is not associated with an increased short-time mortality risk. Medical treatment is effective in PH2; in patients with ESRD, kidney transplantation alone is the treatment of choice, as the defective enzyme is not liver-specific (17). Reports of CLKT for PH2 do exist (32); however, kidney transplantation followed by appropriate measures to decrease oxalate levels is the method of choice (33).

Atypical hemolytic uremic syndrome

aHUS is a rare disease often associated with mutations in genes encoding complement regulatory proteins, causing secondary disorders of complement regulation. CFH mutations (gene encoding factor H) are the most common, but mutations in genes encoding complement factor I (CFI), C3, complement factor B (CFB), and thrombomodulin (THBD) have also been recognized (34). The mortality rate is high (35) and many patients progress to ESRD. Kidney transplantation is a therapeutic measure, but disease recurrence in the transplanted kidney frequently occurs (36) as the liver does not produce the normal protein. Conservative treatment with plasma exchange and plasma infusion reduces mortality rate (35) but is unable to cure the disease or prevent recurrences after kidney transplantation. Several studies documented the efficacy of eculizumab, a human monoclonal antibody directed against the complement protein C5 (37). The best option is still a matter of debate. A comparison between kidney transplantation alone with chronic eculizumab and CLKT is given in Table 4 (38). It should be highlighted that certain gene mutations are associated with altered response to eculizumab. For example, mutations in diacylglycerol kinase epsilon (DGKE) gene are associated with complement-independent forms of aHUS and are resistant to eculizumab (39). Also, genetic variants in C5 confer resistance to eculizumab (40).

Table 3. Different types of primary hyperoxaluria

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene/gene product/locus</th>
<th>PH cases (%)</th>
<th>Definition</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH I</td>
<td>AGXT/AGT/2q37.3</td>
<td>70–80</td>
<td>Uox &gt;1 mmol/1.73 m² per day/elevated urinary oxalate to creatinine ratios</td>
<td>AR</td>
</tr>
<tr>
<td>PH II</td>
<td>GRHPR/GRHPR/9q11</td>
<td>~10</td>
<td>Uox &gt;1 mmol/1.73 m² per day/elevated urinary oxalate to creatinine ratios</td>
<td>AR</td>
</tr>
<tr>
<td>PH III</td>
<td>HOGA1/10q24.2</td>
<td>~10</td>
<td>Uox &gt;1 mmol/1.73 m² per day/elevated urinary oxalate to creatinine ratios</td>
<td>AR</td>
</tr>
</tbody>
</table>

AGXT, Alanine-glyoxylate aminotransferase; AR, Autosomal recessive; GRHPR, Glyoxylate and Hydroxypyruvate Reductase; HOGA 1, 4-hydroxy-2-oxoglutarate aldolase 1.

Table 4. Comparison of transplant approaches in aHUS

<table>
<thead>
<tr>
<th>Kidney transplantation alone with chronic eculizumab</th>
<th>Liver–kidney transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower short-term risk</td>
<td>Higher short-term mortality</td>
</tr>
<tr>
<td>Long-term outcomes yet to emerge</td>
<td>Long-term outcomes stable</td>
</tr>
<tr>
<td>Long-term dependence to prevent aHUS</td>
<td>aHUS recurrence unlikely</td>
</tr>
<tr>
<td>More “immunosuppressive”</td>
<td>Less immunosuppressive</td>
</tr>
<tr>
<td>Increased infection risk?</td>
<td>Lower rejection risk</td>
</tr>
<tr>
<td>Lower rejection risk?</td>
<td>Better lifestyle-no infusions</td>
</tr>
<tr>
<td>IV infusion every 2 weeks</td>
<td>Lower monetary cost</td>
</tr>
<tr>
<td>Limited availability worldwide</td>
<td>More widely available</td>
</tr>
<tr>
<td>Very high financial cost</td>
<td>Limited organ (liver) resource</td>
</tr>
</tbody>
</table>
In 2009, a Consensus Study Group identified the guidelines for CLKT and LTA (41). With the adoption of such measures, the mortality rate decreased, and 16 out of 20 patients (80%) could be safely cured with CLKT (42). In a 2016 international consensus statement by experts from Europe, Canada, Turkey, and the United States, prophylactic eculizumab is the recommended treatment after kidney transplantation alone. The consensus group recognized that LTA or CLKT is the only therapeutic measure to definitively cure aHUS in patients with mutations of complement factors synthesized in the liver (43). They also recommended that CLKT should be discussed with the family and patients, with emphasis on risks and benefits of the alternative treatments.

Organic acidurias

Organic acidurias are inborn errors of organic acid metabolism, characterized by the excretion of nonamino organic acids in the urine. The two commonest forms are methylmalonic acidemia (MMA) and propionic acidemia. Only MMA is of interest to kidney because of the nephrotoxicity of methylmalonate to renal tubular epithelial cells (44). MMA is a rare autosomal recessive disorder caused by complete or partial deficiency of methylmalonyl-CoA mutase de

in such patients the de novo synthesis of propionyl-CoA within methylmalonyl-CoA mutase de

with a 99% survival for children older than 2 years. However, 93%. The same study reports a UNOS 5-year survival of 88%,

MMA patients with CLKT. The results of this study are excel-

(56) who reported six MMA patients with LTA and eight

MMA patients have undergone either LTA or CLKT (48–55). The most recent report is the one by Niemi et al. (56) who reported six MMA patients with LTA and eight MMA patients with CLKT. The results of this study are excellent with a 3-year patient survival of 100% and liver survival of 93%. The same study reports a UNOS 5-year survival of 88%, with a 99% survival for children older than 2 years. However, the effectiveness of LT in patients with MMA caused by methylmalonyl-CoA mutase deficiency is questionable because in such patients the de novo synthesis of propionyl-CoA within the central nervous system leads to brain methylmalonate accumulation that is not affected by transplantation (53).

Transthyretin-type familial amyloidosis polyneuropathy

Transthyretin-type familial amyloidosis polyneuropathy (TTR-FAP) is a rare adult onset progressive disorder characterized by extracellular amyloid fibril formation with polymerized TTR accumulation. The disorder is inherited as an autosomal trait, and about 100 different mutations or deletions in the TTR gene are known (57). Clinical manifestations are repre-

sented by progressive polyneuropathy and in the final stages patients die from ESRD or, most frequently, from heart failure. A number of drugs, for example, Diffunisal (58) and Benzoazoles (59), stabilize TTR or inhibit fibril formation. The most promising drug is Tafamidis (60). As the liver produces most of the amyloidogenetic TTR, LTA has been tried to stop the variant of TTR. The results of LTA for TTR-FAP are good as reported by the data of single institutions (61) or by the transplant registry (62). The worse outcomes are related to cardiac amyloidosis (63), and in a few cases combined heart–liver transplantation has been attempted (64, 65).

Metabolic monogenic diseases affecting both kidney and liver

Glycogen storage disease

GSDs are inherited disorders that affect glycogen metabolism and cause abnormal accumulation of glycogen both in quantity and in quality (66). In general, liver and muscles are the two major tissues abundant in glycogen and thus the most seriously affected in GSDs. To date, 23 types (or subtypes) of GSDs have been identified. In all 23 types, gene mutations have been detected. This has been the result of a gene-by-gene sequencing technique in combination with the detection of biochemical and clinical hallmarks (67). GSDs are classified depending on the organ affected and the enzyme deficiency involved. To date, seven GSDs affect mainly the liver, nine GSDs affect mainly the muscles, and three GSDs the heart. A simplified and useful classification is shown in Table 5 (68), where, in addition to GSDs affecting liver and/or muscles, GSDs also affecting the kidney are shown. The latter are described in detail as may be treated by LTA or CLKT according to the clinical conditions.

GSD type I (GSDI) is an autosomal recessive inborn error of carbohydrate metabolism caused by defects in the glucose-6-phosphate transporter (G6PT)/glucose-6-phosphatase (G6Pase) complex (69, 70). Deficient activity of G6Pase causes GSDIa (71), and deficient activity of G6PT causes GSDIb (72). The human G6Pase gene was cloned by Lei et al. (71). These authors identified mutations causing GSDIa. The human G6PT gene, which causes GSDIb, has also been cloned. Approximately, 80% of people with GSDI have type Ia and 20% have type Ib. GSD type Ia is characterized by hypoglycemia, hepatomegaly, nephromegaly, hyperlipidemia, hyperuricemia, and growth retardation (73). Renal findings may be diverse. Focal segmental glomerulosclerosis caused by hyperfiltration has been frequently found; amyloidosis, Fanconi-like syndrome, renal stones, and nephrocalcinosis may be found as well (66). Interstitial fibrosis may develop and some patients may progress to ESRD (74, 75). Almost 70% of patients affected by GSDI
develop hepatic adenomas with the potential of transforming into hepatocellular carcinoma (HCC) (76, 77).

GSDIII results from a defect in glycogen debranching enzyme activity that leads to the accumulation of an abnormal form of glycogen in affected tissues. In the United States, more than 80% of patients with GSDIII have both liver and muscle involvement (78). Renal function is often normal, but cases of acute renal failure (79) are reported even if the pathogenesis is not clear. Full guidelines on the GSDI diagnosis and management have been published by the American

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>Enzyme defect</th>
<th>Glycogen structure</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucose-6-phosphatase deficiency (Von Gierke’s disease)</td>
<td>Glucose-6-phosphatase</td>
<td>Normal</td>
<td>Enlarged liver and kidneys; failure to thrive; hepatic adenomas; Focal segmental glomerulosclerosis and interstitial fibrosis; Amyloidosis; Fanconi-like syndrome Renal stones/nephrocalcinosis</td>
</tr>
<tr>
<td>2</td>
<td>Infantile acid maltase deficiency (Pompe’s disease)</td>
<td>Acid maltase</td>
<td>Normal</td>
<td>Cardiorespiratory death</td>
</tr>
<tr>
<td>3</td>
<td>Late infantile and adult acid maltase deficiency</td>
<td>Acid maltase</td>
<td>Abnormal short outer chains</td>
<td>Hip weakness; slow motor development</td>
</tr>
<tr>
<td>4</td>
<td>Debrancher deficiency (Cori’s disease)</td>
<td>Amylo-1, 6-glucosidase</td>
<td>Abnormal short outer chains, increased branch points</td>
<td>Hepatomegaly; Renal tubular acidosis</td>
</tr>
<tr>
<td>5</td>
<td>Brancher deficiency</td>
<td>Amylo-1,4→1, 6-transglucosidase</td>
<td>Abnormal</td>
<td>Cirrhosis; growth failure; muscle wasting</td>
</tr>
<tr>
<td>6</td>
<td>Myophosphorylase deficiency (McArdle’s disease)</td>
<td>Muscle phosphorylase</td>
<td>Normal</td>
<td>Atrophy in older patients; myoglobinuria</td>
</tr>
<tr>
<td>7</td>
<td>Hepatophosphorylase deficiency</td>
<td>Muscle phosphorylase</td>
<td>Normal</td>
<td>Hepatomegaly; cirrhosis</td>
</tr>
<tr>
<td>8</td>
<td>Phosphorylase kinase deficiency</td>
<td>Phosphorylase kinase</td>
<td>Normal</td>
<td>Marked hepatomegaly; cirrhosis</td>
</tr>
<tr>
<td>9</td>
<td>Phosphoglucomutase deficiency</td>
<td>Phosphoglucomutase</td>
<td>Normal</td>
<td>Weakness; regression in motor development</td>
</tr>
<tr>
<td>10</td>
<td>Phosphohexose isomerase deficiency</td>
<td>Phosphohexose isomerase</td>
<td>Normal</td>
<td>Myopathy</td>
</tr>
<tr>
<td>11</td>
<td>Phosphofructokinase deficiency</td>
<td>Phosphofructokinase</td>
<td>Normal</td>
<td>Atrophy in older patients; myoglobinuria</td>
</tr>
<tr>
<td>12</td>
<td>Glycogen synthetase deficiency</td>
<td>Glycogen synthetase</td>
<td>Normal</td>
<td>Mental retardation; seizures</td>
</tr>
</tbody>
</table>
Liver transplantation is indicated in case of liver failure and to avoid the transforming of adenomas into HCC. Isolated liver transplantation has been performed in GSD-I patients with multiple unresectable adenomas, poor metabolic control, and progressive liver failure (81, 82). Indications for pediatric liver transplantation in GSD-I children are multiple liver adenomas, growth failure, and poor metabolic control (83). A 15-year follow-up after liver transplantation with an optimal outcome has been reported (84). The Japanese registry (7) reports LDLT for 15 patients with a 10-year graft and patient survival of 67%. However, the group included 70% of patients with GSD type IV. In a recent review, Boers et al. (85) identified 58 patients with GSD-Ia who underwent a liver transplantation between 1982 and 2012. The authors conclude that there are still many complications related to the liver transplant procedure (18/58) as well as complications related to immune suppressive therapy. Taking into account of these complications, the authors highlight the relevance of new therapies such as hepatocyte and liver stem cell transplantation. There have been reports of CLKTs that have been successfully performed in GSD-Ia patients (83, 86–90). The physicians involved in liver–kidney transplantation recommend that CLKT should be considered for patients with ESRD secondary to GSD-Ia.

**Tyrosinemia type I**

Tyrosinemia type I (TT1) is an autosomal recessive metabolic disorder characterized by the deficiency of the enzyme fumarlycetoacetate hydrolase (FAH) involved in the final step of the catabolism of tyrosine and phenylalanine (91). Mutations occur in the gene FAH located on chromosome 15. The incidence of TT1 is around 1:100,000, but is higher in areas where specific programs for diagnosing have been carried out (92, 93). The deficient enzyme causes the accumulation of toxic metabolites such as fumarylacetoacetate and maleylacetoacetate. These metabolites induce apoptosis of both hepatocytes and kidney tubular cells. The toxic metabolites may affect hepatocyte DNA, increasing the risk of HCC. The acute form of tyrosinemia I is characterized by acute renal failure and its incidence is higher up to the fourth month of life. The chronic form is characterized by chronic liver disease, cardiomyopathy, Fanconi-like tubular dysfunction, rickets, and renal failure (94).

A conservative treatment of the disease is available with 2-(2-nitro-trifluoromethylbenzoyl)-1, 3 cycloexemedione (NTBC) (95), which blocks the formation of toxic metabolites. With NTBC and a phenylalanine- and tyrosine-restricted diet, an improvement in kidney and liver function is achieved (96–98). After the introduction in therapy of NTBC, the need for LTA dropped from 35% to 12% (93). To date, the indications for LTA are as follows:

- Patients failing with the first-line medications
- Onset of acute renal failure
- HCC
- Poor quality of life

According to some group, a nodular liver is also an indication for LTA, due to the high risk of HCC (99). CLKT was indicated in the pre-NTBC era, but is no longer indicated. The highest number of LTA for tyrosinemia I are those reported by Arnon et al. (100), who analyzed the UNOS database, and Herzog et al. (101), who reported 27 LTA followed by stabilization or improvement of the renal function. The 1-year graft survival is higher than 88%, and only in selected cases NTBC treatment is needed after LTA.
**Alpha1-antitrypsin deficiency**

The most common genetic cause of liver disease in children is AATD (102), an autosomal recessive disorder caused by mutations in the SERPINA1 gene (103). AAT protects tissues from proteases such as neutrophil elastase. The phenotype PiMM (protease inhibitor MM) is present in 95% of the population. Several mutations have been described, the most common related to alleles being PiZ and PiS that result in reduced circulating levels of AAT. Liver disease develops in children with PiZZ mutation. Lung 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 (104). Glomerular diseases, mainly mesangiocapillary glomerulonephritis, develop in some children with AATD and may progress to ESRD (105).

The pathologic features usually involve the liver, lung, and kidneys. The study by Davis et al. (106) evaluated renal specimens from 34 patients affected by AATD. Glomerular lesions were found in 79%, including mesangial proliferative glomerulonephritis, mesangiocapillary glomerulonephritis, and focal segmental glomerulonephritis. PiM and PiZ were found in the subendothelial region of glomerular basement membrane and this fact suggested a possible role for these proteins in the pathogenesis of these lesions. Several approaches to medical treatment of AATD are possible (107). Deficient AAT can be replaced using recombinant AAT. This replacement therapy (usually by inhalation) may slow the progression of lung disease, but not liver or kidney disease. The same limitations occur with gene therapy and stem cell therapy (108). The indication for LTA in AATD is either end-stage liver disease (ESLD) or HCC. LTA not only cures the ESLD but also prevents the development of lung disease, as the recipient develops the Pi phenotype of the donor. Hughes et al. (109) reported a single-center largest series of LTA with a 5-year patient survival of 76.5%. Concerning the effect of LTA on the kidney, Grewal et al. (105) did not document the reversal of membranoproliferative glomerulonephritis. By contrast, the reversibility of the glomerulonephritis was documented by Elzouki (110) after LTA. The success of CLKT in the case of ESRD has been repeatedly documented (86, 111). The latter authors recommend native kidney biopsy and GFR measurement in all patients with AATD referred for LTA.

**Conclusion**

These monogenic metabolic diseases affecting either kidney or liver account for 10 out of 1000 births, and represent a frequent cause of mortality, mainly in the pediatric population. Effective medical conservative treatments are rarely available with the exception of aHUS and TT1. The introduction of the eculizumab changed the therapeutic prospective of aHUS principally after renal transplantation. The introduction of NTBC for TT1 dropped the indication for LTA from 35% to 12%. For other diseases, organ transplantation remains the standard of care treatment. Whether to adopt LTA or CLKT continues to be a matter of debate. In PH1, CLKT should be the treatment of choice in the case of ESRD. LTA may represent the preferred option if renal function is still over 40 mL/min/1.73 m². Reversal of renal damage after LTA has been observed. LTA offers a curative approach in patients with primary hepatic parenchymal damage and also in liver-based genetic disorders with prevalent extra-hepatic lesions. When the genetic defect is ubiquitous and the liver is one among several targets for systemic injury, the results of liver transplantation may be quite poor. The identification of the genetic defect allows for a better understanding of the disease and an improvement of treatment after transplantation. ERT could represent a viable option, but ERT is extremely expensive and not available everywhere. Gene therapy has recently shown great promise as an effective treatment for a number of metabolic diseases caused by genetic defects in both animal models and human clinical trials. Most of the current success has been achieved using a viral-mediated addition approach (112, 113). Successful studies in animals have been conducted for PH1 (114) and GSDI (115). Studies in humans are ongoing for GSDI and MMA (116). A phase II clinical trial for AATD has been terminated (117).

**References**


