Review Article

Primary Hyperoxalurias

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Received 14 February 2011; Accepted 22 March 2011

Academic Editor: Michel Fischbach

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Primary hyperoxalurias (PH) are inborn errors in the metabolism of glyoxylate and oxalate. The most common type, PH1 (MIM #259900) is caused by a deficiency of the liver-specific enzyme alanine : glyoxylate aminotransferase (AGT; EC 2.6.1.44) [1, 2]. The second type, PH2 (MIM #260000), is caused by a deficiency in glyoxylate reductase/hydroxypyruvate reductase (GRHPR; EC 1.1.1.26/79) [3–5], and the recently identified PH type 3 (MIM #613616) [6] is linked to the gene DHDPSL, encoding a mitochondrial enzyme, although

1. Introduction

Hyperoxaluria may be either inherited or acquired. The primary hyperoxalurias (PH) are inborn errors of metabolism resulting in increased endogenous production of oxalate leading to excessive urinary oxalate excretion. To date, three distinct hereditary enzymatic deficiencies have been linked to PH, namely, PH type 1 (PH1), type 2 (PH2), and type 3 (PH3), and there is evidence to speculate that further causes are yet to be identified. Due to marked hyperoxaluria, recurrent urolithiasis and progressive nephrocalcinosis are the principal manifestations of PH. As a result of kidney injury, glomerular filtration rate (GFR) declines leading to chronic kidney disease, and ultimately to end-stage renal disease (ESRD) and systemic involvement in PH1, the most severe type of PH. Despite recent improvement in disease spectrum knowledge, diagnostic procedure, and treatment strategies, PH1 still represents a challenging issue for both adult and pediatric nephrologists worldwide.

2. Physiopathology

Primary hyperoxalurias are inborn errors in the metabolism of glyoxylate and oxalate (Figure 1). They are characterized by an excessive production of oxalate, a metabolic endproduct. The most common type of PH, PH1 (MIM #259900) is caused by a deficiency of the liver specific, peroxisomal, pyridoxal phosphate-dependent enzyme alanine : glyoxylate amino transferase (AGT; EC 2.6.1.44) [1, 2]. The second type, PH2 (MIM #260000), is caused by a deficiency in glyoxylate reductase/hydroxypyruvate reductase (GRHPR; EC 1.1.1.26/79) [3–5], a cytosolic enzyme. The recently identified PH type 3 (MIM #613616) [6] is linked to the gene DHDPSL, encoding a mitochondrial enzyme, although
the metabolic reactions involved remain to be confirmed. All three are autosomal recessive diseases. AGT catalyses the transamination of glyoxylate to glycine while pyruvate is converted to alanine, whereas GRHPHPR catalyses the reduction of glyoxylate to glycolate [7]. The failure to detoxify glyoxylate in PH1 and 2 results in its conversion into oxalate by cytosolic lactate dehydrogenase. Since the main source of oxalate removal from the body is urine excretion, the deposition of the calcium oxalate salt, which is very poorly soluble, occurs primarily there either as urolithiasis along the urinary tract or in the kidney, or as interstitial deposition in the kidney leading to nephrocalcinosis [8]. The accompanying overproduction of glycolate in PH1 or L-glycerate in PH2 has no identified consequence. The crystal structures for both AGT and GRHPHPR have been solved, and some rationalization of the effect of mutations in the AGXT and GRHPR genes has been possible [9, 10].

3. Epidemiology

PH are rare autosomal-recessive inherited disorders. PH1 is the most common form of PH. The disease has an estimated prevalence ranging from 1 to 3 per million population and an estimated incidence rate of ~1:100,000 live births per year in Europe [11–13]. Higher rates are reported from inbred populations [14]. PH accounts for <1% of pediatric ESRD population in registries from USA, UK, and Japan [15–17]. In contrast, PH is more prevalent in countries where consanguineous marriages are common. Due to lack of registries, epidemiological information from developing countries primarily originates from major referral centers. Approximately 10% of Kuwaiti children and 13% of Tunisian children with ESRD have been reported to have PH [18, 19]. Incidence and prevalence of other types of PH are unknown but appear to be much lower than PH1.

4. Clinical Features and Oxalate Burden

Owing to the high urinary oxalate excretion, the urine become supersaturated for calcium oxalate (CaOx) resulting in the formation of crystals within the tubular lumen. PH1, therefore, manifests as severe urolithiasis and/or nephrocalcinosis (Figure 2). Progressive renal parenchyma inflammation and interstitial fibrosis due to nephrocalcinosis and recurrent urolithiasis cause renal impairment, which usually progresses to ESRD over time [8]. Once the GFR falls below 30–50 mL/min per 1.73 m², reduced renal excretion of oxalate by the kidneys together with continued overproduction by the liver lead to an increase plasma oxalate (Pox) that exceeds the supersaturation point for CaOx (Pox >30 µmol/l). Systemic deposition of CaOx, namely, oxalosis, can then occur in many organs such as bone, retina, skin, soft tissues, heart, vessels, and central nervous system (Figure 3). Severe systemic complications result in high morbidity and poor quality of life and, if treated late or untreated, early death. The bone compartment seems to be the main site for oxalate storage (15 to 910 in PH1 patients versus 2 to 9 µmol of oxalate per gram of bone tissue in non-PH1 ESRD patients) [20]. The skeleton can therefore store huge amounts of oxalate, even though the threshold of GFR at which this occurs is debated. Clinically, PH1 patients can experience severe bone pains and pathological fractures with low-trauma mechanism, as well as EPO-resistant anemia. Joints can also be damaged, with synovitis, chondrocalcinosis and oxalate deposits. Characteristics of oxalate osteopathy on X-ray include dense metaphyseal bands, submarginal
metaphyseal lucency, sclerosis of adjacent diaphysis, cystic bone changes, deformities, subperiosteal resorption, blurred trabecular pattern, radio-opaque rims in flat bones and epiphyseal nuclei, as well as increased bone density in vertebra and iliac crest [21, 22]. Symmetrical transverse lines of increased bone density at areas of rapid growth have been related to crystalline precipitation in cartilage calcification sites as well as in hematopoietic and other highly vascularized areas [23, 24]. Bone biopsies from the iliac crest can show specific features: oxalate crystals often surrounded by a granulomatous reaction corresponding to an invasion of bone surface by macrophages [20]. Instead of invasive bone biopsy, bone mineral density (BMD) measurement could be a valuable and noninvasive tool in determining and monitoring oxalate burden in PH1 [25]. Using a new bone imaging technique (e.g., high-resolution peripheral quantitative computed tomography, HR-pQCT), it has been shown that children with PH1 had decreased compartmental volumetric BMD and bone modifications with disorganized trabecular microarchitecture [26].

5. Diagnosis

5.1. PH1. The median age at initial symptoms of PH1 is 4 to 7 years in Europe and 13 years in Japan, ranging from birth to the sixth decade [13, 27, 28]. PH1 has variable presentation. The infantile form often presents as a life-threatening condition because of rapid progression to ESRD due to both early oxalate load and immature GFR; one half of the patients experience ESRD at the time of diagnosis and 80% develop ESRD by the age of 3 years [29]. Other presentations include recurrent urolithiasis and progressive renal failure in childhood or adolescence, late-onset form with occasional stone passage and sometimes ESRD as the first symptom in adulthood, diagnosis made after recurrence posttransplantation and presymptomatic individuals with a family history of PH1 [30]. Sonographic examination may show either cortical or medullary nephrocalcinosis [31]. Because of the rarity of disease, physicians are likely to encounter few or no PH patients during their practicing lifetime. The diagnosis of PH is, therefore, often delayed for years [12, 27, 32]. At time of diagnosis, a high proportion of patients (10–40%) had already reached ESRD [11–13, 27, 32, 33]. Overall, ESRD is reached by the age of 24 to 33 years in half of the patients with PH1 [27, 33]. The combination of both clinical and sonographic findings, that is, the association of stone passage, nephrocalcinosis, and renal impairment, is a strong argument for clinical diagnosis of PH1. Family history may bring additional information.

Crystalluria and infrared spectroscopy are of major interest for identification (qualitative) and quantitative analysis of crystals and stones (Figure 4), showing CaOx monohydrate crystals (type Ic whewellite) [34]. In patients with normal or significant residual GFR, concomitant hyperoxaluria (urine oxalate >1 mmol/1.73 m² per day, reference value <0.5) and hyperglycoluria (urine glycolate >0.5 mmol/1.73 m², reference value <0.5) are indicative of PH1, but some patients do not present with hyperglycoluria. The measurement of oxalate in a timed 24-hour urine collection corrected for body surface area is preferred for the diagnosis of PH [35]. Random urine oxalate/creatinine ratios can be useful to estimate oxalate excretion, particularly in infants, or patients with inability to provide complete 24-hour collection [36, 37]. Reference age-related values for oxalate and glycolate excretion have been established (Table 1). Urinary oxalate excretion may be falsely low in patients with decreased GFR because of oxalate retention and systemic deposition as calcium oxalate. In PH patients with GFR <30 mL/min per 1.73 m², Pox is usually >20–30 µmol/L, and in those with ESRD, Pox is >50 µmol/L. In ESRD patients, plasma oxalate (± glycolate)/creatinine ratio and oxalate (± glycolate) measurement in dialysate might also be helpful for screening [38].

Until recently, liver biopsy to measure AGT catalytic activity has been essential for definitive diagnosis of PH1. As an alternative approach, genetic analysis of AGXT gene allows to detect mutations in most of suspected patients, thereby, supplanting the need for liver biopsy as a first
step [39]. In the presence of atypical presentation or in patients with no mutation identified, however, a definitive diagnosis requires AGT activity measurement in liver tissue. The AGXT gene is located on chromosome 2 (2p37.3). It is noteworthy that among more than 150 mutations responsible for PH1 found throughout the 11 exons of the AGXT gene [40], many, corresponding to almost 50% of the patients, cosegregate with a so-called minor allele, the most prominent feature of which is a proline to leucine change in position 11 [41]. The frequency of this minor allele is highest in the Caucasian population, and it acts in synergy with some of the mutations, in particular, the common p.Gly170Arg change [41, 42]. If most of the mutations in PH1 are “private” mutations, some mutations occur more commonly [39]. The most frequent mutation, p.Gly170Arg, is found in 20 to 40% of patients and is associated with significant residual catalytic AGT activity in liver biopsies [43]. Some mutations are found among specific ethnic groups, the most obvious example being the p.Ile244Thr mutation which is found in many patients of North African/Spanish origin [44]. Prenatal diagnosis can be performed from DNA obtained from crude chorionic villi or amniocytes, on the basis of a restricted analysis of exons including mutation(s) identified in the index case. Such a procedure allows the identification of fetuses affected or not with PH1. Independently of the diagnostic value,
of pyridoxine which is specific to some PH1 patients.

These measures apply to all types of PH with the exception of the treatment that should be pursued, if the patient is responsive. Once ESRD has been reached, pyridoxine is the only stone treatment that should be pursued, if the patient is responsive. Basal urinary oxalate measures should be initiated as soon as basal urinary oxalate measures have been completed and while renal function persists. Conservative measures should be considered for some PH1 patients, carrying 1 or 2 copies of AGT mutations (p.Gly170Arg or p.Phe152Ile), may be responsive to pharmacological doses of pyridoxine, though this list is not limitative [48, 62]. Responsiveness has been defined as a minimum 30% decrease in urinary oxalate excretion after a test period of a minimum 3 months at maximum dose [61]. The starting dose recommended is 5 mg/kg per day and can be increased to 10 mg/kg per day. No sensory neurotoxicity has been described in PH patients, and a dose of 300 mg per day is thought to be below toxic levels. Absorption of pyridoxine may vary between patients, and assessing plasma levels of pyridoxal phosphate may be useful, though therapeutic levels are not defined.

6.1.2. Diet. Oral calcium can bind oxalate in the bowels, and calcium restriction has been shown to result in higher oxalate intestinal absorption [55, 56]. Calcium intake should thus remain normal. A restriction in oxalate intake is of limited usefulness in PH patients as the main source of oxalate is endogenous. Excessive intake of vitamin C and vitamin D are to be avoided.

6.1.3. Inhibition of Calcium Oxalate Crystallization. Alkali citrate can reduce the urinary calcium oxalate saturation by forming complexes with calcium thus decreasing stone growth or nephrocalcinosis [57]. Potassium, or sodium, citrate at a dose of 100–150 mg/kg body weight per day (0.3–0.5 mmol/kg) is recommended. Pyrophosphate ions may decrease calcium oxalate crystallization although orthophosphate has never been evaluated in isolation of other treatments [58]. Moderate doses of elemental phosphorus 20–30 mg/kg body weight per day may be administered. There is as yet no evidence that probiotics, such as Oxalobacter formigenes despite its ability to metabolize oxalate [59], can significantly decrease urinary oxalate excretion in PH patients.

6.1.4. Pyridoxine. The cofactor of AGT is pyridoxal phosphate, one of the B6 vitamins. The administration of pyridoxine hydrochloride has been shown to be associated with a decrease in urinary oxalate in about 10–30% of patients with PH [60, 61]. The metabolic basis of pyridoxine responsiveness is unclear. All PH1 patients should be tested for pyridoxine responsiveness and treated until liver transplantation is performed, if responsive, even while undergoing hemodialysis. Studies have determined that a subset of patients with PH1, carrying 1 or 2 copies of AGT mutations (p.Gly170Arg or p.Phe152Ile), may be responsive to pharmacological doses of pyridoxine, though this list is not limitative [48, 62]. Responsiveness has been defined as a minimum 30% decrease in urinary oxalate excretion after a test period of a minimum 3 months at maximum dose [61]. The starting dose recommended is 5 mg/kg per day and can be increased to 10 mg/kg per day. No sensory neurotoxicity has been described in PH patients, and a dose of 300 mg per day is thought to be below toxic levels. Absorption of pyridoxine may vary between patients, and assessing plasma levels of pyridoxal phosphate may be useful, though therapeutic levels are not defined.

Added monitoring of the tolerance and efficacy of these measures may require evaluation of stone formation, and nephrocalcinosis by ultrasounds or X-ray, urinary pH and volume, urinary citrate, magnesium and oxalate excretion.

### Table 1: Reference age-related values for urinary oxalate, glycolate, and L-glycerate excretion (adapted from [8]).

<table>
<thead>
<tr>
<th>Units</th>
<th>Oxalate</th>
<th>Glycolate</th>
<th>L-Glycerate</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/1.73 m² per day</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>µmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/mol creatinine</td>
<td>&lt;325–360</td>
<td>&lt;363–425</td>
<td>14–205</td>
</tr>
<tr>
<td>0–6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–24 months</td>
<td>&lt;132–174</td>
<td>&lt;245–293</td>
<td>14–205</td>
</tr>
<tr>
<td>2–5 years</td>
<td>&lt;98–101</td>
<td>&lt;191–229</td>
<td>14–205</td>
</tr>
<tr>
<td>5–14 years</td>
<td>&lt;70–82</td>
<td>&lt;166–186</td>
<td>23–138</td>
</tr>
<tr>
<td>&gt;16 years</td>
<td>&lt;40</td>
<td>&lt;99–125</td>
<td>&lt;138</td>
</tr>
</tbody>
</table>

mutation analysis may bring information on pyridoxine responsiveness, on complex enzyme phenotype, and sometimes on clinical prognosis [27, 40]. Although PH1 usually shows marked inter- and intrafamilial heterogeneity [45–47], genotype-phenotype correlations have been described for some mutations [27, 48].

5.2. Other Types of PH. Symptoms onset in PH2 typically occurs in childhood. Although patients with PH2 are also at risk for ESRD and systemic oxalosis, they appear to form less stones, have a less pronounced nephrocalcinosis, and a lower incidence of ESRD over time than PH1 patients [49, 50]. In the presence of hyperoxaluria without hyperglycoluria, a diagnosis of PH2 should be considered, especially when AGT activity is normal. The diagnosis is based on increased urinary excretion of L-glycerate (reference values in Table 1), but the definitive diagnosis may require the measurement of GRHPR activity in a liver biopsy [51, 52] as some PH2 patients have normal level of L-glycerate in urine [53]. Genotyping can provide reliable diagnosis for PH2. The GRHPR gene is located on chromosome 9 (9q11) [5] and more than 15 mutations have been identified so far.

A few patients referred to as non-1 non-2 PH have been described. These patients have a phenotype similar to PH1 or 2 but no AGT or GRHPR deficiency. Recently, a third type of PH, PH3, caused by mutations in the gene DHDPFL has been characterized among non-1 non-2 PH patients [6].

In this paper, we propose an algorithm for the diagnosis and the conservative treatment of PH as illustrated in the Figure 5.

### 6. Treatment

6.1. Conservative Measures. Conservative measures should be initiated as soon as basal urinary oxalate measures have been completed and while renal function persists. Once ESRD has been reached, pyridoxine is the only stone treatment that should be pursued, if the patient is responsive. These measures apply to all types of PH with the exception of pyridoxine which is specific to some PH1 patients.

6.1.1. High Fluid Intake. The positive effect of high fluid intake has been proven in epidemiological and prospective intervention studies in stone formers [54]. In PH, the fluid intake recommended is >2 L/m² per day (up to 3 L/m² per day), distributed throughout the day and night. In small children and infants, a feeding or gastrostomy tube may be required. Special care should be taken in situations of fluid losses (diarrhea, vomiting, and fever) or limited oral hydration (surgery) and intravenous fluid intake instituted if necessary.
Normal GFR:
 Urinary stones/nephrocalcinosis
 family history of PH

Clinical signs
 Decreased GFR:
 Urinary stones/nephrocalcinosis
 extrarenal involvement

Biochemical evaluation (blood, urine)
 Stone analysis (CaOx, type Ic)
 Uox repeatedly elevated
 + Pox elevated if GFR decreased

Secondary hyperoxaluria?

Orientation PH1/2; confirmation of diagnosis

Uglycolate
 Normal

DNA analysis
 No mutation

Uglycerate
 Normal

AGXT
 DNA analysis
 No mutation

Mutation
 Mutation

PH1
 Liver biopsy:
 Enzyme catalytic activity: AGT, GR
 +/− immunoreactivity/subcellular localization

PH2

Conservative treatment:
 Hyperhydration
 Crystallization inhibitors
 Pyridoxine if responsive
 (decrease in Uox > 30% after 3 months at full dose)

AGT
 Normal

GR
 Normal

PH1

Conservative treatment:
 Hyperhydration
 Crystallization inhibitors

PH2

Conservative treatment:
 Hyperhydration
 Crystallization inhibitors

PH non 1 non 2

Family screening

Further characterization of PH

Figure 5: Proposed algorithm for the diagnosis and conservative treatment of primary hyperoxalurias. Abbreviations: PH: primary hyperoxaluria; GFR: glomerular filtration rate; Uox: urinary oxalate; Pox: plasma oxalate; CaOx: calcium oxalate; AGT: alanine:glyoxylate amino transferase; AGXT: AGT gene; GR/HPR: glyoxylate reductase/hydroxypyruvate reductase.

and supersaturation, and crystalline volume in the urines. In summary, an aggressive supportive management should be started as soon as the diagnosis of PH has been suspected and may improve renal survival provided compliance is optimal [63].

6.2. Urology. The treatment of stones should avoid open and percutaneous surgery because further renal lesions will alter GFR. The use of extracorporeal shock wave lithotripsy may be an available option in selected patients, but the presence of nephrocalcinosis may be responsible for parenchymal
6.3. Dialysis. Conventional dialysis is inadequate for patients who have reached ESRD, because it cannot overcome the ongoing oxalate production [64]. This results in continuing tissue deposition of oxalate and risk of organ damage. The removal of oxalate by hemodialysis exceeds that by peritoneal dialysis [65]. Better results may be obtained by combining daily high-flux hemodialysis and peritoneal dialysis or by long daily hemodialysis sessions [66, 67].

In summary, there are limited indications for dialysis in patients with PH1 [30]: (1) if diagnosis of PH1 has not been established, (2) in small children with infantile oxalosis waiting for organ Tx, (3) in preparation for kidney Tx, before or after liver Tx, in order to deplete oxalate from the body, (4) following isolated kidney or combined liver-kidney Tx with any delay in achieving optimal renal function, as a temporary adjunct in the case of high oxalate burden, or with transient loss of transplant function, (5) very exceptionally in older patients if the only alternative is no dialysis, (6) in developing countries; hemodialysis (or even less satisfactory, peritoneal dialysis) may be indicated as only a preference to absolute withdrawal of all therapy.

7. Organ Transplantation

Ideally, organ transplantation should be planned prior to the onset of ESRD and systemic oxalosis. The different options for organ Tx for PH1 according to residual GFR are summarized in Table 2 [68].

7.1. Kidney Transplantation. Kidney Tx allows significant removal of soluble Pox [69]. However, because the biochemical defect is in the liver, overproduction of oxalate and subsequent deposition in tissues continues unabated. The high rate of urinary oxalate excretion originates from both ongoing oxalate production from the native liver and oxalate deposits in tissues leading to high risk for disease recurrence. Isolated kidney Tx for PH1 is no longer recommended, because frequent recurrence leads to poor graft survival and patient quality of life. In Europe, the European Dialysis Transplantation Association (EDTA) registry reported poor results of isolated kidney Tx two decades ago with a 3-year graft survival of 17 to 23% according to donor source [70]. A United States Renal Data System (USRDS) analysis of 190 adults transplanted in the US between 1988 and 1998 showed superior death-censored kidney graft survival in combined liver-kidney Tx than in isolated kidney Tx, but no difference in patient survival [71]. More recently, data from 58 PH1 patients showed a death-censored kidney graft survival at 3 years of 95% with combined liver-kidney Tx versus 56% with isolated kidney Tx [72]. Proven pyridoxine responsive patients may benefit from isolated kidney Tx, provided pyridoxine is maintained, but the clinical evidence for this is still sparse. Isolated kidney Tx may be also regarded as a temporary solution in some developing countries before managing the patient in a specialized center for further combined liver-kidney procedure.

Isolated kidney Tx might be the treatment of choice in patients with PH2. Indeed, PH2 patients with kidney Tx alone appear to have a more favorable course than PH1 patients, and the benefit of liver Tx in such patients is still unclear.

7.2. Liver Transplantation. Since the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place. Therefore, PH1 can be cured only when the deficient host liver has been removed. Liver Tx is a form of gene therapy as well as enzyme replacement therapy as it will supply the missing enzyme in the correct organ (liver), cell (hepatocyte), and intracellular compartment (peroxisome).

In Europe, combined liver-kidney Tx has been the preferred approach in the past 25 years. A European PH1

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**Table 2: Suggestions for organ transplantation strategies in PH1 patients according to residual GFR (ml/min per 1.73 m²), systemic involvement, and local facilities (from [68])**.

<table>
<thead>
<tr>
<th>Tx strategy</th>
<th>Combined simultaneous liver + kidney</th>
<th>Liver first Kidney as a second step</th>
<th>Isolated kidney</th>
<th>Isolated liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD strategy</td>
<td>Peroperative ± postoperative according to Pox and GFR</td>
<td>Standard HD following liver Tx aiming at Pox &lt;20 μmol/L</td>
<td>Pre- and peroperative</td>
<td>Sometimes peroperative</td>
</tr>
<tr>
<td>40 &lt; GFR &lt; 60</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Optional</td>
</tr>
<tr>
<td>20 &lt; GFR &lt; 40</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GFR &lt; 20</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Infantile form (ESRD &lt;2 years)</td>
<td>Yes</td>
<td>Yes (emergency)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ESRD end-stage renal disease; GFR glomerular filtration rate; HD hemodialysis; Pox plasma oxalate; Tx transplantation.
Transplant registry reported 127 liver Tx including more than 100 liver-kidney Tx in 117 patients between 1984 and 2004 [73]. Results were encouraging with patient survival rates of 86, 80, and 69% at 1 year, 5 years, and 10 years, respectively. There were 13 kidney graft failures. Comparable results have been reported from the USRDS, with a patient survival above 80% at 5 years and a death-censored graft survival of 76% at 8 years post Tx [71]. Such a strategy can be successfully proposed to infants with PH1 [74]. Worldwide experience indicates that once perioperative mortality is avoided, combined liver-kidney Tx seems to be an acceptable treatment for PH1 [75–77]. The strategy of combined liver-kidney Tx may be influenced by the stage of the disease (Table 2). Simultaneous liver and kidney Tx is logical in patients with a GFR between 15 and 40 mL/min per 1.73 m², because, at this level, oxalate retention increases rapidly. A sequential procedure (first liver Tx, then dialysis until sufficient oxalate has been cleared from the body, followed by kidney Tx) may be proposed to ESRD patients, mainly infants with a long waiting time [78].

Preemptive isolated liver Tx might be the first option in selected patients before advanced chronic renal fail-ure has occurred, that is, at a GFR between 60 and 40 mL/min/1.73 m². In the Hamburg experience, 4 pediatric recipients with a GFR between 27 and 98 mL/min per 1.73 m² received a preemptive liver transplant, and 3 of them still have significant residual renal function after a median followup of ~12 years [79]. Another group reported good results at 5 years in 4 PH1 children who received a preemptive liver Tx with a mean pretransplant GFR of 81 mL/min/1.73 m² [80]. Such a strategy has a strong rationale but raises ethical controversies especially when the GFR is superior to 60 mL/min per 1.73 m². Indeed PH1 is the only peroxisomal disease without psychomotor delay due to cerebral involvement, and the conservative management of PH1 patients has significantly improved during the last 10 years; this may influence the role of preemptive liver Tx in such patients.

The choice of donor source may be based either on immunological bases (i.e., using the same donor for both organs) or on biochemical rationale (i.e., using a two-step procedure according to oxalate body store). Indeed most publication currently report on the use of cadaver donors but a living related donor may be considered under certain conditions [78].

7.3. Posttransplantation Reversal of Renal and Extrarenal Involvement. After combined liver-kidney Tx, urinary glycolate immediately returns to normal and Pox returns to normal before urine oxalate does [81]. Indeed, urinary oxalate can remain elevated for as long as several years post-Tx, due to the slow resolubilization of systemic CaOx deposition [72]. Therefore, recurrent nephrocalcinosis or renal calculi are still a risk and may jeopardize graft function. Thus, independent of the Tx strategy, the kidney must be protected against the damage that can be induced by heavy oxalate load suddenly released from tissues. Forced fluid intake (3–5 L per 1.73 m² per day) supported by the use of crystallization inhibitors is the most important approach.

Pox, crystalluria, and CaOx saturation are helpful tools in renal management after combined liver-kidney Tx. The benefit of daily high-efficiency post-transplant hemodialysis is still debated and should be limited to patients with significant systemic involvement (Table 2). It will provide a rapid drop in Pox and, therefore, reduce the exposure of the transplanted organs to high Pox, but it may also increase the risk of CaOx supersaturation due to reduction in urinary volume in the case of inappropriate fluid removal. However, posttransplant hemodialysis is mandatory in patients with acute tubular necrosis or delayed graft function.

8. Conclusion and Future Prospects

Patients with hyperoxaluria should be referred for diagnosis and management to reference centers with interest and experience in the conditions and access to the appropriate biochemical and molecular biological facilities. Major advances in biochemistry, enzymology, genetics, and management have been achieved during recent years. Improved knowledge of the disease, early and accurate diagnosis, before renal failure occurs, and aggressive supportive treatment are of critical importance for the prognosis. In (pre)ESRD patients, the greatest experience has been obtained with one-step combined liver-kidney transplantation. New insights into potential therapies including the restoration of defective enzymatic activity through the use of chemical chaperones and hepatocyte cell transplantation, or recombinant gene therapy for enzyme replacement [82–84], provide hope for curative treatments of primary hyperoxalurias in the future.

References


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