Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Polycystic liver and kidney disease: post-transplant kidney function in patients receiving pre-emptive kidney transplantation

Adrian P. Martin, Michael Bartels, Adrien Kiehle, Johann Hauss and Josef Fangmann

Universitatsklinikum Leipzig, Abteilung fur Viszeral-, Transplantations-, Thorax- und Gefasschirurgie, Liebigstrasse 20, 04103 Leipzig, Germany

Keywords
polycystic liver and kidney disease, post-transplant kidney function, pre-emptive kidney transplantation, Tc99m MAG3 scintigraphy.

Correspondence
Adrian P. Martin, Universitatsklinikum Leipzig, Liebigstrasse 20 A, 04103 Leipzig, Germany.
Tel.: 0049 03421 9717200; fax: 0049 03421 9717209; e-mail: patriciumartin@hotmail.com

Received: 10 April 2007
Revision requested: 4 May 2007
Accepted: 29 October 2007

doi:10.1111/j.1432-2277.2007.00601.x

Summary

The aim of the study is to evaluate the changes in kidney function after pre-emptive kidney transplantation in patients with polycystic liver and kidney disease (PLKD) and to establish whether pre-emptive kidney transplantation is warranted. Between 1998 and 2006, five patients with severe anatomical changes in both native kidneys but only mild alteration of the clearance function received combined liver and kidney transplantation. Preoperatively, Technetium-99m mercaptoacetyltriglycine (Tc99m MAG3) scintigraphy was used to evaluate separately the function of each native kidney. This examination was repeated six months after transplantation, additionally measuring the function of the transplanted kidney. Pretransplant creatinine levels were 77–115 μmol/l and Tc99m MAG3 clearance was 141–163 ml/min/1.73 sqm (74 ± 8% of minimum-for-age values). Six months after transplant, creatinine values were not significantly different. Minimum-for-age clearance decreased by 12.5 ± 11.5% in four patients, and increased by 26% in one patient. In four patients, the transplanted and the native kidneys assumed each about one third of total tracer clearance. In one patient, the transplanted kidney assumed 92% of the clearance function. Kidney function decreases despite pre-emptive kidney transplantation. Native kidneys are not functionally excluded and the clearance seems to be divided between native and transplanted organs. Kidney transplantation in nonuremic PLKD patients does not improve the overall kidney function and should be performed only in exceptional cases.

Introduction

Polycystic liver and kidney degeneration (PLKD) is a rare entity with autosomal dominant transmission. The continuously improving results of liver transplantation have established this procedure as an accepted therapy for advanced, disabling polycystic liver disease. Several therapeutic alternatives like fenestration, resection and aspiration of liver cysts to alleviate the symptomatology caused by advanced polycystic liver disease have been used with modest success [1–6].

Kidney transplantation for PLKD is classically performed in patients already on dialysis or with severely impaired kidney function. These patients often have severely reduced kidney parenchyma, although with preserved clearance function, which raises the question whether they will have sufficient reserves to maintain adequate kidney function after transplantation. The severity of kidney dysfunction that would warrant combined liver–kidney transplantation has not been established.

Technetium-99m mercaptoacetyltriglycine (Tc99m MAG3) was introduced in 1986 as an alternative for iodine-131 orthoiodohippurate [7,8] in the clinical investigation of kidney function. Tc99m MAG3 is eliminated through tubular secretion to an extent of 98% (2% by glomerular filtration) and its clearance is an index of effective renal plasma flow [9]. It has been shown in

nontransplant patients, that there is a good correlation between the tracer clearance and 24-h creatinine clearance [10]. The use of camera-based techniques that do not require plasma or urine samples [11] also allows for separate evaluation of the function of each native kidney before transplantation, and of the native and transplanted kidney after transplantation.

We present five patients who received combined liver and kidney transplantation for PLKD; they all had severe liver dysfunction, but only mild impairment of the kidney function. Using Tc99m MAG3 scintigraphy examination of the kidney function both before and after transplant, we tried to determine the impact of transplantation on the renal function and whether the pre-emptive kidney transplantation was warranted.

Patient and methods

We retrospectively reviewed the medical records of eleven patients who underwent simultaneous combined cadaveric liver and kidney transplantation for PLKD between December 1999 and February 2006 at the Transplantation Department of the University Clinic of Leipzig, Germany.

Patients with advanced symptomatic cystic degeneration of the liver were considered for transplantation. All patients had well-preserved liver function with normal bilirubin, transaminases, prothrombin time, gamma-glutamil-transpeptidase and alkaline phosphatase. All patients' debilitating symptoms related to liver enlargement; they all experienced a steady increase in abdominal girth and abdominal pressure sensation resulting in permanent discomfort and limitation of daily activities. Abdominal pain, dyspnoea and nutritional problems related to early satiety and nausea were also present to various extents in all patients. One patient had repeated episodes of collapse upon bending forward, which were attributed to the compression of the vena cava by the enlarged liver.

Six patients had advanced kidney dysfunction, while five patients had only mild impairment of the renal function and are the subject of our study.

Our center's policy was to offer combined liver and kidney transplantation to all patients with advanced kidney disease and to those who had or were planned to have a native kidney nephrectomy before or at time of transplantation. Also, patients with evidence of severe reduction in renal parenchymal mass on preoperative imaging studies were scheduled for a combined transplant, if they showed signs of alteration in kidney function.

During the pretransplant evaluation, all patients had ultrasound and computed tomography (CT) evaluation of the liver and kidneys. Starting from 2000, we have been using camera-based Tc99m-MAG3 scintigraphy in the pretransplant evaluation of all PLKD patients, quantifying the participation of each native kidney to the global kidney function.

All five patients who received pre-emptive kidney transplantation were waitlisted based on Eurotransplant criteria for liver transplantation, while having mild kidney dysfunction with normal or mildly elevated creatinine levels. In all five patients, there were prominent anatomical changes in both kidneys, with the presence of severe cystic degeneration and only minimal residual parenchyma identifiable on both CT and ultrasound. The indication for kidney transplantation in these patients was based on slow progressive deterioration of kidney function and on the assumption that the native kidney function will further decrease after transplantation and will possibly not be able to be sustained under immunosuppression. All these patients underwent preoperative Tc99m MAG3 scintigraphy. The function of the native and transplanted kidneys in these patients was evaluated by 99mTc MAG3 scintigraphy 6 months after transplantation at the same nuclear medicine laboratory that performed the pretransplant evaluations.

All patients received liver and kidney grafts from cadaveric donors. All liver transplantations were whole-organ transplants, performed with vena cava interposition, without the use of veno-venous bypass [12]. The kidney was implanted retroperitoneally through a separate incision in all cases.

Donor age ranged between 18 and 64 years (mean 43.2 years), with kidney cold ischemia times between 15 and 19 h (mean 16 h).

All patients had postoperative immunosuppression regimens based on tacrolimus (target level 8–12 ng/ml within the first 3 months, 6–8 ng/ml thereafter), mycophenolate mofetil 500×2 mg/day, and steroids, which were gradually tapered and discontinued in all patients by 6 months after transplantation.

Results

Pretransplant creatinine levels ranged between 77 and 115 μmol/l (mean 95 μmol/l) and Tc99m MAG3 tracer clearance was between 141and163 ml/min/1.73 sqm ($74 \pm 8\%$ of the minimum-for-age normal values).

The evaluation at 6 months after transplant showed that the creatinine values ranged between 70 and 121 μmol/l (mean 99 μmol/l), not significantly different from the pretransplant creatinine values.

The Tc99m MAG3 clearance 6 months after transplantation ranged between 105 and 157 ml/min/1.73 sqm ($73 \pm 22\%$ of the minimum-for-age normal values). This

Table 1. Pre- and post-transplant evaluation of kidney function.

		Pretransplant values				Post-transplant values			
Patient no.	Follow-up (days)	Creatinine (μmol/l)	Tc99MAG3 clearance (ml/min/1.73 sqm)	% of minimal clearance for age	% Tc 99m MAG3 Cl for each kidney	Creatinine (μmol/l)	Tc99MAG3 clearance (ml/min/1.73 sqm) (%)	% of minimal clearance for age	% Tc 99m MAG3 Cl for each kidney
1	617	109	163	76	LK 27%, RK 73%	121	105 (–35.5)	51	RK 47%, LK 23%, TxK 30%
2	403	95	149	69	LK 48%, RK 52%	84	157 (+5)	95	RK 4%, LK 4%, TxK 92%
3	233	77	161	82	LK 65%, RK 35%	70	157 (–2.5)	81	RK 32%, LK 33%, TxK 34%
4	205	115	141	67	LK 30%, RK 70%	112	119 (–15.5)	56	RK 47%, LK 27%, TxK 26%
5	214	79	164	82	LK 45%, RK 55%	107	144 (–16)	73	RK 47%, LK 19%, TxK 31%

was slightly decreased compared to the preoperative values. The minimum-for-age tracer clearance decreased by 12.5 ± 11.5% in four of five patients, while in one patient, it increased by 26% (Table 1).

In four patients, the transplanted kidney and the native kidneys assumed each about one third of the total tracer clearance. The kidney that had a higher participation at the global filtration rate before transplantation seems to retain a slightly higher function thereafter.

One patient (Table 1, patient no. 2) had an increase in tracer clearance at 6 months after transplantation as compared to the pretransplant evaluation. This specific patient received a graft from an 18-year-old donor with 18 h cold ischemia time. In this patient, the transplanted kidney assumed the tracer clearance almost integrally and the native kidneys seemed to retain only minimal function.

Discussion

Separate evaluation of the native kidneys with camera-based Tc99m MAG3 scintigraphy may find a role in patients with PLKD and advanced cystic degeneration of the kidney, especially when native kidney nephrectomy is anticipated before or at the time of transplantation. If nephrectomy is required for space reasons, it could help clinicians to determine which kidney should be sacrificed. If nephrectomy is necessary for infection or other reasons, it could give an estimate on the degree of impairment of kidney function afterwards and help decide if a combined LKTx is warranted.

Pretransplant kidney function has long been established as one of the important predictors of transplant outcome [13]. In the general liver transplant population, patients are expected to experience decreasing glomerular filtration [13–15], and some patients will require hemodialysis and/or kidney transplantation later on [16,17]. Gonwa *et al.* [17] showed that patients with normal and mildly decreased kidney function have a brisk decrease in glomerular filtration rate at 3 months after liver transplantation, and the renal function largely stabilizes after this point. Kim *et al.* found that 78% of 407 studied patients had altered kidney function at 6 months; however, only 8% had severe, stage 4 or 5 kidney disease.

In patients with advanced polycystic liver and kidney degeneration undergoing liver transplantation, prolonged waiting times and postoperative treatment with nephrotoxic agents may adversely impact an already affected renal function, but terminal kidney insufficiency seems to occur in a rather small percentage of patients. In a study [18] including 14 patients with liver and kidney cysts, Ueno *et al.* suggested that PLKD patients with glomerular filtration rates (GFR) higher than 30 ml/min should not receive a combined liver kidney transplant. In this study, eight PLKD patients underwent liver transplantation alone; even though there was a significant decrease in GFR after transplantation, only two of these patients required a kidney transplant four years later.

In another study [19], out of 13 patients liver transplanted and having liver and kidney cystic degeneration, only one required kidney transplantation later on, while the other patients maintained their renal function.

Data from solitary pancreas transplantation show that in nonuremic patients, there is a significant alteration in the native kidney function after transplantation. Still terminal renal dysfunction requiring hemodialysis is not a frequent event [20,21].

In discrepancy with data published from kidney-pancreas transplant patients receiving pre-emptive kidney transplantation [22], in our series, the native kidneys were not functionally excluded by the transplanted kidney, except in one patient who received a graft from a very young donor. The transplanted kidney seems to assume about one third of the clearance function, while the native kidneys share the remaining two thirds.

In our patients, the post-transplant scintigraphic evaluation showed that the total clearance function has not improved at six months after transplantation except for one patient, while the other four patients demonstrated a stable or slightly decreased tracer clearance. A quantification of the percentage of assumed tracer clearance will show, however, that the actual quantity of tracer filtered by each native kidney is lower than it was before transplantation, the difference being assumed by the transplanted kidney. One can speculate that this 'competition' does not benefit any of the kidneys, and that the transplanted kidney also has a lesser function than it would have in the absence of concurrently functional native kidneys.

To summarize, it appears that pre-emptive kidney transplantation did not offer any important advantage to our patients, at least in the first six months. Some mild deterioration of the global kidney function, although less prominent than reported by other authors, still occurs. Potential drawbacks such as surgical complications related specifically to the kidney transplantation as well as the wasting of a transplantable organ are important considerations. The only argument to favor the pre-emptive approach would be that *if* these patients ever reached terminal kidney insufficiency after liver transplantation, they would face prolonged waiting times on hemodyalysis, but data in the literature do not indicate a high rate of terminal kidney dysfunction after liver transplantation in PLKD patients. This rate could further be reduced by carefully using nephrotoxic immunosuppressive agents. Switching to renal sparing protocols using rapamycin may be considered as an alternative in these patients, especially as this drug may allow some degree of recovery of kidney function after transplantation [23]. Recent animal research also shows a potential of rapamycin to reduce cyst formation [24–26].

Based on literature data, it seems that the frequency of terminal kidney failure in the liver transplanted PLKD population can be compared to that in the general liver transplant population. Our findings show that adding a functional kidney does not bring any additional benefit to these patients, at least in the first six months. We, therefore, conclude that pre-emptive kidney transplantation should not be routinely used in patients with PLKD. Simultaneous liver and kidney transplantation in this patient population should be offered only in the presence of established or imminent kidney failure or if nephrectomy is envisioned.

Authorship

APM elaborated the concept, coordinated the data gathering and wrote the paper. MB participated in the final review. AK participated in data gathering. JH participated in concept. JF participated in concept formulation, design elaboration and final review.

References

1. Gigot JF, Jadoul P, Que F, *et al.* Adult polycystic liver disease, is fenestration the most adequate operation for long-term management? *Ann Surg* 1997; **3**: 286.
2. Madariaga JR, Iwatsuki A, Starzl TE, Todo S, Selby R, Zetti G. Hepatic resection for cystic lesions of the liver. *Ann Surg* 1993; **5**: 610.
3. Newman KD, Torres VE, Rakela J, Nagorney DM. Treatment of highly symptomatic polycystic liver disease. *Ann Surg* 1990; **212**: 30.
4. Turnage RH, Eckhauser FE, Knol JA, Thompson NW. Therapeutic dilemmas in patients with symptomatic polycystic liver disease. *Am Surg* 1988; **4**: 365.
5. Soravia C, Mentha G, Giostra E, Morel P, Rohner A. Surgery for adult polycystic liver disease. *Surgery* 1995; **117**: 272.
6. Ammori BJ, Jenkins BL, Lim PC, *et al.* Surgical strategy for cystic diseases of the liver in a western hepatobiliary center. *World J Surg* 2002; **26**: 462.
7. Fritzberg AR, Kasina S, Eshima D, Johnson DL. Synthesis and biological evaluation of technetium- 99m MAG3 as a hippuran replacement. *J Nucl Med* 1986; **27**: 111.
8. Taylor A Jr, Eshima D, Fritzberg AR, Christian PE, Kasina S. Comparison of iodine-131 OIH and technetium- 99m MAG3 renal imaging in volunteers. *J Nucl Med* 1986; **27**: 795.
9. Eshima D, Taylor A Jr. Technetium-99m mercaptoacetyltriglycine: update on the new 99mTc renal tubular function agent. *Semin Nucl Med* 1992; **22**: 61.
10. Esteves FP, Halkar RK, Issa MM, Grant S, Taylor A. Comparison of camera-based 99mTc-MAG3 and 24-hour creatinine clearances for evaluation of kidney function. *AmJRadiology* 2006; **187**: W316.
11. Taylor A, Manatunga A, Morton K, *et al.* Multicenter trial validation of a camera-based method to measure Tc-99m

mercaptoacetyltriglycine, or Tc-99m MAG3, clearance. *Radiology* 1997; **204**: 47.
12. Lerut J, Ciccarelli O, Rutgers M, *et al.* Liver transplantation with preservation of the inferior vena cava in case of symptomatic adult polycystic disease. *Transpl Int* 2005; **18**: 513.
13. Gonwa TA, Klintmalm GB, Levy M, *et al.* Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995; **59**: 361.
14. Gonwa TA, Jennings L, Mai ML, *et al.* Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl* 2004; **10**: 301.
15. Gonwa TA, Mai ML, Melton LB, *et al.* End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001; **72**: 1934.
16. Davis CL, Gonwa TA, Wilkinson AH. Pathophysiology of renal disease associated with liver disorders: implications for liver transplantation. Part I. *Liver Transpl* 2002; **8**: 91. (Review).
17. Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver–kidney transplantation: part II. *Liver Transpl* 2002; **8**: 193. (Review).
18. Ueno T, Barri YM, Netto GJ, *et al.* Liver and kidney transplantation for polycystic liver and kidney-renal function and outcome. *Transplantation* 2006; **82**: 501.
19. Pirenne J, Aerts R, Yoong K, *et al.* Liver transplantation for polycystic liver disease. *Liver Transpl* 2001; **7**: 238.
20. Genzini T, Marchini G, Chang A, *et al.* Rangel influence of pancreas transplantation alone on native renal function. *Transplant Proc* 2000; **38**: 1939.
21. Mazur MJ, Rea DJ, Griffin MD, *et al.* Decline in native renal function early after bladder-drained pancreas transplantation alone. *Transplantation* 2004; **77**: 844.
22. Piccoli GB, Mezza E, Picciotto G, *et al.* The grafted kidney takes over: disappearance of the nephrotic syndrome after preemptive pancreas-kidney and kidney transplantation in diabetic nephropathy. *Transplantation* 2004; **78**: 627.
23. Sanchez EQ, Martin AP, Ikegami T, *et al.* Sirolimus conversion after liver transplant: improvement in measured glomerular filtration rate after two years. *Transplant Proc* 2005; **37**: 4416.
24. Mostov KE. mTOR is out of control in polycystic kidney disease. *Proc Natl Acad Sci* 2006; **103**: 5247.
25. Wahl PR, Serra AL, Le Hir M, Molle KD, Hall MN, Wüthrich RP. Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD). *Nephrol Dial Transplant* 2006; **21**: 598.
26. Shillingford JM, Murcia NS, Larson C, *et al.* The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. *Proc Natl Acad Sci* 2006; **103**: 5466.