Urol Res (2005) 33: 376–379
DOI 10.1007/s00240-005-0495-1

INVITED REVIEW

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The role of preemptive liver transplantation in primary hyperoxaluria type 1

Received: 7 June 2005 / Accepted: 8 June 2005 / Published online: 13 November 2005

Abstract In primary hyperoxaluria the deficiency or mistargeting of hepatic alanine-glyoxylate aminotransferase (AGT) leads to the overproduction of oxalate resulting in hyperoxaluria and renal damage due to urolithiasis and/or nephrocalcinosis. Presently, the cure of the metabolic defect can be achieved only by liver transplantation. While for patients with end-stage renal disease combined hepatorenal transplantation is recommended, the concept of preemptive liver transplantation (PLTX), i.e. cure of the metabolic defect before renal damage occurs, has received considerable attention. Due to the heterogenous clinical course in PH1, optimal timing of PLTX is a matter of debate. Advocators of PLTX would consider a patient with a slowly declining GFR, reaching levels of 40–60 ml/min/1.73 m^2, as an ideal candidate, while others would continue medical treatment in these patients and opt for rapid combined liver-kidney transplantation if GFR reaches even lower levels. This review will discuss the background and rationale of PLTX and gives an update on 11 patients with PLTX who have been reported in the literature to date.

Keywords Primary Hyperoxaluria Type 1 · Liver transplantation · Preemptive · Treatment · Prognosis

Introduction

Primary hyperoxaluria types 1 and 2 (PH1 and PH2) are characterized by an increased production and urinary excretion of oxalate [1, 2]. In PH1, the enzyme defect (deficiency or mistargeting of hepatic alanine glyoxylate aminotransferase, AGT) is solely located in the liver and the clinical symptoms include (recurrent) urolithiasis and nephrocalcinosis. Without treatment there is a high risk of renal damage by urolithiasis and nephrocalcinosis which may result in renal insufficiency. With decreasing glomerular filtration rate (GFR) to about 50% of normal, oxalate clearance is severely reduced leading to systemic oxalate deposition (oxalosis) in slow turnover tissue such as bone, retina, blood vessels etc. According to earlier large surveys, end stage renal disease (ESRD) in PH1 had to be anticipated in 50% of patients by the age of 15 and in 80% by the end of the third decade [3, 4].

In recent years, the prognosis of PH1 has improved greatly because increased awareness and earlier diagnosis led to earlier treatment. Conservative treatment modalities include the administration of the AGT-coenzyme pyridoxine, crystallization inhibitors (citrate and orthophosphate), and, most importantly, a high fluid intake. Recent data suggest that with strict adherence to these treatments renal function can be maintained for prolonged periods [5, 6]. Despite this, some patients show a progressing course and some are even diagnosed at advanced stages when irreversible renal damage has already occurred. Furthermore, clinical deterioration may occur even in stable patients. If systemic oxalate deposition occurs at a low GFR, the pace of renal impairment is often also increased. The treatment of patients with ESRD is problematic as insufficient oxalate removal is achieved with conventional blood purification methods as a result of concomitant hepatic overproduction and mobilization of insoluble oxalate pools. Intensified, sometimes daily hemodialysis may be necessary and sometimes peritoneal dialysis and hemodialysis are combined. Mortality and morbidity is greatly increased in patients with PH1 in ESRD [7].

Options for organ transplantation in PH1 have undergone a considerable change within the last two decades. Early experience with isolated kidney

Dedicated to Professor Dirk E. Müller-Wiefel on occasion of his 60th birthday.

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transplantation (KTx) in PH1 was frustrating because of high recurrence rates and low patient survival as the metabolic defect was not corrected [8]. Although mortality after isolated KTx seems to have improved in recent years, high recurrence rates (despite optimised conservative treatment) remain problematic [9]. Nevertheless isolated KTx may be justified for individual patients with pyridoxine sensitivity or a slowly progressive course. Combined liver/kidney Tx (LKTx) is now viewed as the procedure of choice for patients (especially children) with PH1 on renal replacement therapy. The European Oxalosis Registry recently reported a 5 year patient survival of 79% and a 5-year graft survival of 71% [10]. Patients on dialysis for more than 2 years clearly had the worst prognosis, indicating the problems of systemic oxalosis. Other centers report a patient survival of 100% in selected patients [11], however, less optimistic results have also been reported for combined liver/kidney transplantation, especially in small children [12]. One specific problem is the mobilization of oxalate from slow turnover tissues that potentially threatens renal survival for prolonged periods (years), requiring conservative treatment and close follow-up.

Due to the potential risks of systemic oxalosis before and after isolated renal and combined liver/kidney transplantation, the concept of preemptive liver transplantation (PLTX) in PH1 has emerged [13–17]. The primary concept is to correct the metabolic defect (and eliminate the risk of systemic oxalosis) before advanced renal insufficiency occurs, allowing for the stabilization of renal function, abolishing or delaying the need for renal replacement therapy.

Ethical concerns apply in discussing PLTX [18]. Removal of an otherwise intact liver is necessary and short and long-term surgical complications (bleeding, graft thrombosis, bile duct complications) and the risks of chronic immunosuppression (infection, PTLT, nephrotoxicity) have to be anticipated.

The actual number of published patients undergoing PLTX is low, and of these only a proportion can be regarded as truly preemptive, that is, liver transplantation allowing the conservation of renal function for a sustained period of several years.

Patients

Table 1 summarizes the clinical data on published patients with PLTX. In these patients indications and entry criteria varied widely. For instance patient 6 represents a sequential combined liver/kidney transplantation. Two patients (patients 2 and 7) with advanced renal dysfunction could be stabilized and renal replacement therapy could be delayed for several years. Two patients underwent living related PLTX.

No perioperative mortality has been reported for the patients, although patient 7 died after 1 year. One patient required retransplantation due to surgical complications

Table 1 Published patients with PLTX

No.	Age at PLTX (years)	GFR (ml/min/1.73 m^2)	Clinical details	Follow-up	Comment (latest available update)	Reference
1	5	62	Aggressive urolithiasis	GFR 44 ml/min/1.73 m^2	Approaching ESRD 13 years after PLTX (2001)	[22]
2	1.8	15	Systemic oxalosis	Renal transplantation after 5.5 years	(2004)	[14]
3	8	70	Retransplantation with 8.6 years	GFR 55 ml/min/1.73 m^2 after 2 years		[23]
4	1.8	27	CRF, LRD	GFR 37 ml/min/1.73 m^2		[24]
5	38	30	Kidney transplant 250 days before	GFR 42.6 ml/min/1.73 m^2		[15]
6	17	-	Renal transplant after 6 weeks	Died after 1 year		[25]
7	9.8	27	Nephrocalcinosis	After 6 years hemodialysis followed by successful KTx	(2004)	[16, 17]
8	6	98	Nephrocalcinosis, FTT	GFR 84 ml/min/1.73 m^2 after 4 years		[16, 17]
9	3.3	82	Nephrocalcinosis, LRT	GFR 85 ml/min/1.73 m^2 after 4 years		[16, 17, 26]
10	2.8	54	Nephrocalcinosis	GFR 75 ml/min/1.73 m^2 after 8 years, normal growth	(2004)	[16, 17, 26]
11	2.5	-	Failure to thrive	GFR 93 ml/min/1.73 m^2		[26]

(patient 3). Patients 8 and 9 have been included in reports from two centres.

Discussion

The published results on PLTX indicate that a correction of the metabolic defect in PH1 is possible, and, if performed early enough, can preserve renal function over prolonged periods. It should be noted, however, that not all patients with PLTX have been published or included in registries, including patients with a good outcome as well as one with advanced renal failure who experienced further deterioration after the procedure and died (K. Latta, pers comm).

The ideal timing of PLTX has been the subject to repeated discussions. The original concept emerged as a way of preventing further progression of renal insufficiency in PH1. Individual patients can benefit from PLTX even with advanced chronic renal failure (as patients 2 and 7) showing either improving renal function or a significant delay before renal replacement therapy. In some instances, however, PLTX was performed to late and has to be viewed as a strategy of sequential combined transplantation. In defining PLTX, it should therefore be noted that indications and outcome of *late* PLTX (e.g. below a GFR of 30) may be different from PLTX at a higher GFR, due to the further compromise of residual function because of medication (calcineurin inhibitors, antibiotics) or perioperative complications, e.g. infection.

PLTX at a *normal* GFR (>80) is the other extreme, and has to be viewed equally critical in view of the potent non-toxic conservative treatment modalities available nowadays. Patients can be perfectly stabilized with conservative treatment and some authorities believe that with the avoidance of complications (non-compliance, vigorous fluid intake in times of intermittent dehydration), the risk of renal insufficiency can be delayed for many years if not even prevented. If ESRD is likely or occurs, an alternative approach in this view would be the immediate initiation and planning of combined liver/kidney transplantation, as patient and graft survival improve significantly if LKTx is performed within 2 years.

The group of patients with slowly progressive GFR, despite optimal treatment, and those with recurrent, "malignant" urolithiasis, have been viewed as ideal candidates for PLTX by some authors [19]. Because systemic oxalate disposal increases below a GFR of 40, it could be concluded that PLTX should be performed above this threshold (e.g. 40–60 ml/min/1.73 m^2). On the other hand, GFR may remain stable over long periods even within this range, or may decline rapidly so that no universal recommendation can be given. If one tends to discuss PLTX with the family, a GFR of 40–60 ml/min/1.73 m^2 seems to give sufficient time for preparation, e.g. for smaller children and infants that might be candidates for living-related liver segment Tx. Patients 4 and 10 are excellent examples for such a situation.

No clinical, biochemical or molecular markers to predict the clinical course in PH1 are as yet available. The natural history may vary even in families with identical biochemical and genetic profiles. Therefore, a recommendation for transplantation to correct the metabolic defect is difficult, especially concerning the optimal timing. The decision of whether or not to opt for PLTX may be influenced by personal experience (availability and success of a liver transplantation program locally; favorable or unfavorable success with transplantation or conservative management in individual patients, complications and others).

If the results of conservative management and combined LKTx improve even further, the use of PLTX will decrease. Successful strategies to prevent systemic oxalate disposal in ESRD (intensified dialysis, treatment with *Oxalaobacter* species, rapid combined LKTx and others) will also have an impact in the same direction. On the other hand, the technique, logistics and potential complications for combined hepatorenal transplantation are much more complex than for isolated LTx. In addition, the results of isolated liver transplantation are excellent nowadays, even in small children [20, 21]. A direct comparison between treatment modalities in PH1, i.e. the different transplantation strategies and conservative management, is not possible, although such data would help to define the best strategy. In addition, the tendency to not report unfavorable outcomes in either conservative treatment or transplantation make independent evidence recommendations difficult if not impossible, especially in rare disorders like PH1.

In summary, for patients with PH1 diagnosis and conservative treatment should be established as early as possible to optimize the long-term prognosis. ESRD and systemic oxalosis should be avoided. PLTX is able to correct the metabolic defect in PH1 and thereby improve renal outcome; however, the timing of this procedure remains a medical and ethical problem. For patients with ESRD, LKTx should be the preferred strategy unless arguments for isolated KTx are present, such as complete pyridoxine responsiveness. For patients approaching ESRD (GFR <30 ml/min/1.73 m^2), "late" PLTX may be able to stabilize the renal course despite immunosuppression, however, deterioration may also occur, resulting in the need for combined liver/kidney transplantation. Selected patients with a progressive loss of renal function or recurrent aggressive urolithiasis despite optimal conservative treatment seem to be the best candidates for PLTX.

In conclusion, PLTX is a powerful tool for the treatment of PH1 and the prevention of ESRD in this disorder. Risks associated with surgery and long-term immunosuppression have to be weighed against oxalosis related complications and morbidity, thus making patient selection and the ideal timing difficult. Advocators of PLTX would consider a patient with a slowly declining GFR, reaching levels of 40–60 ml/min/1.73 m^2, as an ideal candidate, while others would continue medical treatment in these patients and opt for rapid combined

transplantation if GFR reaches even lower levels. As long as a direct comparison of outcome data of these strategies are not available, evidence based recommendations are difficult to generate. Therefore, generally accepted policies on PLTX, preventing either over- or under use, are pending. Due to the rarity of the disorder, clinical care, including the decision for a transplantation procedure, should be in experienced specialist hands.

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