Check for updates

Received: 20 December 2018 | Revised: 7 February 2019 | Accepted: 12 February 2019

DOI: 10.1111/petr.13406

ORIGINAL ARTICLE

WILEY

The experience of combined and sequential liver and kidney transplantation from a single living donor in patients with primary hyperoxaluria type 1

Ali Ozer[1] | Hikmet Aktas[1] | Burcu Bulum[2] | Remzi Emiroglu[1]

[1]Department of Organ Transplantation, Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Istanbul, Turkey

[2]Department of Pediatric Nephrology, Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Istanbul, Turkey

Correspondence
Ali Ozer, Department of Organ Transplantation, Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Istanbul, Turkey.
Email: draliozerr@gmail.com

Abstract

LKT is the only effective treatment for PH1 because it replaces both the source (liver) and the target (kidney) of the disease. Most studies report on LKT in patients with PH1 from deceased donors. This study reports on five patients who underwent LKT from a single living donor between April 2017 and March 2018. Combined LKT was performed for 1 patient and sequential LKT for the remainder. The median age of the patients at the time of diagnosis and transplantation was 5.5 (0.3-18) and 10 (6-21) years, respectively. All patients received left lateral liver segment transplantation, except one patient who received right liver lobe transplantation. No liver graft loss was observed, and liver function tests were stable at the final evaluation of all patients. Renal function tests of the patients were also stable at the final assessment, except for the young adult patient. None of the patients suffered from acute rejection. One patient died at the second month following liver transplantation due to severe pneumonia and sepsis. This study concludes that combined or sequential LKT from a single living donor can be safely performed and provides encouraging results for even the youngest and smallest patients with PH1.

KEYWORDS

kidney transplantation, liver transplantation, living donor, Primary hyperoxaluria

1 | INTRODUCTION

PH1 is a rare autosomal recessive disease caused by a deficiency in the hepatic peroxisomal enzyme AGT. This disorder leads to overproduction of oxalate that causes recurrent urolithiasis and nephrocalcinosis followed by progressive decline in renal function and, consequently, systemic oxalosis and ESRD, resulting in severe morbidity and mortality.[1]

RRTs cannot overcome the continuous excess production of oxalate and disastrous course of systemic oxalosis. Therefore, LKT is the only effective treatment for PH1 because it replaces both the source (liver) and the target (kidney) of the disease. Outcomes of transplantation in PH1 have improved over time, but the choice of optimal transplantation strategy of CLKT/SLKT still remains a challenge that requires individualization in regard to stage of disease, presence of systemic oxalosis, peri-operative risks, availability of deceased or living donors, facilities, and experience of the center.[2,3]

Most studies report on CLKT and SLKT in patients with PH1 from deceased donors. There are a few reports in which both organs were taken from a single living donor from countries where a shortage of organ donation remains a problem, as in Turkey.[4,5] The aim of this report was to describe our experience with CLKT and SLKT from single living donors in patients with PH1.

Abbreviations: AGT, Alanine-glyoxylate aminotransferase; CLKT, Combined liver and kidney transplantation; CVVHDF, Continuous venovenous hemodiafiltration; ESRD, End-stage renal disease; HD, Hemodialysis; KT, Kidney transplantation; LKT, Liver and kidney transplantation; LT, Liver transplantation; PH1, Primary hyperoxaluria type 1; POx, Plasma oxalate; RRTs, Renal replacement therapies; SLKT, Sequential liver and kidney transplantation; UOx, Urinary oxalate.

 © 2019 Wiley Periodicals, Inc.

2 | PATIENTS AND METHODS

Five patients (four males and one female) diagnosed with PH1 underwent CLKT or SLKT at the study institute between April 2017 and March 2018. They were reviewed on a retrospective basis, and the characteristics of the recipients and donors were recorded.

The indications for CLKT or SLKT were decided based on individual features, clinical parameters, presence of systemic oxalosis, and consent of the patients and their parents with regard to recommendations of the OxalEurope expert group.[2] A final council with all the medical disciplines involved was convened to reach a conclusive decision. The decision was made to perform SLKT for four patients and CLKT for one patient. It was planned to perform both CLKT and SLKT from single living donors. Before transplantation, all of the donors were assessed with regard to psychosocial conditions to confirm their willingness to donate two organs. They were also evaluated clinically and genetically to be donors with regard to PH1 disorder. Donor nephrectomy was performed laparoscopically in all donors for SLKT and by the same midline incision that was used for hepatectomy in the CLKT case.

CVVHDF was performed in anuric patients to provide fluid balance during the entire surgery. All SLKT patients were treated with an intensified HD protocol (6 d/wk, 4-6 h/d) after LT for four months to achieve POx levels below the saturation level of 30 μmol/L[6] before KT. Diuresis was strictly monitored after CLKT and SLKT. It was also planned to perform CVVHDF in cases of delayed renal graft function after transplantation.

Monoclonal antibody basiliximab was administered prior to LT and again four days after transplantation. Standard triple immunosuppressive therapy, consisting of prednisone, tacrolimus, and mycophenolate mofetil, was also administered to all patients. Hyperhydration (2-3 L/m^2/d) and citrate supplementation were initiated to prevent post-transplant oxalate deposition in the graft kidneys.

All the patients and donors were closely followed up in the outpatient clinic after discharge. Only one SLKT patient returned to his country to receive HD therapy during the interval between liver and kidney transplantation. Serum creatinine, liver enzymes, tacrolimus trough levels, and post-transplant serum and UOx levels were monitored at routine outpatient clinic evaluations. Estimated glomerular filtration rate was calculated according to the Schwartz formula.

The study was designed as a retrospective study. As such, it was approved by the ethics committee of Acibadem Mehmet Ali Aydinlar University (protocol number: 2018-18/15).

3 | RESULTS

The median age of the patients at the time of diagnosis and transplantation was 5.5 (0.3-18) and 10 (6-21) years, respectively. Two patients had the infantile form of the disease, and 4 patients had severe systemic oxalosis. The clinical diagnosis of PH1 was genetically confirmed in all patients. None of the patients were significantly responsive to pyridoxine therapy. All patients were on an intensified HD protocol (6 d/wk, 4-6 h/d) prior to transplantation. The median duration of HD before transplantation was 2 (0.3-5.5) years. Demographic and clinical features of the patients are presented in Table 1.

CLKT was performed for one PH1 patient and SLKT for the remainder, except *Patient-4* who returned to his country of origin to

TABLE 1 Demographic and clinical features of the patients

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5
Gender	Female	Male	Male	Male	Male
Age at Tx (y)	10	10	6	6	21
Age at diagnosis (y)	2	8	5.5	0.3	18
Clinical presentation	Urolithiasis Nephrocalcinosis	Urolithiasis	Urolithiasis Nephrocalcinosis	Nephrocalcinosis Failure to thrive	Recurrent urolithiasis
AGT gen analysis	Homozygous c.584T>G (p.Met195Arg)	Homozygous c.322T>C (p.Trp108Arg)	Homozygous c.322T>C (p.Trp108Arg)	Homozygous c.584T>G (p.Met195Arg)	Homozygous c.322T>C (p.Trp108Arg)
Parental consanguinity	+	+	+	+	+
Family history of PH1	Brother (Exitus)	Brother (Exitus)	Brother, Cousin (Exitus)	None	None
Systemic oxalosis	Severe	No	Severe	Severe	Severe
Type/Duration of RRT before Tx	HD/5.5 y	HD/4 mos	HD/3 mos	HD/5.5 y	HD/2 y
UOx level before Tx (mg/1.73 m^2/d)	Anuria	63	Anuria	Anuria	Anuria
Weight at Tx (kg)	20	30	14	8	68

AGT, alanine-glyoxylate aminotransferase; PH1, primary hyperoxaluria type 1; RRT, renal replacement therapy; Tx, transplantation; UOx, urinary oxalate.

receive HD therapy during the interval between liver and kidney transplantation. This patient died in his country at the second month following LT due to severe pneumonia and sepsis, so only LT was performed for this patient. When this patient was excluded, the CLKT and SLKT patients underwent follow-up for 11-19 months after LT and 7-15 months after KT.

The POx levels of all SLKT patients were <30 μmol/L before KT. The UOx level of the CLKT patient was high before transplantation and returned to normal within 3 months after transplantation. The UOx levels of the SLKT patients could not be evaluated before transplantation because of anuria. However, after transplantation, all SLKT patients still had high UOx levels at the final evaluation because of systemic oxalosis.

All of the donors were young (28-42 years) and ABO-compatible. Three of the donors were mothers, and two of them were fathers. The donors did not experience any peri- or post-operative complications.

The CLKT patient (*Patient-2*) received left lateral segments of the liver and the left kidney of his father. He was re-operated on due to bleeding from the hepatic artery anastomosis. Except for this, he had an uneventful post-operative course. The SLKT cases also received left lateral segments as liver grafts, except *Patient-5* who received a right lobe graft. Two patients received left kidneys, and one received a right kidney from their living donors in SLKT cases. *Patient-4*, who underwent hepaticojejunostomy, had biliary sepsis after LT and was treated for 20 days in the intensive care unit (ICU). He was discharged with a well-functioning liver.

The CLKT patient stayed in the ICU for 4 days following transplantation. The length of stay in the ICU for the SLKT patients was 2-20 days following LT and 1-2 days after KT. Diuresis and renal graft functions were all normal, and none of the patients needed CVVHDF in the early post-operative period. On follow-up, *Patient-1* had cytomegalovirus infection in the fourth month after transplantation and was successfully treated with intravenous ganciclovir. No liver graft loss was observed, and liver functions were stable at the final evaluation of all patients. None of the patients suffered from acute rejection. The renal functions of the patients were also stable at the final evaluation, except the young adult patient (*Patient-5*). He received HD after 2 months of transplantation due to loss of renal graft function because of accumulation of oxalate which was shown by biopsy. Outcomes of the patients are summarized in Table 2.

4 | DISCUSSION

Even though most publications about PH1 patients who have undergone transplantation have reported on deceased donors, studies reporting on living donors with good outcomes have increased in recent years.[4,5] Most of the CLKT reports have been on cases from single deceased donors. For SLKT cases, most often one of the organs is procured from a living donor and the other from a deceased donor.[3,7,8] Reports about CLKT and SLKT from a single living donor are limited from countries where a shortage of deceased donors remains a problem.[4,5] In this single-center series, it is illustrated that CLKT and SLKT are feasible and safe from a single living donor, even in pediatric patients.

TABLE 2 Outcomes of CLKT and SLKT patients

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5
Tx strategy	SLKT	CLKT	SLKT	LT	SLKT
Donors	Mother	Father	Mother	Mother	Father
Interval between LT and KT	4 mos	-	4 mos	-	4 mos
POx level before KT (μmol/L)	<30	-	<30	-	<30
Stay time in ICU (days) (LT/KT)	3/2	4	3/2	20	2/1
RRT early post-operative period	-	-	-	-	-
Follow-up time (LT/KT) (months)	19/15	12/12	11/7	2	15/11
Early post-operative complications	-	Bleeding	-	Biliary sepsis	-
Complications in the follow-up	CMV infection	-	-	Pneumonia and sepsis	-
Liver outcome	Functional	Functional	Functional	Functional	Functional
Kidney outcome	Present/Functional	Present/Functional	Present/Functional	-	2 mos/ Dialysis
Patient survival	Alive	Alive	Alive	Exitus	Alive
Acute Rejection	-	-	-	-	-
Current Cre (mg/dL)	1.2	0.8	1.1	-	CKD/HD
Current eGFR (mL/min)	51	125	52	-	<15

CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; KT, kidney transplantation; LT, liver transplantation; POx, plasma oxalate; RRT, renal replacement therapy; Tx, transplantation; UVJ, ureterovesical junction.

Unfortunately, the number of deceased organ donations is only 6.9 per million people, with only 27% of brain death cases choosing organ donation in Turkey in 2017.[9] This unfortunate circumstance obligates transplantation teams to rely on living donations as a reasonable alternative to overcome the scarcity of deceased organ donations. The procurement of a segmental liver graft and a kidney from a single living donor is considered a high-risk procedure. However, over the years, significant experience has been gained in liver and kidney transplantations from living donors performed at different ages and weights (even <1 year and <10 kg) of recipients for various aetiologies due to the situation explained above. So, in this study, liver and kidney transplantations from single living donors for CLKT and SLKT patients were performed successfully without any peri- or post-operative morbidity.

Making the right decision for a transplantation procedure is very important both for patients with PH1 and for living donors. The clinical care before and after transplantation is complex and requires specialist expertise in a multidisciplinary team.[10] The strategy of liver and kidney transplantation depends on the stage of the disease, patients' medical and anatomical condition, local facilities, and, especially, experience of the center.[11] It may also be an option when living-related transplantation is requested by the parents because sequential living-related donation is probably less traumatic for the donor than concurrent donation. While globally there is more experience with CLKT for PH1, published data on SLKT are limited and mostly restricted to children. SLKT seems more feasible as a two-step procedure: the liver first and then the kidney. Therefore, the strategy of CLKT or SLKT can be based on the patient's clinical condition (including stage of disease and presence of systemic oxalosis) and the preferences of the donors, but not related to difficulties of required surgical techniques due to the surgeons' experience with live donors. CLKT was performed for the patient who had a short period of dialysis and did not have systemic oxalosis. He was also in good medical condition. However, SLKT was performed for the remainder who had systemic oxalosis and a long duration of RRTs. All patients with systemic oxalosis have the anamnesis of bone fractures, growth retardation, and gait disturbance. Hypothyroidism was present in three patients (*Patient-1*, *Patient-3*, *and Patient-5*). One patient (*Patient-1*) had arrhythmia and pulmonary venous hypertension.

An immunoprotective effect of the liver on the kidney when procured from the same (mostly deceased) donor in CLKT (mainly in non-sensitized patients) has previously been reported.[7,11] Kitajima et al[4] also reported the same protective effect in SLKT patients when both grafts were procured from a single living donor in 2017.

Although the organ responsible for PH1 is eliminated by LT, it is still a challenge to protect kidney grafts from oxalate accumulation due to mobilization and renal elimination of systemic oxalate deposits.[6,12] Therefore, SLKT is a reasonable strategy to maintain POx levels below the saturation level due to intensified dialysis protocol before KT. However, there is no consensus for the best interval between liver and kidney transplantations. A minimum of 22 days and a maximum of 10 months for the interval have been reported.[5] All of the SLKT patients in this study were treated with an intensified HD protocol after LT for four months in accordance with the literature. They were also treated with hyperhydration and crystallization inhibitors after KT. Despite these interventions, there was a failure to protect the kidney allograft from oxalate injury of only the young adult patient who, unfortunately, had a delayed diagnosis of PH1 with ESRD and severe systemic oxalosis at 18 years of age, despite recurrent nephrolithiasis in childhood. To protect organs from oxalate injury, it is recommended initiating dialysis (5 to 7 sessions per week using large dialyzers with high blood flows) early, when GFR is between 20 and 30 mL/min/1.73 m^2, with the aim to maintain plasma oxalate below 50 μmol/L.[12]

We have lost the Patient-5 in his country at the second month following LT due to severe pneumonia and sepsis. We believed that the patient should have remained close to the transplant center for a longer period of time or until the kidney transplant.

PH1 is a rare disease and transplantations should be performed by teams who have experience, especially in pediatric cases. In addition, it is necessary to continue documentation of results to further improve outcomes in this rare but severe disease.

5 | CONCLUSIONS

Combined or sequential liver and kidney transplantation is the definitive therapy for patients with PH1. Procurement of liver and kidney allografts from a single living donor obviously requests more attention for donors and should be performed by experienced surgical and multidisciplinary teams. This series confirms that when the required conditions are provided, CLKT or SLKT from a single living donor seemed to be safe but indication of recipient should be strict.

AUTHORS' CONTRIBUTIONS

AO: Contributed to the critical writing and revising the intellectual content, designing the study, performing the surgery, and collecting the data; HA: Contributed to designing the study, performing the surgery, researching the literature, and revising the intellectual content; BB: Contributed to conceiving and designing the study, following the patients, collecting the data, and revising the intellectual content; and RE: Contributed to conceiving and designing the study, performing the surgery, revising the intellectual content, and final reviewing of the paper.

ORCID

Ali Ozer https://orcid.org/0000-0003-1825-6736

REFERENCES

1. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658.

2. Cochat P, Fargue S, Harambat J. Primary hyperoxaluria type 1: strategy for organ transplantation. *Curr Opin Organ Transplant*. 2010;15:590-593.
3. Büscher R, Büscher AK, Cetiner M, et al. Combined liver and kidney transplantation and kidney after liver transplantation in children: Indication, postoperative outcome, and long-term results. *Pediatr Transplant*. 2015;19:858-865.
4. Kitajima K, Ogawa Y, Miki K, et al. Longterm renal allograft survival after sequential liver-kidney transplantation from a single living donor. *Liver Transpl*. 2017;23(3):315-323.
5. Mor E, Nesher E, Ben-Ari Z, et al. Sequential liver and kidney transplantation from single living donor in two young adults with primary hyperoxaluria type 1. *Liver Transpl*. 2013;19(6):646-648.
6. Bollée G, Cochat P, Daudon M. Recurrence of crystalline nephropathy after kidney transplantation in APRT deficiency and primary hyperoxaluria. *Can J Kidney Health Dis*. 2015;2:31.
7. Grenda R, Kalicinski P. Combined and sequential liver-kidney transplantation in children. *Pediatr Nephrol*. 2018;33(12):2227-2237.
8. Duclaux-Loras R, Bacchetta J, Berthiller J, et al. Pediatric combined liver-kidney transplantation: a single-center experience of 18 cases. *Pediatr Nephrol*. 2016;31(9):1517-1529.
9. The statistical data of liver and kidney transplantation in Turkey in 2017. Available at: www.saglik.gov.tr Accessed November 5, 2018 .
10. Harps E, Brinkert F, Ganschow R, et al. Immediate postoperative intensive care treatment of pediatric combined liver-kidney transplantation: outcome and prognostic factors. *Transplantation*. 2011;91(10):1127-1131.
11. Jalanko H, Pakarinen M. Combined liver and kidney transplantation in children. *Pediatr Nephrol*. 2014;29(5):805-814.
12. Illies F, Bonzel KE, Wingen AM, Latta K, Hoyer PF. Clearance and removal of oxalate in children on intensified dialysis for primary hyperoxaluria type 1. *Kidney Int*. 2006;70(9):1642-1648.

How to cite this article: Ozer A, Aktas H, Bulum B, Emiroglu R. The experience of combined and sequential liver and kidney transplantation from a single living donor in patients with primary hyperoxaluria type 1. *Pediatr Transplant*. 2019;23:e13406. https://doi.org/10.1111/petr.13406