Combined liver–kidney transplantation for primary hyperoxaluria type 1 in young children

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Abstract

Background. Primary hyperoxaluria type 1 (PH1) is a rare condition in which deficiency of the liver enzyme alanine:glyoxylate aminotransferase leads to renal failure and systemic oxalosis. Combined liver–kidney transplantation (LKT) is recommended for end-stage renal failure (ESRF) in adults, but management of infants and young children is controversial. We retrospectively reviewed six children who underwent LKT for PH1.

Methods. The median age at diagnosis was 1.8 years (range 3 weeks to 7 years). Two children presented with severe infantile oxalosis at 3 and 9 weeks, five patients had ESRF with nephrocalcinosis and systemic oxalosis, (median duration of dialysis 1.3 years), and one had progressive chronic renal failure. Four children underwent combined LKT, one child staged liver then kidney, and one infant had an isolated liver transplant. The median age at transplantation was 8.9 years (range 1.7–15 years).

Results. Overall patient survival was four out of six. The two infants with PH1 and severe systemic oxalosis died (2 and 3 weeks post-transplant) due to cardiovascular oxalosis and sepsis. The other four children are well at median follow-up of 10 months (range 6 months to 7.4 years). No child developed hepatic rejection and all have normal liver function. Renal rejection occurred in three patients. Despite maximal medical management, oxalate deposits recurred in all renal grafts, contributing to graft loss in one (one of the infants who died), and significant dysfunction requiring haemodialysis post-transplant for 6 months.

Conclusions. LKT is effective therapy for primary oxalosis with ESRF but has a high morbidity and mortality rate in children who present in infancy with nephrocalcinosis and systemic oxalosis. We feel that earlier LKT, or pre-emptive liver transplantation, may be a better therapeutic strategy to improve the outlook for these patients.

Keywords: kidney; liver; nephrocalcinosis; primary hyperoxaluria; systemic oxalosis; transplantation

Introduction

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inherited condition due to a functional deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT). More than 20 mutations have been identified in the gene encoding AGT (AGXT). Two mutations, G630A and T853C, account for ~30% of disease alleles in PH1 [1,2] and are associated with mitochondrial mistargeting and defective peroxisomal uptake of the AGT protein.

Deficiency of AGT results in accumulation of glyoxylate and subsequent over-production of oxalate and glycolate. Hyperoxaluria and hyperglycolic aciduria are the biochemical hallmarks of PH1. The kidney, the sole route of excretion of oxalate, is the primary target organ of the disease process. Progressive calcium oxalate urolithiasis and nephrocalcinosis result in renal failure, which in turn leads to accumulation of oxalate in the soft tissues and bone (systemic oxalosis). Without treatment death usually occurs in the second or third decade [3].

PH1 shows marked phenotypic, enzymatic and genotypic heterogeneity [4]. Although most patients present with renal calculi in childhood or adolescence, the clinical presentation ranges from death in infancy to asymptomatic cases in adulthood [3]. The clinical course may differ among family members with the same mutation, and the relationship between genotype and phenotype is not established [5]. This diversity, together with the rarity of the disease, has made decisions with respect to the planning and timing of intervention for these patients difficult.

Increased understanding of PH1 over the past decade has led to the introduction of liver transplantation as a form of gene and enzyme replacement therapy [6]. Furthermore, combined hepatorenal transplantation replaces an irreversibly damaged target organ (the
kidney) as well as the enzyme-deficient organ (the liver). It is now generally accepted that combined liver–kidney transplantation is the therapy of choice for end-stage renal failure (ESRF) due to PH1 in teenagers and adults, but the situation in infants and young children can be more complex.

We report our experience of six children with PH1 who underwent combined transplantation between 1990 and 1999. This paediatric group constitute a more severe phenotype and demonstrate the difficulties associated with significant systemic disease in younger patients.

**Subjects and methods**

**Subjects**

A retrospective review of patients with PH1 identified 14 children who were assessed by our unit between 1990 and 1999. Five had a glomerular filtration rate (GFR) > 80 ml/min/1.73 m² and were not considered for transplantation. Combined LKT was recommended in nine patients, but the families of three children (GFR < 25 ml/min/m²) declined transplant despite intensive counselling. Six patients underwent transplantation and are reviewed here (Table 1).

The children, 4 girls and 2 boys, were symptomatic from a median age of 1 year (range 1 week to 6 years 9 months). Systemic oxalosis was present in all children except patient 4. Nephrocalcinosis was present in five out of six cases, renal calculi in only one. All children had renal impairment. Two out of six presented with severe infantile PH1 in acute renal failure, and four out of six with chronic renal failure (two of these in ESRF). The median age at diagnosis was 1 year 10 months (range 3 weeks to 7 years 10 months).

All children had hyperoxaluria at presentation but hyperglycolic aciduria was documented in only four cases. The diagnosis was confirmed in five out of six patients by a reduction in liver AGT enzyme activity. One patient was diagnosed on the basis of a renal biopsy showing extensive oxalate deposition, elevated plasma oxalate, urinary oxalate and glycolate levels.

Despite maximal medical management (high fluid intake, crystallization inhibitors and pyridoxine), five out of six patients progressed to ESRF with systemic oxalosis and commenced dialysis at a median age of 7 years (range 2 months to 14 years 4 months). Two patients showed a partial response to pyridoxine. The median time between presentation and referral for transplant was 11 months (range 3 months to 13 years).

Pre-transplant assessments of cardiac function with echocardiography and electrocardiography revealed no significant abnormalities. Patient 5 underwent pre-operative assessment of myocardial and cardiovascular responsiveness to inotropes, which was reported as normal.

At assessment all patients met our criteria for combined LKT, namely correction of the underlying enzyme defect, management of the effects of systemic oxalosis and GFR < 25 ml/min/1.73 m².

**Analytical methods**

Plasma oxalate measurements were performed by the Dr R. Kasidas at the Department of Chemical Pathology, University College London Hospitals (UK). Urine oxalate was determined in our hospital by a kit method quantitative enzymatic assay of oxalate by oxalate oxidase adapted for a Cobas Farer instrument (Sigma-Aldrich, Poole, Dorset, UK). Liver AGT (EC 2.6.1.44) enzyme activity and immunoreactive protein studies were performed by the laboratories of Dr C. Danpure and Dr G. Rumsby, University College London Hospitals [7]. GFR was measured by standard isotopic EDTA-chelation technique in patient 4 and calculated by the Schwarz formula in all other cases.

**Results**

The transplant data and clinical condition of each patient is summarized in Table 2. The median age at transplantation was 8 years 11 months (range 20 months to 15 years 2 months) and median time on Table 1. Patient demographics and case histories

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Con/FH</th>
<th>Age at presentation</th>
<th>Presentation</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Plasma oxalate μmol/l (NR 1.0–3.0)</th>
<th>Age at ESRF/dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>+/+</td>
<td>3 weeks</td>
<td>ARF</td>
<td>13</td>
<td>63.0</td>
<td>1 year 6 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>−/−</td>
<td>9 weeks</td>
<td>ARF on CRF</td>
<td>&lt;10</td>
<td>53.0</td>
<td>2 months</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>+/+</td>
<td>7 years</td>
<td>ESRF</td>
<td>3</td>
<td>360.0</td>
<td>7 years</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>−/−</td>
<td>2 years 9 months</td>
<td>Renal Calculi</td>
<td>Renal Calculi</td>
<td>27</td>
<td>71.0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>−/+</td>
<td>1 year 1 month</td>
<td>CRF</td>
<td>N/A</td>
<td>N/A</td>
<td>14 years 4 months</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>−/−</td>
<td>7 years 10 months</td>
<td>CRF</td>
<td>4</td>
<td>243.0</td>
<td>7 years 11 months</td>
</tr>
</tbody>
</table>

Con = consanguinity; FH = family history; GFR = glomerular filtration rate; NR = normal range; ESRF = end-stage renal failure; ARF = acute renal failure; CRF = chronic renal failure.
Table 2. Transplant data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Tx</th>
<th>Date of Tx</th>
<th>Time on HD/PD</th>
<th>Clinical condition</th>
<th>Perioperative HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 years 4 months</td>
<td>1992</td>
<td>1 year 9 months</td>
<td>Anuric Fractures, bone pain + + Opiate dependent hypotension (60/24) LVH</td>
<td>Pre-op HD Post-op HD/HF daily</td>
</tr>
<tr>
<td>2</td>
<td>1 year 8 months</td>
<td>1994</td>
<td>1 year 4 months</td>
<td>Anuric Fractures, bone pain + + Wide pulse pressure (103/37)</td>
<td>Pre-op HD Post-op CAVHD then HF</td>
</tr>
<tr>
<td>3</td>
<td>9 years 2 months OLT</td>
<td>1992</td>
<td>2 years 2 months</td>
<td>Anuric Osteopenia, bone pain + + Fractures post OLT</td>
<td>Pre and post-op HD</td>
</tr>
<tr>
<td></td>
<td>10 years 5 months KT</td>
<td>1993</td>
<td>3 years 5 months</td>
<td></td>
<td>HD awaiting KT HD (3 wks post-op)</td>
</tr>
<tr>
<td>4</td>
<td>3 years 10 months</td>
<td>1999</td>
<td>nil</td>
<td>CRF</td>
<td>No HD</td>
</tr>
<tr>
<td>5</td>
<td>15 years 2 months</td>
<td>1999</td>
<td>10 months</td>
<td>Anuric Bone pain Hypertension, normal response to inotropes</td>
<td>Hydration (3/l/m²/d) crystallisation inhibitors, thiazides Pre-op HD No post-op HD</td>
</tr>
<tr>
<td>6</td>
<td>8 years 8 months</td>
<td>1999</td>
<td>9 months</td>
<td>Anuric Osteopenia, bone pain + + Impaired chronotropic response to stress, LVH</td>
<td>Hydration (3/l/m²/d) crystallisation inhibitors, thiazides HD/HF daily due to graft failure</td>
</tr>
</tbody>
</table>

Pt = patient; Tx = transplant; HD = haemodialysis; HF = haemofiltration; OLT = orthotopic liver transplant; KT = kidney transplant; LVH = left ventricular hypertrophy.
dialysis at transplantation was 1 year 4 months (range 0 to 2 years 2 months). Patient 1 was planned as a two-stage transplant procedure (liver then kidney), but died shortly after the liver transplant. The other five cases were put forward for combined LKT, but patient 3 underwent a staged procedure due to concerns about the donor kidney. Six livers (two whole, three reduced, one split) and five kidneys were transplanted; all grafts were cadaveric. A triple immunosuppressive regime was used: cyclosporin A (three patients) or tacrolimus (three patients), azathioprine and prednisolone. Three patients received routine post-operative dialysis; hyperhydration and enforced diuresis, without routine dialysis, were planned in the other three.

The clinical outcome following transplantation is summarized in Table 3. All hepatic grafts functioned normally, with no hepatic rejection. Two out of five renal grafts showed acute tubular necrosis (ATN) and three out of five developed acute cellular rejection, with ongoing chronic rejection in one. Oxalate deposits recurred in all renal grafts contributing to graft loss in one child and significant dysfunction in another (patient 6). Complications included bacterial sepsis (four patients), cytomegalovirus infection (one patient), cardiovascular instability (five patients, significant in three) and cyclosporin toxicity (one patient). Two children died, at 2 and 3 weeks post-transplant, respectively. Post-mortem examination in these children confirmed systemic oxalosis with deposits noted in renal, myocardiad, skeletal and retinal tissues as well as lymph nodes, coronary artery and peripheral blood vessels. The remaining four children are well at median follow-up of 10 months (range 6 months to 7 years 5 months).

Cardiovascular oxalosis complicated the post-operative course in both cases of Infantile PH1; significant inotropic support was required despite good left ventricular function and filling. Profound hypotension resistant to inotropes and compounded by sepsis resulted in the death of both infants.

Figure 1 shows the effect of continuous arteriovenous haemodialysis (CAVHD) and haemodialysis on plasma oxalate levels following combined LKT in patient 2. Despite a significant reduction in plasma oxalate levels, the renal graft never functioned and biopsy on day 8 showed oxalate deposition. Patient 3 (staged LKT) had intensive haemodialysis (HD) for 6 weeks post-renal transplant and three times a week for a further 6 weeks. Plasma oxalate levels stabilized for 9 months post-operation but subsequently increased at 1 year (Figure 2), when a renal biopsy showed recurrent oxalosis. Patient 4 made good progress until she failed to comply with the hydration regime. Patient 6 experienced a difficult early post-operative course and required haemodialysis for 6 months post-operatively as a result of prolonged acute tubular necrosis and oxalate deposition. He remained anuric for 4 months, followed by a very gradual increase in urine output allowing cessation of dialysis at 6 months.

All patients showed a reduction in plasma and urinary oxalate concentration post-transplant; median reduction in plasma oxalate between presentation and 4 weeks post-transplant was 52.5 µmol/l (range 34.5–304.8 µmol/l).

Discussion

Three transplantation options have emerged for patients with PH1 in whom conservative management is unsuccessful: (i) isolated renal transplantation to correct ESRF; (ii) isolated liver transplantation to correct the metabolic defect prior to significant renal damage occurring; and (iii) combined hepatorenal transplantation to correct both problems simultaneously [8]. The latter has the added immunological advantage that the liver graft may protect the renal graft against rejection [9]. Isolated renal transplantation in established ESRF offers only a temporary solution as oxalate deposition results in graft failure, with only 17–45% 3-year graft survival [10,11].

Isolated liver transplantation is an attractive treatment option in cases where residual renal function is preserved because it corrects the metabolic defect before systemic complications occur. However, the timing of pre-emptive liver transplant remains controversial [3,12,13]. The procedure is invasive, not without risk, and the decision to remove the native liver can be particularly difficult when the course of the disease is hard to predict.

The results of combined hepatorenal transplantation in 93 patients between 1984 and 1999 have been reported by The European Transplant Registry and have shown continuing improvement in patient and graft survival [14,15]. Overall, 1-, 2- and 5-year patient survival rates are 88, 80 and 72%, respectively, with corresponding graft survival rates of 82, 78 and 62%. The outcome in children is more guarded, particularly in those presenting early with ESRF and systemic oxalosis. Mortality following transplantation in children with PH1 aged 0–5 years may be as high as 40% in the first 6 months, although in the 5–10 year olds survival is ~80% and in the over tens survival rates are comparable to those found in adults [15]. Few reports have focussed on LKT in infants and young children, and the outcome has been variable [14,16–18]. The aim of this report is to document our results of combined LKT in the paediatric age group and to highlight some of the problems we have encountered.

The children in this series differed from other reported patients with PH1 in several respects. First, they presented early with severe disease. Nephrocalcinosis was common and only one child presented with renal calculi. Although the mortality rate in our series was high (2/6), the two deaths occurred in children at the most severe end of the spectrum, presenting with ESRF and systemic oxalosis in infancy. Our experience supports other reported data showing that patients with PH1 who present with renal failure in infancy, those with systemic oxalosis and those who have had a prolonged period of dialysis
Table 3. Outcome following transplantation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Follow-up</th>
<th>Outcome: early (&lt; 2 months)</th>
<th>Outcome: long-term</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Plasma oxalate (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 days</td>
<td>Died day 13</td>
<td>Died</td>
<td>–</td>
<td>10.5</td>
</tr>
<tr>
<td>2</td>
<td>23 days</td>
<td>Died day 23</td>
<td>Died</td>
<td>–</td>
<td>8.4</td>
</tr>
<tr>
<td>3</td>
<td>7 years 5 months Post-OLT 6 years 2 months Post-KT</td>
<td>LFT normal</td>
<td>30 Fractures, bone pain Chronic renal rejection Oxalate in renal graft Hypertension Bone pain improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10 months</td>
<td>LFT normal Renal function normal at discharge (day 17) (non-compliance with hydration regime)</td>
<td>LFT normal Renal function impaired</td>
<td>55</td>
<td>7.7</td>
</tr>
<tr>
<td>5</td>
<td>6 months</td>
<td>LFT normal Mild acute renal rejection Oxalate in renal graft (day 25) CMV enteritis Hypertension</td>
<td>Nasogastric hydration LFT normal Acute renal rejection</td>
<td>95</td>
<td>36.2</td>
</tr>
<tr>
<td>6</td>
<td>7 months</td>
<td>LFT abnormal day 1 to 5, then severe cholestasis due to sepsis Primary renal graft non-function Oxalate in renal graft (day 12) Hypertension</td>
<td>LFT normal Anuric for 4 months HD for 6 months Gradual spontaneous return of renal function</td>
<td>20</td>
<td>26.9</td>
</tr>
</tbody>
</table>

ATN = acute tubular necrosis; LFT = liver function tests.
have a higher morbidity and mortality rate following transplantation [14,15]. Many of the theoretical problems associated with transplantation in infantile PH1, as reviewed by Parekh et al. [16], occurred in patients 1 and 2. Cardiovascular instability as a result of oxalate deposition in coronary vessels was a major problem, but difficult to prevent as the pre-operative assessment of myocardial and vascular responsiveness to inotropes was unhelpful in predicting outcome.

Renal graft outcome is known to be less satisfactory in smaller children independent of their primary disease [19], and this is further complicated in PH1 by the enormous oxalate load. Renal graft survival in our series was 4/5, but oxalate recurred in all renal grafts despite measures aimed at minimizing deposition of oxalate in the transplanted kidney, namely fluid management and intensive pre-operative and, in some cases, post-operative haemodialysis/haemofiltration.
Pre-operative haemodialysis is generally recommended immediately before transplantation as it lowers plasma oxalate and may reduce the risk of oxalate deposition in the renal graft [8]. The routine use of post-operative dialysis is more controversial. Our initial practice was to continue routine post-operative dialysis, but results were variable. The importance of maximizing urine output and the use of crystallization inhibitors is now well recognized and this was borne out by our own experience (patient 4).

Attempts have been made to establish guidelines for transplantation based on the GFR and clinical condition of the patient: LKT is the recommended treatment when the GFR is <25 ml/min/1.73 m² [12]. Oxalate accumulation increases rapidly when the GFR falls below 40 ml/min/1.73 m² and this corresponds to a plasma oxalate concentration > 50 μmol/l [20]. Combined LKT should therefore be considered when the GFR is between 25 and 40 ml/min/1.73 m², especially if there is rapid deterioration or severe extrarenal involvement. Isolated liver transplant is the preferred option when the GFR is between 40 and 60 ml/min/1.73 m² and the disease is following an aggressive course [12].

As a result of our experiences we have reviewed our indications for LKT in young children and recommend transplantation earlier than most authors. Nephrocalcinosis implies significant disease in this age group, and thus we suggest that in children under 3 years of age, LKT should be performed if there is significant nephrocalcinosis with evidence of systemic oxalosis, irrespective of the GFR. Since the nephrotoxic effects of immunosuppressive therapy and recurrent oxalosis inevitably result in a decline in GFR post-transplant, we further propose that in older children presenting with nephrocalcinosis and systemic oxalosis, LKT be considered when the GFR approaches 50 ml/min/1.73 m². In the absence of urinary obstruction and significant nephrocalcinosis, isolated liver transplant in young PH1 children could be delayed until the GFR falls below 40 ml/min/1.73 m². Close monitoring at this point should enable intervention to be planned before further significant deterioration occurs.

In conclusion, infants and young children with PH1, nephrocalcinosis and systemic oxalosis represent a difficult management problem. While some centres have reported good outcome following LKT in this age group [18], our experience is more guarded. ESRF and poor quality of life mean the potential long-term benefits of transplantation are great, but morbidity and mortality are high. Combined hepatorenal transplantation at the earliest opportunity, or pre-emptive liver transplantation in selected cases, should minimize such complications and improve the outcome for these children.

Acknowledgements. We are grateful to Drs D. V. Milford, C. M. Taylor, M. M. Fitzpatrick and M. G. Coulthard for allowing us to review their patients. Our thanks also to Dr N. V. Plant and M. A. Preece for providing plasma oxalate data on patient 3, and to Drs C. Danpure and G. Rumsby for the AGT enzyme data.

References

20. Barratt TM, van’t Hoff WG. Are there guidelines for a strategy according to glomerular filtration rate, plasma oxalate determination and the risk of oxalate accumulation? Nephrol Dial Transplant 1995; 10 [Suppl 8]: 22–23

Received for publication: 20.3.00
Accepted in revised form: 22.8.00