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REVIEW ARTICLE

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

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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

Diseases affecting the kidney
- Primary hyperoxaluria types I and II
- Atypical hemolytic uremic syndrome
- Methylmalonic acidosis
- Transthyretin amyloidosis
Diseases affecting kidney and liver
- Glycogen storage disease
- Tyrosinemia type I
- α-1-antitrypsin deficiency

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%), organic acidurias (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/hydroxypyruvate 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).

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

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

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 hydroxylase; MMA, Methylmalonic academia; *MUT*, Methylmalonyl-CoA mutase; *PI*, Protease inhibitor; *TTR*, Transthyretin; TTR1-FAP, Transthyretin-type familial acidosis polyneuropathy.

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 3. Different types of primary hyperoxaluria

Type	Gene/gene product/locus	PH cases (%)	Definition	Mode of inheritance
PH 1	*AGXT*/AGT/2q37.3	70–80	U_{ox} >1 mmol/1.73 m^2 per day/elevated urinary oxalate to creatinine ratios	AR
PH II	*GRHPR*/GRHPR/ 9q11	~10	U_{ox} >1 mmol/1.73 m^2 per day/elevated urinary oxalate to creatinine ratios	AR
PH III	*HOGA1*/ HOGA1/ 10q24.2	~10	U_{ox} >1 mmol/1.73 m^2 per day/elevated urinary oxalate to creatinine ratios	AR

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

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 m^2 (28). CLKT is the preferred option when GFR is below 40 mL/min/1.73 m^2 (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 4. Comparison of transplant approaches in aHUS

Kidney transplantation alone with chronic eculizumab	Liver–kidney transplant
Lower short-term risk	Higher short-term mortality
Long-term outcomes yet to emerge	Long-term outcomes stable
Long-term dependence to prevent aHUS	aHUS recurrence unlikely
More "immunosuppressive"	Less immunosuppressive
Increased infection risk?	Lower rejection risk
Lower rejection risk?	Better lifestyle-no infusions
IV infusion every 2 weeks	Lower monetary cost
Limited availability worldwide	More widely available
Very high financial cost	Limited organ (liver) resource

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 methylmalonil-CoA mutase or by defects in the synthesis of its cofactor adenosylcobalamin (45). If the acute metabolic crises are not corrected by maintenance therapy, ESRD may occur. In such conditions, a CLKT may be indicated (46). Otherwise, LTA can be performed (47).

Conservative management to correct acute metabolic crisis relies on protein restriction (low-protein and high-caloric diet with overnight continuous feeding), amino acids supplementation, carnitine, and cobalamin (44). Although dietary management has been the major component of MMA therapy for a long time, patients are at risk for renal, cardiac, ophthalmological, and neurological complications (47). Due to poor prognosis, LTA has been attempted and CLKT is indicated when ESRD occurs. In addition to the aforementioned series, and the one from Kasahara et al. (45) who reported 13 children who received LTA and 5 who received CLKT, numerous patients with MMA 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 represented by progressive polyneuropathy and in the final stages patients die from ESRD or, most frequently, from heart failure. A number of drugs, for example, Diflunisal (58) and Benzoxazoles (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-phospate 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 1a 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

Table 5. Different types of glycogen storage diseases and main clinical findings

Number	Name	Enzyme defect	Glycogen structure	Clinical manifestations
1	Glucose-6-phospha-tase deficiency (Von Gierke's disease)	Glucose-6-phosphatase	Normal	Enlarged liver and kidneys; failure to thrive; hepatic adenomas; Focal segmental glomerulosclerosis and interstitial fibrosis; Amyloidosis; Fanconi-like syn-drome Renal stones/ nephrocalcinosis
2	Infantile acid maltase deficiency (Pompe's disease)	Acid maltase	Normal	Cardiorespiratory death
3	Late infantile and adult acid maltase deficiency	Acid maltase	Abnormal short outer chains	Hip weakness; slow motor development
4	Debrancher deficiency (Cori's disease)	Amylo-1, 6-glucosidase	Abnormal short outer chains, increased branch points	Hepatomegaly; Renal tubular acidosis
5	Brancher deficiency	Amylo-1,4→1, 6-transglucosidase	Abnormal	Cirrhosis; growth failure; muscle wasting
6	Myophosphorylase deficiency (McArdle's disease)	Muscle phosphorylase	Normal	Atrophy in older patients; myoglobinuria
7	Hepatophosphorylase deficiency	Muscle phosphorylase	Normal	Hepatomegaly; cirrhosis
8	Phosphorylase kinase deficiency	Phosphorylase kinase	Normal	Marked hepatome-galy; cirrhosis
9	Phosphoglucomutase deficiency	Phosphoglucomutase	Normal	Weakness; regression in motor development
10	Phosphohexose isomerase deficiency	Phosphohexose isomerase	Normal	Myopathy
11	Phosphofructokinase deficiency	Phosphofructokinase	Normal	Atrophy in older patients; myoglobinuria
12	Glycogen synthetase deficiency	Glycogen synthetase	Normal	Mental retardation; seizures

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

College of Medical Genetics and Genomics (80). The differential diagnosis among the different types of GSD is essential. Laboratory testing and genetics are essential. The principal findings are the following:

- Blood/plasma hypoglycemia, lactic acidosis, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia are consistent with GSDI.
- Neutropenia suggests GSD Ib.
- Diagnosis should be confirmed by full gene sequencing of the *GSPC* and *SLC37A4* genes.
- If liver biopsy is performed, histology typically shows fat and glycogen in hepatocytes without fibrosis.
- Diagnostic studies should be performed to follow renal manifestations, including:
  - Renal ultrasound to assess kidney size, nephrolithiasis, and nephrocalcinosis
  - Urinalysis for hematuria and proteinuria
  - Measurement of blood urea nitrogen and serum creatinine with calculation of estimated GFR (eGFR)

Medical and nutritional treatment

- Maintaining blood glucose levels > 70 mg/dL is important to achieve a good metabolic control.
- Avoid fasting for more than 5 h.
- Access via NG or G tube placement is recommended for emergencies in infants.
- Multivitamins, calcium, and vitamin D are necessary because of the restricted nature of the diet.

For the kidney

- Consider initiating an ACE inhibitor or ARB with the evidence of hyperfiltration.
- Initiate an ACE inhibitor or ARB for persistent microalbuminuria.
- Initiate citrate supplementation for hypocitraturia.
- Consider a thiazide diuretic for hypercalciuria.
- Maintain normal blood pressure for age.

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 GSDI patients with multiple unresectable adenomas, poor metabolic control, and progressive liver failure (81, 82). Indications for pediatric liver transplantation in GSDI 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 GSDIa 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 GSDIa patients (83, 86–90). The physicians involved in liver–kidney transplantation recommend that CLKT should be considered for patients with ESRD secondary to GSDIa.

Tyrosinemia type I

Tyrosinemia type I (TT1) is an autosomal recessive metabolic disorder characterized by the deficiency of the enzyme fumarylacetoacetate 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 malelylacetoacetate. 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 *SERPINA 1* 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 m^2. 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 gene 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

1. Fagiuoli S, Daina E, D'Antiga L, Colledan M, Remuzzi G. Monogenic diseases that can be cured by liver transplantation. J Hepatol. 2013 Sep;59(3):595–612. http://dx.doi.org/10.1016/j.jhep.2013.04.004
2. Milani A, Zaccaria R. Combined liver and kidney transplantation. Open Transplant J. 2011;5:63–6. http://dx.doi.org/10.2174/1874418401105010063
3. Lachmann RH. Enzyme replacement therapy for lysosomal storage diseases. Curr Opin Pediatr. 2011 Dec;23(6):588–93. http://dx.doi.org/10.1097/MOP.0b013e32834c20d9
4. Fischer A, Cavazzana-Calvo M. Gene therapy of inherited diseases. Lancet. 2008 Jun;371(9629):2044–7. http://dx.doi.org/10.1016/S0140-6736(08)60874-0
5. Chava SP, Singh B, Pal S, Dhawan A, Heaton ND. Indications for combined liver and kidney transplantation in children. Pediatr Transplant. 2009 Sep;13(6):661–9. http://dx.doi.org/10.1111/j.1399-3046.2008.01046.x
6. Strobele B, Loveland J, Britz R, Gottlich E, Welthagen A, Botha J. Combined paediatric liver-kidney transplantation: Analysis of our experience and literature review. S Afr Med J. 2013 Oct;103(12):925–9. http://dx.doi.org/10.7196/samj.7304.
7. Kasahara M, Sakamoto S, Horikawa R, Koji U, Mizuta K, Shinkai M. et al. Living donor liver transplantation for pediatric patients with metabolic disorders: The Japanese multicenter registry. Pediatr Transplant. 2014 Feb;18(1):6–15. http://dx.doi.org/10.1111/petr.12196
8. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, et al. Simultaneous liver-kidney transplantation summit: Current state and future directions. Am J Transplant. 2012 Nov;12(11):2901–8. http://dx.doi.org/10.1111/j.1600-6143.2012.04190.x
9. Davis CL, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, et al. Simultaneous liver-kidney transplantation: Evaluation to decision making. Am J Transplant. 2007 Jul;7(7):1702–9. http://dx.doi.org/10.1111/j.1600-6143.2007.01856.x

10. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). Am J Transplant. 2008 Nov;8(11): 2243–51. http://dx.doi.org/10.1111/j.1600-6143.2008.02416.x
11. Bacchetta J, Mekahli D, Rivet C, Demède D, Leclerc AL. Pediatric combined liver-kidney transplantation: A 2015 update. Curr Opin Organ Transplant. 2015 Oct;20(5):543–9. http://dx.doi.org/10.1097/MOT.0000000000000225
12. Hoppe B. An update on primary hyperoxaluria. Nat Rev Nephrol. 2012 Jun 12;8(8):467–75. http://dx.doi.org/10.1038/nrneph.2012.113
13. Lieske JC, Monico CG, Holmes WS, Bergstralh EJ, Slezak JM, Rohlinger AL, et al. International registry for primary hyperoxaluria. Am J Nephrol. 2005 May–Jun;25(3):290–6. http://dx.doi.org/10.1159/000086360
14. Mandrile G, van Woerden CS, Berchialla P, Beck BB, Acquaviva Bourdain C, Hulton SA. OxalEuropeConsortium Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int. 2014 Dec;86(6):1197–204. http://dx.doi.org/10.1038/ki.2014.222
15. Danpure CJ. Molecular aetiology of primary hyperoxaluria type 1. Nephron Exp Nephrol. 2004;98(2):e39–44. http://dx.doi.org/10.1159/000080254
16. Danpure CJ, Lumb MJ, Birdsey GM, Zhang X. Alanine:glyoxylate aminotransferase peroxisome-to-mitochondrion mistargeting in human hereditary kidney stone disease. Biochim Biophys Acta. 2003 Apr;1647(1–2):70–5. http://dx.doi.org/10.1016/S1570-9639(03)00055-4
17. Cregeen DP, Williams EL, Hulton S, Rumsby G. Molecular analysis of the glyoxylate reductase (GRHPR) gene and description of mutations underlying primary hyperoxaluria type 2. Hum Mutat. 2003 Dec;22(6):497. http://dx.doi.org/10.1002/humu.9200
18. Milliner DS, Wilson DM, Smith LH. Phenotypic expression of primary hyperoxaluria: Comparative features of types I and II. Kidney Int. 2001 Jan;59(1):31–6. http://dx.doi.org/10.1046/j.1523-1755.2001.00462.x
19. Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet. 2010 Sep;87(3):392–9. http://dx.doi.org/10.1016/j.ajhg.2010.07.023
20. Williams EL, Bockenhauer D, van't Hoff WG, Johri N, Laing C, Sinha MD, et al. The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type 3. Nephrol Dial Transplant. 2012 Aug;27(8):3191–5. http://dx.doi.org/10.1093/ndt/gfs039
21. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. 2009 Jun;75(12):1264–71. http://dx.doi.org/10.1038/ki.2009.32
22. Leumann E, Hoppe B. The primary hyperoxalurias. J Am Soc Nephrol. 2001 Sep;12(9):1986–93.
23. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med. 1994 Dec;331(23):1553–8. http://dx.doi.org/10.1056/NEJM199412083312304
24. Monico CG, Rossetti S, Olson JB, Milliner DS. Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int. 2005 May;67(5):1704–9. http://dx.doi.org/10.1111/j.1523-1755.2005.00267.x
25. Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, et al. Oxalobacter formigenes: A potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006 Oct;70(7): 1305–11. http://dx.doi.org/10.1038/sj.ki.5001707
26. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: Still challenging! Pediatr Nephrol. 2006 Aug;21(8):1075–81. http://dx.doi.org/10.1007/s00467-006-0124-4
27. Cochat P, Fargue S, Harambat J. Primary hyperoxaluria type 1: Strategy for organ transplantation. Curr Opin Organ Transplant. 2010 Oct;15(5):590–3. http://dx.doi.org/10.1097/MOT.0b013e32833e35f5.
28. Scheinman JI. Liver transplantation in oxalosis prior to advanced chronic kidney disease. Pediatr Nephrol. 2010 Nov;25(11): 2217–22. http://dx.doi.org/10.1007/s00467-010-1594-y
29. Brinkert F, Ganschow R, Helmke K, Harps E, Fischer L, Nashan B, et al. Transplantation procedures in children with primary hyperoxaluria type 1: Outcome and longitudinal growth. Transplantation. 2009 May;87(9):1415–21. http://dx.doi.org/10.1097/TP.0b013e3181a27939
30. Bergstralh EJ, Monico CG, Lieske JC, Herges RM, Langman CB, Hoppe B, et al. Transplantation outcomes in primary hyperoxaluria. Am J Transplant. 2010;10(11):2493–501. http://dx.doi.org/10.1111/j.1600-6143.2010.03271.x
31. Compagnon P, Metzler P, Samuel D, Camus C, Niaudet P, Durrbach A, et al. Long-term results of combined liver-kidney transplantation for primary hyperoxaluria type 1: The French experience. Liver Transplant. 2014 Dec;20(12):1475–85. http://dx.doi.org/10.1002/lt.24009
32. Naderi G, Latif A, Tabassomi F, Esfahani ST. Failure of isolated kidney transplantation in a pediatric patient with primary hyperoxaluria type 2. Pediatr Transplant. 2014 May;18(3): E69–73. http://dx.doi.org/10.1111/petr.12240
33. Filler G, Hoppe B. Combined liver-kidney transplantation for hyperoxaluria type II? Pediatr Transplant. 2014 May;18(3): 237–9. http://dx.doi.org/10.1111/petr.12243
34. Cha D, Concepcion K, Gallo A, Concepcion W. Combined liver kidney transplantation in pediatrics: Indications, special considerations, and outcomes. Clin Surg. 2017 Mar;2:1–8.
35. Lara PN Jr, Coe TL, Zhou H, Fernando L, Holland PV, Wun T. Improved survival with plasma exchange in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Am J Med. 1999 Dec;107(6):573–9. http://dx.doi.org/10.1016/S0002-9343(99)00286-7
36. Loirat C, Fremeaux-Bacchi V. Hemolytic uremic syndrome recurrence after renal transplantation. Pediatr Transplant. 2008 Sep;12(6):619–29. http://dx.doi.org/10.1111/j.1399-3046.2008.00910.x
37. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011 Sep;6:60. http://dx.doi.org/10.1186/1750-1172-6-60
38. Saland J. Liver-kidney transplantation to cure atypical HUS: Still an option post-eculizumab? Pediatr Nephrol. 2014 Mar; 29(3):329–32. http://dx.doi.org/10.1007/s00467-013-2722-2
39. Lemaire M, Frémeaux-Bacchi V, Schaefer F, Choi M, Tang WH, Le Quintrec M, et al. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet. 2013 May;45(5): 531–6. http://dx.doi.org/10.1038/ng.2590
40. Nishimura J, Yamamoto M, Hayashi S, Ohyashiki K, Ando K, Brodsky AL, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014 Feb;370(7):632–9. http://dx.doi.org/10.1056/NEJMoa1311084
41. Saland JM, Ruggenenti P, Remuzzi G, Consensus Study Group. Liver-kidney transplantation to cure atypical hemolytic uremic

syndrome. J Am Soc Nephrol. 2009 May;20(5):940–9. http://dx.doi.org/10.1681/ASN.2008080906
42. Sung RS, Wiseman AC. Simultaneous liver-kidney transplant: Too many or just enough? Adv Chronic Kidney Dis. 2015 Sep; 22(5):399–403. http://dx.doi.org/10.1053/j.ackd.2015.06.005
43. Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016 Jan;31(1):15–39. http://dx.doi.org/10.1007/s00467-015-3076-8
44. Darwish AA, McKiernan P, Chardot C. Paediatric liver transplantation for metabolic disorders. Part 1: Liver-based metabolic disorders without liver lesions. Clin Res Hepatol Gastroenterol. 2011 Mar;35(3):194–203. http://dx.doi.org/10.1016/j.clinre.2011.01.006
45. Kasahara M, Horikawa R, Tagawa M, Uemoto S, Yokoyama S, Shibata Y, et al. Current role of liver transplantation for methylmalonic acidemia: A review of the literature. Pediatr Transplant. 2006 Dec;10(8):943–7. http://dx.doi.org/10.1111/j.1399-3046.2006.00585.x
46. Ganschow R, Hoppe B. Review of combined liver and kidney transplantation in children. Pediatr Transplant. 2015 Dec;19(8): 820–6. http://dx.doi.org/10.1111/petr.12593
47. Fraser JL, Venditti CP. Methylmalonic and propionic acidemias: Clinical management update. Curr Opin Pediatr. 2016 Dec;28(6): 682–93. http://dx.doi.org/10.1097/MOP.0000000000000422
48. Hörster F, Baumgartner MR, Viardot C, Suormala T, Burgard P, Fowler B, et al. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, mut-, cblA, cblB). Pediatr Res. 2007 Aug;62(2):225–30. http://dx.doi.org/10.1203/PDR.0b013e3180a0325f
49. Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM, et al. Long-term survival after liver transplantation in children with metabolic disorders. Pediatr Transplant. 2002 Aug;6(4):295–300. http://dx.doi.org/10.1034/j.1399-3046.2002.02009.x
50. Nagarajan S, Enns GM, Millan MT, Winter S, Sarwal MM. Management of methylmalonic acidaemia by combined liver-kidney transplantation. J Inherit Metab Dis. 2005;28(4):517–24. http://dx.doi.org/10.1007/s10545-005-0517-8
51. Morioka D, Kasahara M, Takada Y, Corrales JP, Yoshizawa A, Sakamoto S. Living donor liver transplantation for pediatric patients with inheritable metabolic disorders. Am J Transplant. 2005 Nov;5(11):2754–63. http://dx.doi.org/10.1111/j.1600-6143.2005.01084.x
52. Morioka D, Kasahara M, Horikawa R, Yokoyama S, Fukuda A, Nakagawa A. Efficacy of living donor liver transplantation for patients with methylmalonic acidemia. Am J Transplant. 2007 Dec;7(12):2782–7. http://dx.doi.org/10.1111/j.1600-6143.2007.01986.x
53. Kaplan P, Ficicioglu C, Mazur AT, Palmieri MJ, Berry GT. Liver transplantation is not curative for methylmalonic acidopathy caused by methylmalonyl-CoA mutase deficiency. Mol Genet Metab. 2006 Aug;88(4):322–6. http://dx.doi.org/10.1016/j.ymgme.2006.04.003
54. Mc Guire PJ, Lim-Melia E, Diaz GA, Raymond K, Larkin A, Wasserstein MP, Sansaricq C. Combined liver-kidney transplant for the management of methylmalonic aciduria: A case report and review of the literature. Mol Genet Metab. 2008 Jan;93(1): 22–9. http://dx.doi.org/10.1016/j.ymgme.2007.08.119
55. Vernon HJ, Sperati CJ, King JD, Poretti A, Miller NR, Sloan JL, er al. A detailed analysis of methylmalonic acid kinetics during hemodialysis and after combined liver/kidney transplantation in a patient with mut (0) methylmalonic acidemia. J Inherit Metab Dis. 2014 Nov;37(6):899–907. http://dx.doi.org/10.1007/s10545-014-9730-7
56. Niemi AK, Kim IK, Krueger CE, Cowan TM, Baugh N, Farrell R, et al. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. J Pediatr. 2015 Jun;166(6): 1455–61.e1. http://dx.doi.org/10.1016/j.jpeds.2015.01.051
57. Araki S, Ando Y. Transthyretin-related familial amyloidotic polyneuropathy-Progress in Kumamoto, Japan (1967–2010)-. Proc Jpn Acad Ser B Phys Biol Sci. 2010;86(7):694–706. http://dx.doi.org/10.2183/pjab.86.694
58. Adamski-Werner SL, Palaninathan SK, Sacchettini JC, Kelly JW. Diflunisal analogues stabilize the native state of transthyretin. Potent inhibition of amyloidogenesis. J Med Chem. 2004 Jan; 47(2):355–74. http://dx.doi.org/10.1021/jm030347n
59. Razavi H, Palaninathan SK, Powers ET, Wiseman RL, Purkey HE, Mohamedmohaideen NN, et al. Benzoxazoles as transthyretin amyloid fibril inhibitors: Synthesis, evaluation, and mechanism of action. Angew Chem Int Ed Engl. 2003 Jun;42(24):2758–61. http://dx.doi.org/10.1002/anie.200351179
60. Bulawa CE, Connelly S, Devit M, Wang L, Weigel C, Fleming JA, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. Proc Natl Acad Sci USA. 2012 Jun;109(24):9629–34. http://dx.doi.org/10.1073/pnas.1121005109
61. Bittencourt PL, Couto CA, Farias AQ, Marchiori P, Bosco Massarollo PC, Mies S. Results of liver transplantation for familial amyloid polyneuropathy type I in Brazil. Liver Transplant. 2002 Jan;8(1):34–9. http://dx.doi.org/10.1053/jlts.2002.29764
62. Herlenius G, Wilczek HE, Larsson M, Ericzon BG, Familial Amyloidotic Polyneuropathy World Transplant Registry. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: Results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation. 2004 Jan;77(1):64–71. http://dx.doi.org/10.1097/01.TP.0000092307.98347.CB
63. Muller KR, Padbury R, Jeffrey GP, Poplawski NK, Thompson P, Tonkin A, et al. Poor outcome after liver transplantation for transthyretin amyloid neuropathy in a family with an Ala36Pro transthyretin mutation: Case report. Liver Transplant. 2010 Apr; 16(4):470–3. http://dx.doi.org/10.1002/lt.22019
64. Pilato E, Dell'Amore A, Botta L, Arpesella G. Combined heart and liver transplantation for familial amyloidotic neuropathy. Eur J Cardiothorac Surg. 2007 Jul;32(1):180–2. http://dx.doi.org/10.1016/j.ejcts.2007.03.023
65. Marriott AJ, Hwang NC, Lai FO, Tan CK, Tan YM, Lim CH, et al. Combined heart-liver transplantation with extended cardiopulmonary bypass. Singapore Med J. 2011 Mar;52(3):e48–51.
66. Chen YT. Type I glycogen storage disease: Kidney involvement, pathogenesis and its treatment. Pediatr Nephrol. 1991 Jan;5(1): 71–6. http://dx.doi.org/10.1007/BF00852851
67. Vega AI, Medrano C, Navarrete R, Desviat LR, Merinero B, Rodríguez-Pombo P, et al. Molecular diagnosis of glycogen storage disease and disorders with overlapping clinical symptoms by massive parallel sequencing. Genet Med. 2016;18(10):1037–43. http://dx.doi.org/10.1038/gim.2015.217
68. Ozen H. Glycogen storage diseases: New perspectives. World J Gastroenterol. 2007 May 14;13(18):2541–53. http:dx.doi.org/10.3748/wjg.v13.i18.2541
69. Chou JY, Jun HS, Mansfield BC. Glycogen storage disease type I and G6Pase-β deficiency: Etiology and therapy. Nat Rev Endocrinol. 2010 Dec;6(12):676–88. http://dx.doi.org/10.1038/nrendo.2010.189

70. Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, et al. Glucose-6-phosphatase deficiency. Orphanet J Rare Dis. 2011 May;6:27. http://dx.doi.org/10.1186/1750-1172-6-27
71. Lei KJ, Shelly LL, Lin B, Sidbury JB, Chen YT, Nordlie RC, et al Mutations in the glucose-6-phosphatase gene are associated with glycogen storage disease types 1a and 1aSP but not 1b and 1c. J Clin Invest. 1995 Jan;95(1):234–40. http://dx.doi.org/10.1172/JCI117645
72. Hiraiwa H, Pan CJ, Lin B, Moses SW, Chou JY. Inactivation of the glucose 6-phosphate transporter causes glycogen storage disease type 1b. J Biol Chem. 1999 Feb;274(9):5532–6.
73. Chou JY, Matern D, Mansfield BC, Chen YT. Type I glycogen storage diseases: Disorders of the glucose-6-phosphatase complex. Curr Mol Med. 2002 Mar;2(2):121–43. http:dx.doi.org/10.2174/1566524024605798
74. Simöes A, Domingos F, Fortes A, Prata MM. Type 1 glycogen storage disease and recurrent calcium nephrolithiasis. Nephrol Dial Transplant. 2001 Jun;16(6):1277–9.
75. Iida S, Matsuoka K, Inoue M, Tomiyasu K, Noda S. Calcium nephrolithiasis and distal tubular acidosis in type 1 glycogen storage disease. Int J Urol. 2003 Jan;10(1):56–8. http://dx.doi.org/10.1046/j.1442-2042.2003.00569.x
76. Kelly PM, Poon FW. Hepatic tumours in glycogen storage disease type 1 (von Gierke's disease). Clin Radiol. 2001 Jun;56(6):505–8. http://dx.doi.org/10.1053/crad.2000.0457
77. Franco LM, Krishnamurthy V, Bali D, Weinstein DA, Arn P, Clary B, et al. Hepatocellular carcinoma in glycogen storage disease type Ia: A case series. J Inherit Metab Dis. 2005;28(2):153–62. http://dx.doi.org/10.1007/s10545-005-7500-2
78. 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 Mar;12(2):137–45. http://dx.doi.org/10.1111/j.1399-3046.2007.00803.x
79. Shirasawa Y, Nomura T, Yoshida A, Hashimoto T, Kimura G, Ito M. Liver transplantation-associated hypercalcemia followed by acute renal dysfunction. Intern Med. 2004 Sep;43(9):802–6. http://dx.doi.org/10.2169/internalmedicine.43.802
80. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, et al. Diagnosis and management of glycogen storage disease type I: A practice guideline of the American College of Medical Genetics and Genomics. Genet Med. 2014 Nov;16(11):e1. http://dx.doi.org/10.1038/gim.2014.128
81. Faivre L, Houssin D, Valayer J, Brouard J, Hadchouel M, Bernard O. Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. J Inherit Metab Dis. 1999 Aug;22(6):723–32. http://dx.doi.org/10.1023/A:1005544117285
82. Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A, et al. Liver transplantation for glycogen storage disease types I, III, and IV. Eur J Pediatr. 1999 Dec;158(Suppl 2):S43–8. http://dx.doi.org/10.1007/PL00014320
83. Labrune P. Glycogen storage disease type I: Indications for liver and/or kidney transplantation. Eur J Pediatr. 2002 Oct;161(Suppl 1):S53–5. http://dx.doi.org/10.1007/s00431-002-1004-y
84. Maya Aparicio AC, Bernal Bellido C, Tinoco González J, Garcia Ruíz S, Aguilar Romero L, Marín Gómez LM, et al. Fifteen years of follow-up of a liver transplant recipient with glycogen storage disease type Ia (Von Gierke disease). Transplant Proc. 2013;45(10):3668–9. http://dx.doi.org/10.1016/j.transproceed.2013.10.033
85. Boers SJ, Visser G, Smit PG, Fuchs SA. Liver transplantation in glycogen storage disease type I. Orphanet J Rare Dis. 2014 Apr;9:47. http://dx.doi.org/10.1186/1750-1172-9-47
86. Benedetti E, Pirenne J, Troppmann C, Hakim N, Moon C, Gruessner RW, et al. Combined liver and kidney transplantation. Transplant Int. 1996;9(5):486–91. http://dx.doi.org/10.1111/j.1432-2277.1996.tb00993.x
87. Lee PJ, Muiesan P, Heaton N. Successful pregnancy after combined renal-hepatic transplantation in glycogen storage disease type Ia. J Inherit Metab Dis. 2004;27(4):537–8. http://dx.doi.org/10.1023/B:BOLI.0000037397.39725.57
88. Panaro F, Andorno E, Basile G, Morelli N, Bottino G, Fontana I, et al. Simultaneous liver-kidney transplantation for glycogen storage disease type IA (von Gierke's disease). Transplant Proc. 2004 Jun;36(5):1483–4. http://dx.doi.org/10.1016/j.transproceed.2004.05.070
89. Belingheri M, Ghio L, Sala A, Menni F, Trespidi L, Ferraresso M, et al. Combined liver-kidney transplantation in glycogen storage disease Ia: A case beyond the guidelines. Liver Transplant. 2007 May;13(5):762–4. http://dx.doi.org/10.1002/lt.21147
90. Marega A, Fregonese C, Tulissi P, Vallone C, Gropuzzo M, Toniutto PL, et al. Preemptive liver-kidney transplantation in von Gierke disease: A case report. Transplant Proc. 2011 May;43(4):1196–7. http://dx.doi.org/10.1016/j.transproceed.2011.03.003
91. Lindblad B, Lindstedt S, Steen G. On the enzymic defects in hereditary tyrosinemia. Proc Natl Acad Sci U S A. 1977 Oct;74(10):4641–5. http://dx.doi.org/10.1073/pnas.74.10.4641
92. De Braekeleer M, Larochelle J. Genetic epidemiology of hereditary tyrosinemia in Quebec and in Saguenay-Lac-St-Jean. Am J Hum Genet. 1990 Aug;47(2):302–7.
93. Paradis K, Weber A, Seidman EG, Larochelle J, Garel L, Lenaerts C, et al. Liver transplantation for hereditary tyrosinemia: The Quebec experience. Am J Hum Genet. 1990 Aug;47(2):338–42.
94. Mitchell G, Larochelle J, Lambert M, Michaud J, Grenier A, Ogier H, et al. Neurologic crises in hereditary tyrosinemia. N Engl J Med. 1990 Feb;322(7):432–7. http://dx.doi.org/10.1056/NEJM199002153220704
95. Lindstedt S, Holme E, Lock EA, Hjalmarson O, Strandvik B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. Lancet. 1992 Oct;340(8823):813–17. http://dx.doi.org/10.1016/0140-6736(92)92685-9
96. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. Clin Liver Dis. 2000 Nov;4(4):805–14. http://dx.doi.org/10.1016/S1089-3261(05)70142-2
97. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. Drugs. 2006;66(6):743–50. http://dx.doi.org/10.2165/00003495-200666060-00002
98. Shah I, Shah F. Tyrosinemia type I: Case series with response to treatment to NTBC. Indian J Gastroenterol. 2016 May;35(3):229–31. http://dx.doi.org/10.1007/s12664-016-0650-3
99. Freese DK, Tuchman M, Schwarzenberg SJ, Sharp HL, Rank JM, Bloomer JR, et al. Early liver transplantation is indicated for tyrosinemia type I. J Pediatr Gastroenterol Nutr. 1991 Jul;13(1):10–15. http://dx.doi.org/10.1097/00005176-199107000-00002
100. Arnon R, Annunziato R, Miloh T, Wasserstein M, Sogawa H, Wilson M, et al. Liver transplantation for hereditary tyrosinemia type I: Analysis of the UNOS database. Pediatr Transplant. 2011 Jun;15(4):400–5. http://dx.doi.org/10.1111/j.1399-3046.2011.01497.x
101. Herzog D, Martin S, Turpin S, Alvarez F. Normal glomerular filtration rate in long-term follow-up of children after orthotopic liver transplantation. Transplantation. 2006 Mar;81(5):672–7. http://dx.doi.org/10.1097/01.tp.0000185194.62108.a7

102. Gartner JC Jr, Zitelli BJ, Malatack JJ, Shaw BW, Iwatsuki S, Starzl TE. Orthotopic liver transplantation in children: Two-year experience with 47 patients. Pediatrics. 1984 Jul;74(1): 140–5.
103. Jalanko H, Pakarinen M. Combined liver and kidney transplantation in children. Pediatr Nephrol. 2014 May;29(5): 805–14; quiz 812. http://dx.doi.org/10.1007/s00467-013-2487-7
104. Parfrey H, Mahadeva R, Lomas DA. Alpha(1)-antitrypsin deficiency, liver disease and emphysema. Int J Biochem Cell Biol. 2003 Jul;35(7):1009–14. http://dx.doi.org/10.1016/S1357-2725(02)00250-9
105. Grewal HP, Brady L, Cronin DC 2nd, Loss GE, Siegel CT, Oswald K, et al. Combined liver and kidney transplantation in children. Transplantation. 2000 Jul;70(1):100–5.
106. Davis ID, Burke B, Freese D, Sharp HL, Kim Y. The pathologic spectrum of the nephropathy associated with alpha 1-antitrypsin deficiency. Hum Pathol. 1992 Jan;23(1):57–62. http://dx.doi.org/10.1016/0046-8177(92)90012-R
107. Wood AM, Stockley RA. Alpha one antitrypsin deficiency: From gene to treatment. Respiration. 2007;74(5):481–92. http://dx.doi.org/10.1159/000105536
108. Li H, Lu Y, Witek RP, Chang LJ, Campbell-Thompson M, Jorgensen M, et al. Ex vivo transduction and transplantation of bone marrow cells for liver gene delivery of alpha1-antitrypsin. Mol Ther. 2010 Aug;18(8):1553–8. http://dx.doi.org/10.1038/mt.2010.116
109. Hughes MG Jr, Khan KM, Gruessner AC, Sharp H, Hill M, Jie T, et al. Long-term outcome in 42 pediatric liver transplant patients with alpha 1-antitrypsin deficiency: A single-center experience. Clin Transplant. 2011 Sep–Oct;25(5):731–6. http://dx.doi.org/10.1111/j.1399-0012.2010.01371.x.
110. Elzouki AN, Lindgren S, Nilsson S, Veress B, Eriksson S. Severe alpha1-antitrypsin deficiency (PiZ homozygosity) with membranoproliferative glomerulonephritis and nephrotic syndrome, reversible after orthotopic liver transplantation. J Hepatol. 1997 Jun;26(6):1403–7. http://dx.doi.org/10.1016/S0168-8278(97)80478-3
111. Loreno M, Boccagni P, Rigotti P, Naccarato R, Burra P. Combined liver-kidney transplantation in a 15-year-old boy with alpha1-antitrypsin deficiency. J Hepatol. 2002 Apr;36(4): 565–8. http://dx.doi.org/10.1016/S0168-8278(02)00012-0
112. Chandler RJ, Venditti CP. Gene therapy for metabolic diseases. Transl Sci Rare Dis. 2016;1(1):73–89. http://dx.doi.org/10.3233/TRD-160007
113. Baruteau J, Waddington SN, Alexander IE, Gissen P. Gene therapy for monogenic liver diseases: Clinical successes, current challenges and future prospects. J Inherit Metab Dis. 2017 May; 40(4):497–517. http://dx.doi.org/10.1007/s10545-017-0053-3
114. Castello R, Borzone R, D'Aria S, Annunziata P, Piccolo P, Brunetti-Pierri N. Helper-dependent adenoviral vectors forliver-directed gene therapy of primary hyperoxaluria type 1. Gene Ther. 2016 Feb;23(2):129–34. http://dx.doi.org/10.1038/gt.2015.107
115. Crane B, Luo X, Demaster A, Williams KD, Kozink DM, Zhang P, et al. Rescue administration of a helper-dependent adenovirus vector with long-term efficacy in dogs with glycogen storage disease type Ia. Gene Ther. 2012 Apr;19(4):443–52. http://dx.doi.org/10.1038/gt.2011.86
116. Kattenhorn LM, Tipper CH, Stoica L, Geraghty DS, Wright TL, Clark KR, et al. Adeno-associated virus gene therapy for liver disease. Hum Gene Ther. 2016 Dec;27(12):947–61. http://dx.doi.org/10.1089/hum.2016.160
117. Flotte TR, Trapnell BC, Humphries M, Carey B, Calcedo R, Rouhani F, et al. Phase 2 clinical trial of a recombinant adeno-associated viral vector expressing α1-antitrypsIn: Interim results. Hum Gene Ther. 2011;22(10):1239–47. http://dx.doi.org/10.1089/hum.2011.053