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Practical pediatric nephrology

Should liver transplantation be performed before advanced renal insufficiency in primary hyperoxaluria type 1?

Pierre Cochat[1] **and Karl Schärer**[2]

[1] Unité de Néphrologie Pédiatrique, Hôpital E Herriot and Université Claude Bernard, Lyon, France
[2] Sektion für pädiatrische Nephrologie, Universitäts-Kinderklinik, Heidelberg, Germany

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Abstract. Primary hyperoxaluria type 1 (PH1) is a rare recessive autosomal inborn error of glyoxylate metabolism leading to oxalate retention, the first target of which is the kidney. The disease is caused by a defect of the liver-specific peroxisomal enzyme alanine: glyoxylate aminotransferase. Patients with pyridoxine-resistant forms of PH1 usually require organ replacement therapy, i.e. liver transplantation to supply the deficient enzyme and/or kidney transplantation to replace the affected organ. The current experience of the management of PH1 has emphasized two main points: (1) end-stage renal failure must be avoided since it increases dramatically the risk of systemic involvement, (2) the correction of oxalate overproduction and organ overload requires the removal of the host liver. Practical attitudes towards these ideas are difficult to assess and an individualized strategy is therefore required. Isolated kidney transplantation should be limited to adult patients with late-onset and a mild course of the disease. The present experience of combined liver-kidney transplantation was gained mainly in adult patients with severe systemic involvement; the 3-year patient survival rate recently increased to 82%. This figure might be improved if the procedure were performed earlier while the glomerular filtration rate (GFR) is above 25 ml/min per 1.73 m^2. Isolated liver transplantation should be considered in carefully selected children with severe forms of pyridoxine-resistance (PH1) before GFR has dropped to less than 30 ml/min per 1.73 m^2; it seems to be indicated especially in the presence of a rapid decline of GFR in the preceding year. In two young children who underwent isolated liver transplantation in our units 4 years ago, renal function could be stabilized and severe extrarenal involvement prevented.

Key words: Primary hyperoxaluria type 1 – Oxalosis – Chronic renal failure – Inborn error of metabolism – Liver transplantation – Kidney transplantation

Correspondence to: P. Cochat, Unité de Néphrologie Pédiatrique, Hôpital E Herriot, 69437 Lyon, France

Introduction

Primary hyperoxaluria type 1 (PH1, McKusick 25990) is a rare autosomal recessive disorder characterized by increased urinary excretion of calcium oxalate, leading to recurrent urolithiasis, nephrocalcinosis and accumulation of insoluble oxalate throughout the body, called oxalosis. Although some patients do not survive the 1st year of life, others suffer from a less rapidly progressive condition and die in the 2nd or 3rd decade from systemic involvement [1].

PH1 is due to a functional defect of the liver-specific peroxisomal alanine: glyoxylate aminotransferase (AGT) [1, 2]. In two-thirds of homozygous patients, catalytic activity of the enzyme is absent: most have no immunoreactive AGT, whereas a minority have correctly located but inactive AGT. The remaining third of homozygous patients exhibit 3%–48% AGT catalytic activity but the enzyme is located in the mitochondria instead of the peroxisome. The resulting decreased transamination of glyoxylate to glycine leads to a subsequent increase in its oxidation to oxalate, which is a poorly soluble, non-degradable end-product. There is no obvious relationship between the level of hepatic AGT and the severity of the disease [1, 3].

Symptoms of the disease are present in half of the affected children before 5 years of age. End-stage renal disease (ESRD) is reached by the age of 15 years in 50% of PH1 patients; however, only 1%–2% of children with ESRD are affected by oxalosis [4, 5]. Most PH1 patients develop ESRD over a short period of time and infants usually have the most rapid course [6, 7]. When the glomerular filtration rate (GFR) falls to below 20–25 ml/min per 1.73 m^2, continuing overproduction of oxalate in the liver is combined with reduced oxalate excretion by the kidneys, leading to increasing oxalate stores of variable size in many organs, i.e. bones, heart, arteries, retina, nerves, etc. [3, 5, 8, 9].

The disease can be diagnosed by measurement of urine oxalate and glycolate excretion rates and by plasma oxalate measurement. The enzyme activity can be measured in a freshly frozen liver specimen taken by percutaneous biopsy [2, 5].

Theoretical basis of treatment

Inhibition of stone formation

Since the formation of calcium oxalate stones is the most frequent sign of PH1, therapeutic interventions should focus on the prevention of urolithiasis. Dietary restriction of oxalate-rich foods may be helpful [4], but the most efficient strategy is to reduce oxalate crystallization in the urine by lowering the calcium oxalate concentration. This can be achieved by a high fluid intake, supported by the use of calcium-oxalate crystallization inhibitors, i.e. sodium citrate, magnesium or phosphate [10]. Diuretics may also be useful to maintain high urine output. Although thiazides have the advantage of not increasing calcium excretion, their effect is compromised by progressive uraemia associated with decreased citrate excretion. In advanced chronic renal failure (CRF), frusemide might be used despite its calciuretic action [9, 10].

Renal replacement therapy

Haemodialysis and haemofiltration are unable to remove sufficient amounts of oxalate in ESRD patients. Kidney transplantation has been attempted since 1969 [11] and seems to be efficient for increasing the clearance of soluble oxalate [3]. However, since the biochemical defect is in the liver, overproduction of oxalate continues unabated. Although plasma oxalate levels are lower after kidney transplantation than in dialysed patients, they remain elevated and oxalate deposition in tissues, including the graft, continues posttransplant [4]. The high rate of urinary oxalate excretion originates from oxalate production as well as from oxalate deposits in tissues [12].

The amount of oxalate accumulated in the grafted kidney is variable and is not always related to the rate of clinical recurrence of the disease after kidney transplantation [13]. Some recipients develop oxalate stones or nephrocalcinosis in the kidney graft, others do not [14]. Data from the European Dialysis and Transplant Association Registry [15] showed that 3 years post kidney transplant, only 23% of living donor and 17% of cadaver kidney donor grafts were functioning, but the overall 1-year graft survival rate has improved in recent years; 26% of the recipients had died after 3 years (Fig. 1). In this series, neither time on dialysis nor age at start of renal replacement therapy (RRT) influenced the results. However, other factors such as initial dysfunction of the graft, the number of rejection episodes and the use of cyclosporine may endanger the graft survival [4, 14].

The long-term outcome of PH1 after kidney transplantation remains uncertain, with a 5- to 10-year patient survival rate ranging from 9% to 50%. Because it is not universally successful, kidney transplantation does not necessarily prevent the progression of skeletal and vascular complications either [14, 15, 16]. However, the chances of a successful transplant are improved if this is performed in the presence of a substantial residual renal function, i.e. a GFR greater than 25 ml/min per 1.73 m^2, and in the absence of important extrarenal involvement [5]. Good results have been reported by early performance of kidney transplantation using living-related donors and vigorous perioperative dialysis [17]; however, 3 out of 7 young patients with severe presentation of oxalosis reported by Katz et al. died after graft failure (17). In the European experience, living related donors should be avoided because the overall result is poor compared with other primary kidney disorders and is not better than with cadaver donors in PH1 [13, 15].

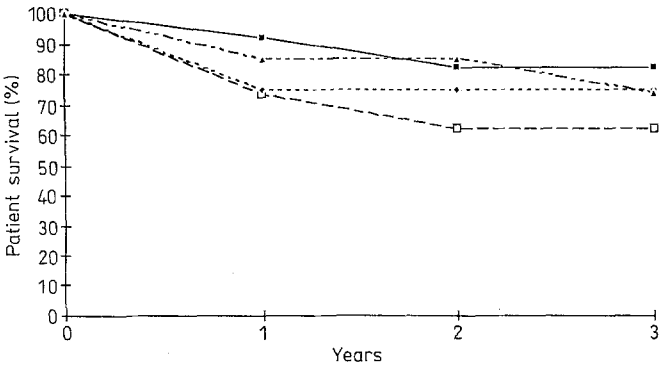


Fig. 1. Percentage patient survival: (1) after orthotopic liver transplantation in metabolic diseases before 1991 (◆) (n = 132) [23], (2) after combined liver/kidney transplantation in primary hyperoxaluria type 1 (PH1) patients before 1991 (□) (n = 32) [9, 12, 16, 27–33], (3) after combined liver/kidney transplants in PH1 patients in 1992 (■)(n = 39) (Second European Workshop, September 15 1992, Cambridge), (4) after isolated kidney transplantation in PH1 patients (▲)(n = 60) [15]

Enzyme therapy

Since pyridoxal phosphate is a cofactor of AGT, oral pharmacological doses of pyridoxine have been suggested for PH1 patients. However, urinary oxalate excretion may be reduced by this drug in some patients [5]. Since the deficiency of peroxisomal AGT is located in the liver [2], it seems logical to use liver transplantation as an enzyme replacement therapy. As long as the patients's own liver is present, the administration of AGT in any form or location, other than that in which it is required, would not be appropriate. This rules out the injection of AGT or the transplantation of carrier cells, as has been tried in some lysosomal storage diseases [3]. Although the liver is an excellent target organ for gene therapy, transfection of hepatocytes using retroviral vectors seems at present unlikely to correct the biochemical defect [18].

Liver transplantation

Rationale

Transplantation is considered to provide an adequate source of a deficient protein in a number of inborn errors of metabolism. The first disorders considered in this respect were associated with severe hepatic injury, such as type I glycogen storage disease [19, 20]. Liver replacement therapy (in the presence of a grossly normal hepatic structure and function) to correct a defect responsible for extrahepatic complications was first performed in homozygous familial hypercholesterolaemia [21].

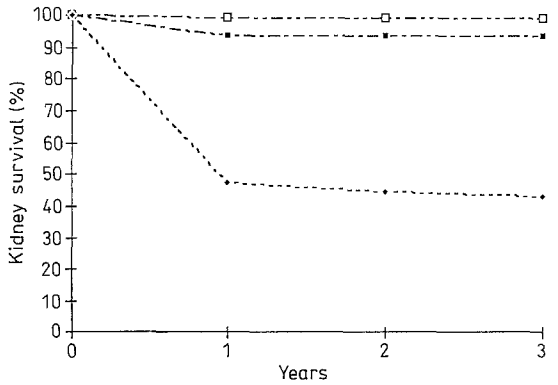


Fig. 2. Percentage kidney survival in living patients: (1) after orthotopic liver transplant in non-PH1 patients without hepatorenal syndrome (□) [26], (2) after combined liver/kidney transplant in PH1 patients (■) [9, 12, 16, 27–33], (3) after isolated kidney transplant in PH1 patients (◆) (data calculated from [15])

In patients with pyridoxine-resistant PH1, liver transplantation is able to supply the missing enzyme in its normal cellular and subcellular location [3, 16]. Before liver transplantation is considered, a liver biopsy is always needed to confirm the suspected AGT deficiency [9]. The ultimate goal of organ replacement in PH1 is to change a positive whole body accretion rate into a negative one by reducing endogenous oxalate synthesis and providing a good oxalate clearance. The liver is the only organ responsible for the detoxification of glyoxylate by AGT and therefore any form of enzyme replacement therapy is successful only when the deficient host liver is removed concomitantly [3, 5]. As a consequence, there is no rationale for auxiliary or partial liver transplantation. Moreover, heterotopic auxiliary liver transplantation is currently not recommended because of poor results and competition from the patient's own liver [16, 22].

Results

Metabolic diseases account for 5%–23% of all indications for liver transplantation, mainly in children. Some of these patients may require simultaneous grafts of other organs such as kidney or heart [20, 23, 24]. In the Cambridge/Kings series, PH1 comprises 16% of liver transplantation for metabolic disorders [24]. When orthotopic liver transplantation is considered in inborn errors of metabolism, the clinical status of these patients at the time of transplant is usually better than for other chronic hepatobiliary diseases and, in most series, the survival rate of patients with metabolic diseases is 6%–16% higher than in other groups [16, 19, 23, 25, 26].

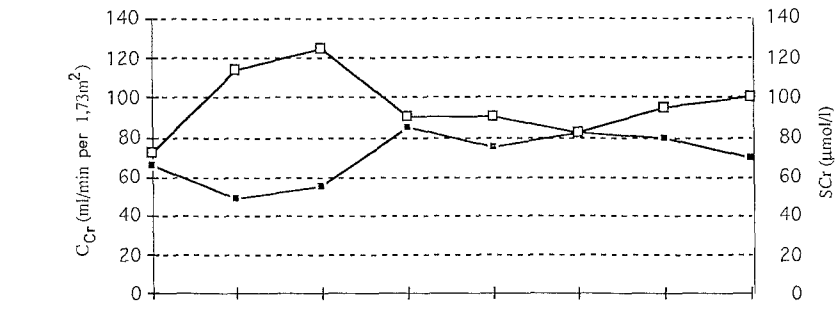
Since the first patient reported by Watts et al. in 1985 [27], more than 60 *combined liver/kidney transplants* have been performed worldwide in PH1 patients. Sufficient clinical data are so far available from 32 individual cases published before 1991 [9, 12, 16, 27–33]. The mean (± SD) age at onset was 7.8 ± 6.1 (range, 1–19) years and the age at ESRD was 17.0 ± 8.5 (range, 3–41) years. Nineteen cases (59%) have had one or more previous kidney transplant. The age at the time of combined liver/kidney transplant was 21.0 ± 8.6 (range, 4–45) years, after a period of 3.7 ± 2.6 years on RRT; 8 patients (25%) were younger than 15 years of age when the combined grafts were performed. The patient survival rate at 2 and 3 years after combined transplant was 62% (Fig. 1) and the kidney survival rate was 95% in living recipients (Fig. 2). This result is disappointing, but is should be borne in mind that it relates to ESRD patients with prolonged RRT for advanced systemic oxalosis. Recent (unpublished) data from the Second European Workshop on PH1 (September 16, 1992, Cambridge) exhibit a consistent improvement in patient survival rate that reaches 82% at 2 and 3 years posttransplant (Fig. 1). One would expect that this survival rate would increase further if combined liver/kidney transplantation is performed before ESRD is reached and extended oxalosis has developed [3]. However, the results will probably remain inferior to those observed in liver transplant patients with other inborn errors of metabolism because of the associated risk of kidney transplantation in PH1 [16, 23, 34].

Although synchronous liver/kidney transplantation seems to enhance the tolerance of the renal graft [9], combined transplantation bears the known risk of a decline of GFR observed in long-term liver transplant patients treated with cyclosporine (25%–35% after 1 year; 19%–39% after 3 years) [26, 35, 36]. After combined transplantation, the grafted kidney may be further damaged in PH1 patients by high amounts of oxalate released from the body stores, in addition to the usual causes of graft failure such as rejection, cyclosporine toxicity, etc. [16, 37]. Finally, the prognosis of PH1 patients undergoing combined transplantation after long periods of dialysis treatment is endangered by the increased risk of severe bone disease [38], heart disease, retinopathy and peripheral gangrene due to extensive arteriolopathy and subcutaneous calcinosis.

For these reasons, we believe that *isolated liver transplantation* is a first choice treatment for patients with PH1 prior to having reached an advanced stage of CRF [3, 16]. To our knowledge, four cases of isolated liver transplantation have been reported so far [28, 37, 39, 40].

McDonald et al. [37] described a 38-year-old man with a previous kidney transplant; because GFR decreased and oxalate deposition occurred in the graft, liver transplantation was performed 9 months after the kidney transplant. Seven months later, there was no evidence of oxalate crystals in the graft kidney and, 14 months after liver transplantation, creatinine clearance (C_{Cr}) had increased from 32 to 43 ml/min per 1.73 m^2. Jamieson et al. [28] performed an isolated liver transplant in a 17-year-old patient which was followed by kidney transplant 6 weeks later. The patient died after 1 year because of thromboembolic complications due to advanced oxalosis. These two isolated liver transplantations were performed in adult recipients whilst signs of severe extrarenal oxalosis and ESRD were already present.

Cochat et al. [39] reported a 5-year-old boy who suffered from recurrent urolithiasis (i.e. about 200 stones over 1 year) and who had experienced a rapid decline in GFR (16% within 1 year). He underwent isolated liver transplantation at a C_{Cr} of 65 ml/min per 1.73 m^2. Urinary oxalate excretion was normalized within a few days and



Months	0	6	12	18	24	30	36	42
UOx/UCr (mmol/mol)	866	43	61	61	54	69	62	64
ALAT (IU/l)	17	11	120	14	15	16	26	13
GGT (IU/l)	14	8	352	7	20	21	21	22

Fig. 3. Evolution of renal function [creatinine clearance (C_{Cr} ■), serum creatinine (*SCr* □)], [calcium oxalate excretion urinary oxalate (*UOx*)], urinary creatinine (*UCr*) and liver tests [transaminase (*ALAT*), gamma glutamyl transpeptidase (*GGT*)] in a child who underwent isolated liver transplantation. The immunosuppressive regimen consisted of prednisone and cyclosporine A. The patient experienced kidney dysfunction during the first 6 months post transplantation that was related to cyclosporine nephrotoxicity. The cyclosporine daily dosage was then tapered; this was responsible for a mild acute rejection of the liver by the end of the 1st year post transplant. This episode responded to steroids and subsequent immunosuppression included low-dose cyclosporine, prednisone and azathioprine

the graft function remained good despite an episode of mild acute rejection. Four years later, the liver tests were normal and the GFR remained stable (Fig. 3). A renal biopsy performed in the 7th month posttransplant revealed no crystals, but mild interstitial fibrosis; the radiological follow-up of the native kidneys showed a progressive reduction of nephrocalcinosis (Fig. 4). The child is now 9 years old and has no evidence of extrarenal involvement so far. Schürmann et al. [40] reported a girl with signs of severe PH1 and advanced renal insufficiency since the age of 6 weeks, complicated by bone disease at 1 year of age. The girl received a liver transplant at 22 months. Despite several medical and surgical post-transplant complications (bone fracture, retinopathy, cholangitis), she has since improved and the GFR is almost unchanged (serum creatinine 230 µmol/l at liver transplantation, 212 µmol/l after 4 years).

Although patients are not comparable, the expected results of liver transplantation alone should be better than for combined liver/kidney transplantation, since patients are usually younger and free of systemic oxalosis, and obviously the morbidity of associated kidney transplantation is not added.

Reversal of the complications of oxalosis by liver transplantation

Deposits of calcium oxalate in tissues can be remobilized or dissolved by decreasing the synthesis and/or increasing the clearance of oxalate [3]. Remobilization is probably a slow event which depends, among other factors, on the accessibility of the oxalate stores to the vascular system [3]. After combined transplantation, plasma oxalate returns to normal prior to urine oxalate excretion which may remain elevated up to 8 months post transplant. Oxalate crystals were shown to be washed out after plasma oxalate had returned to normal [39–41] and usually the remobilization of oxalate deposits from tissues parallels the improvement in GFR [10, 12, 16, 37]. Glycolate, which is not highly insoluble and does not accumulate, is excreted in normal amounts immediately after liver transplantation [3, 16, 27]. In contrast to isolated kidney transplantation, combined liver/kidney transplantation seems able to normalize oxaluria [29]. However, recurrent nephrocalcinosis or renal calculi have been reported that were not responsible for graft loss [9, 10]. We would advise combined transplantation only if the GFR has decreased to about 25 ml/min per 1.73 m^2, because at this level oxalate retention increases rapidly in all patients with CRF, independent of the presence of PH1 [8, 9]. It seems that even at this late stage other damaged organs besides the kidney, such as the heart or the skeleton, may benefit from enzyme replacement [9, 16, 33, 37].

Which transplant strategy for which patient?

Two main strategies for the management of patients with pyridoxine-resistant PH1 are currently proposed in the literature. Scheinman et al. [6] favour isolated kidney transplantation, preferably from living donors, after aggressive pre- and post-transplant dialysis, associated with high fluid intake, diuretic drugs and possibly phosphorus and magnesium [14, 17, 42]. In contrast, Watts and Mansell [5] pioneered combined liver/kidney transplantation and consider that PH1 patients should undergo this procedure [9, 12, 16, 27, 28]. However, the patients who have been treated by these two groups are difficult to compare as illustrated by the difference in median age when ESRD was reached: 7.6 years [6, 17] versus 28 years [16]. Consequently, it is impossible to establish uniform therapeutic guidelines from these experiences and an individualized strategy is required.

The modalities and timing of transplantation must depend on the severity of the disease and the risk of the transplant procedure [3]. One of the main difficulties is to evaluate the individual progression of PH1. Follow-up of plasma oxalate and GFR are the main criteria [16].

Early isolated kidney transplantation is apparently able to remove oxalate stores at least partially and to improve the patient's condition without liver transplantation [14, 37]. However, since the kidney is highly susceptible to oxalate damage following grafting, it seems preferable to perform isolated liver transplantation first as long as renal function is more or less preserved [3]. If liver precedes kidney transplantation in patients with advanced CRF [16], intercurrent dialysis procedures are unable to provide a negative oxalate accretion rate despite normalization of

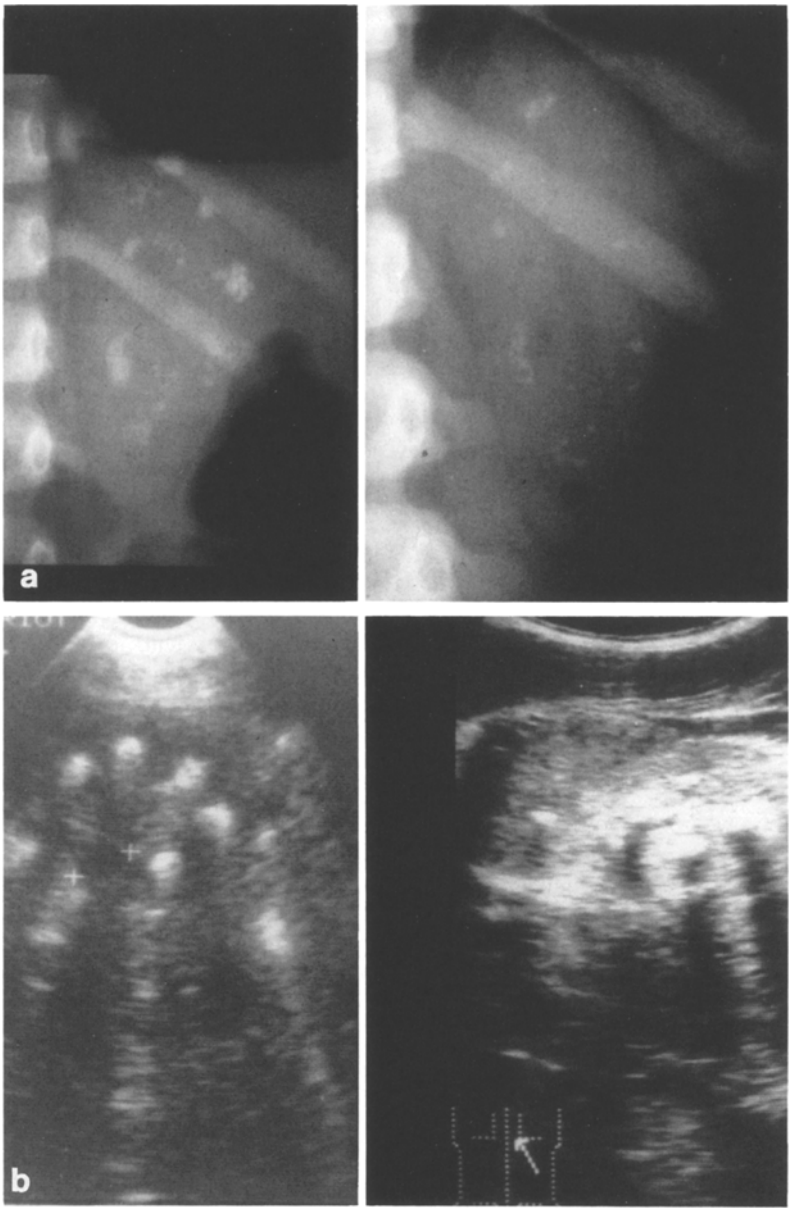


Fig. 4 a. Standard X-ray of the left native kidney before (*left*) and 3 years after (*right*) liver transplantation. **b** Ultrasonography of the native kidney before (*left*) and 3 years after (*right*) liver transplantation

oxalate synthesis, and kidney function might be further compromised by remobilized oxalate [3].

Consequently, *combined liver/kidney transplantation* seems to be the most reasonable procedure for treatment of PH1 patients with *advanced or terminal* kidney failure; in this situation the liver graft replaces the enzyme-deficient organ, while the renal graft substitutes for the function of the main target organ. The success of *combined transplantation* depends largely on the resumption of kidney function after surgery which is more endangered by the combined than by a single transplantation procedure [3, 43]. The primary obstacle for application of this strategy is the restricted number of potential biorgan donors for synchronous cadaver liver/kidney transplantation.

Figure 1 compares the *survival data* from orthotopic liver transplantation in metabolic diseases and from combined transplantation and isolated kidney transplantation in PH1 patients. It is interesting to note that a few years ago the best survival of PH1 patients was obtained with isolated kidney transplantation. It should be noted that combined liver/kidney transplantation was mainly practised in adult recipients who had reached ESRD long before the procedure (59% had received one or more previous kidney transplants). The current experience of specialized centres (unpublished report from the Second European Workshop, September 15 1992, Cambridge) has shown that the survival of patients who underwent combined transplantation during recent years has dramatically improved. In fact, mortality and morbidity following combined transplantation were mainly related to systemic oxalosis [9, 12, 16, 27–33]. Extrarenal complications occurred less frequently in survivors with combined transplants whose kidney survival rate is about 95% (Fig. 2). It should also be borne in mind that the quality of life of patients on long-term dialysis or after unsuccessful isolated kidney transplantation is poor, except in some cases with adult onset. Therefore, we believe that the treatment of choice for most children and young adults with pyridoxine-resistant PH1 is liver/kidney

transplantation. We speculate, however, that the young age of the recipients, the absence of primary liver insufficiency and the improved results of liver transplantation will finally yield a patient survival rate similar to that obtained in isolated liver transplantation for other metabolic diseases [23], with an adequate quality of life and rehabilitation [44].

Isolated liver transplantation in our opinion should only be considered if kidney function is more or less preserved, i.e. in those patients with a GFR above 30 ml/min per 1.73 m^2, but who show a rapid decline (10%–20% the preceding year). Such a procedure seems usually to be reserved for young patients with an aggressive course of disease and for patients with repeated episodes of urinary obstruction leading to rapid progression. However, it should be borne in mind that isolated liver or combined transplantation bears the long-term risk of a decline in renal function during cyclosporine A treatment [26, 35, 36]. Irrespective of the grafting procedure chosen, the question arises if native kidneys should be removed in PH1 at the time of combined or isolated kidney transplantation, since the risk of obstruction and/or infection is regarded as high; however, that kind of nephrectomy is known to be risky.

Supportive therapy

Several valuable adjuvant drugs exist which must be adjusted to the transplant strategy. Pharmacological doses of pyridoxine have been proposed in patients undergoing isolated kidney transplantation, since this cofactor may be efficient when the enzyme defect persists. In contrast, pyridoxine seems to be of minor importance in patients undergoing enzyme replacement by liver transplantation. After all three procedures (liver, kidney and combined transplantation), the kidney must be protected against the damage induced by the heavy oxalate load suddenly released from tissues. This may require daily repeated or continuous post-transplant haemodialysis or haemofiltration, forced fluid intake supported by diuretics and the use of crystallization inhibitors in view of the elevated calcium oxalate excretion in the post-transplant period [9, 10].

Conclusion

The present strategies for RRT in PH1 are still experimental. In the European experience, neither long-term dialysis nor kidney transplantation prevent the progression of the disabling disease. Replacement of the deficient hepatic enzyme AGT can be accomplished by *isolated liver transplantation.* By the concomitant removal of the host liver, oxalate production is stopped and oxalate overload reduced. Although the clinical experience with isolated liver transplantation is very limited, this procedure appears to be promising for pyridoxine-resistant patients with severe forms of PH1, before advanced CRF. In such cases, renal function might be stabilized by liver transplantation alone. *Combined liver/kidney transplantation* seems to improve the long-term outcome of PH1 in most patients with advanced CRF. The indication and the timing should be based mainly on repeated GFR measurements. We suggest that in the average patient, combined liver/kidney transplantation be considered when GFR has dropped to 40 ml/min per 1.73 m^2 and should actually be performed when GFR has reached 25 ml/min per 1.73 m^2. Rapid deterioration of GFR and severe extrarenal involvement are factors in favour of early liver/kidney transplantation. This procedure is also the treatment of choice in patients who have already reached ESRD. *Isolated kidney transplantation* should be limited to adult patients with mild forms of late-onset PH1. It is expected that in the future new methods may be developed to assess more precisely the rate of progression of the disease and thereby to determine the optimal timing of transplantation.

The presented strategy raises delicate ethical problems, because it implies that a functioning liver be removed in a child without hepatic failure or with advanced CRF. Arguments for such a decision must therefore rely on current knowledge of the outcome of severely affected patients and on the long-term results of various therapeutic schedules. Above all, the quality of life to be expected in the survivors should be taken into consideration.

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References

1. Danpure CJ (1991) Molecular and clinical heterogeneity in primary hyperoxaluria type 1. Am J Kidney Dis 17: 366–369
2. Danpure CJ, Jennings PR (1986) Peroxisomal alanine: glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett 201: 20–24
3. Danpure CJ (1991) Scientific rationale for hepato-renal transplantation in primary hyperoxaluria type I. Transplant Clin Immunol 22: 91–98
4. Latta K, Brodehl J (1990) Primary hyperoxaluria type I. Eur J Pediatr 149: 518–522
5. Watts RWE, Mansell MA (1990) Oxalate, livers, and kidneys. Combined renal and hepatic transplants transform the outlook in primary hyperoxaluria type I. B M J 301: 772–773
6. Scheinman JI, Najarian JS, Mauer SM (1984) Successful strategies for renal transplantation in primary oxalosis. Kidney Int 25: 804–811
7. Leumann EP, Niederwieser A, Fanconi A (1987) New aspects of infantile oxalosis. Pediatr Nephrol 1: 531–535
8. Morgan SH, Purkiss P, Watts RWE, Mansell MA (1987) Oxalate dynamics in chronic renal failure. Comparison with normal subjects and patients with primary hyperoxaluria. Nephron 46: 253–257
9. Watts RWE, Danpure CJ, De Pauw L, Toussaint C and the European Study Group on Transplantation in Hyperoxaluria Type 1 (1991) Combined liver-kidney and isolated liver-transplantation for primary hyperoxaluria type 1: the European experience. Nephrol Dial Transplant 6: 502–511
10. Lloveras JJ, Dupré-Goudable C, Rey JP, Sporer P, Durand D, Ton That H, Suc JM (1991) Expérience européenne de transplantation hépato-rénale dans l'hyperoxalurie primitive de type 1. Prévention de la récidive des dépots d'oxalate au niveau du rein. Presse Med 20: 2016–2018
11. Deodhar SD, Tung KSK, Zühlke V, Nakamoto S (1969) Renal homotransplantation in a patient with primary familial oxalosis. Arch Pathol 87: 118–124

12. Watts RWE, Calne RY, Rolles K, Danpure CJ, Morgan SH, Mansell MA, Williams R, Purkiss P (1987) Successful treatment of primary hyperoxaluria type 1 by combined hepatic and renal transplantation. Lancet II: 474–475
13. Watts RWE, Morgan SH, Purkiss P, Mansell MA, Baker LRI, Brown CB (1988) Timing of renal transplantation in the management of pyridoxine-resistant type 1 primary hyperoxaluria. Transplantation 45: 1143–1145
14. Katz A, Mauer SM (1992) Transplantation in primary hyperoxaluria type 1. Am J Med 92: 341–342
15. Broyer M, Brunner FP, Brynger H, Dykes SR, Ehrich HH, Fassbinder W, Geerlings W, Rizzoni G, Selwood NH, Tufveson G, Wing AJ (1990). Kidney transplantation in primary oxalosis: data from the EDTA registry. Nephrol Dial Transplant 5: 332–336
16. Watts RWE, Morgan SH, Danpure CJ, Purkiss P, Calne RY, Rolles K, Baker LRI, Mansell MA, Smith LH, Merion RM, Lucey MR (1991) Combined hepatic and renal transplantation in primary hyperoxaluria type 1: clinical report of 9 cases. Am J Med 90: 179–188
17. Katz A, Kim Y, Scheinman JI, Najarian JS, Mauer SM (1989) Long-term outcome of kidney transplantation in children with oxalosis. Transplant Proc 21: 2033–2035
18. Friedmann T (1991) Approaches to human gene therapy. In: Schaub J, Van Hoof F, Vis HL (eds) Inborn errors of metabolism. Nestlé Nutrition Workshop Series, vol. 24. Raven, New York, pp 275–282
19. Cochat P, Guibaud P (1991) Principles of organ transplantation in inborn errors of metabolism. Transplant Clin Immunol 22: 73–82
20. Malatack JJ, Finegold DN, Iwatsuki S, Shaw BW, Gartner JC, Zitelli BJ, Roe T, Starzl TE (1983) Liver transplantation for type 1 glycogen storage diseases. Lancet I: 1073–1075
21. Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS (1984) Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. N Engl J Med 311: 1658–1664
22. Terpstra OT, Reuvers CB, Schlam SW (1989) Auxiliary heterotopic liver transplantation. Transplantation 45: 1003–1007
23. Gordon RD, Todo S, Tzakis AG, Fung JJ, Stieber A, Staschak SM, Iwatsuki S, Starzl TE (1991) Liver transplantation under cyclosporine: a decade of experience. Transplant Proc 23: 1393–1396
24. Cohen AT, Mowat AP, Bhaduri BH, Noble-Jamieson G, Williams R. Barnes, Calne RY (1991) Liver transplantation for inborn errors of metabolism and genetic disorders. In: Schaub J, Van Hoof F, Vis HL (eds) Inborn errors of metabolism; Nestlé Nutrition Workshop Series, vol. 24. Raven, New York, pp 213–222
25. Bismuth H, Castaing D, Ericzon BG, Otte JB, Ringer B, Rolles K, Sloff MJH (1991) European liver transplant registry: updating 30.06.91. Sandoz (ed), Paris
26. Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB (1991) Long term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome. Experience in 300 patients. Transplantation 51: 428–430
27. Watts RWE, Calne RY, Williams R, Mansell MA, Veall N, Purkiss P, rolles K (1985) Primary hyperoxaluria (type 1): attempted treatment by combined hepatic and renal transplantation. Q J Med 57: 697–703
28. Jamieson NV, Watts RWE, Evans DB, Williams R, Calne RY (1991) Liver and kidney transplantation in the treatment of primary hyperoxaluria. Transplant Proc 23: 1557–1558
29. Polinski MS, Dunn S, Kaiser BA, Schulman SL, Wolfson BJ, Elfenhein IB, Baluarte HJ (1991) Combined liver-kidney transplantation in a child with primary hyperoxaluria. Pediatr Nephrol 5: 332–334
30. Jouvet P, Hubert P, Jan D, Niaudet P, Beringer A, Narcy C, Daudon M, Broyer M, Révillon Y (1991) Transplantation hépatique et rénale dans le traitement de l'hyperoxalurie de type 1. Arch Fr Pediatr 48: 637–639
31. Ruder H, Otto G, Schutgens RBM, et al. (1991) Excessive urinary oxalate excretion after combined renal and hepatic transplantation for correction of hyperoxaluria type 1. Eur J Pediatr 150: 56–58
32. De Pauw L, Gelin M, Danpure CJ, Vereerstraeten P, Adler M, Abramowicz D, Toussaint C (1990) Combined liver-kidney transplantation in primary hyperoxaluria type 1. Transplantation 50: 866–887
33. Rodby RA, Tyszka TS, Williams JW (1991) Reversal of cardiac dysfunction secondary to type 1 primary hyperoxaluria after combined liver-kidney transplantation. Am J Med 90: 468–504
34. Cuervas-Mons V (1986) An analysis of the early causes of death in 40 consecutive cases. Hepatology 6: 495–501
35. McDiarmid SV, Ettenger RB, Fine RN, Busutill RW, Ament ME (1989) Serial decrease in glomerular filtration rate in long-term pediatric liver transplantation survivors treated with cyclosporine. Transplantation 47: 314–318
36. Andrews WA, Arant BS, Byock B, Gray S, Schlatter MG, Coulin C (1991) The effect of cyclosporine A on long-term renal function in pediatric liver recipients. Transplant Proc 23: 1452–1453
37. McDonald JC, Landreneau MD, Rohr MS, De Vault GA Jr (1989) Reversal by liver transplantation of the complications of primary hyperoxaluria as well as the metabolic defect. N Engl J Med 321: 1100–1103
38. Porayko MK, Wiesner RH, Hay JE, Krom RAF, Dickson ER, Beaver S, Schwerman L (1991) Bone disease in liver transplant recipients: incidence, timing, and risk factors. Transplant Proc 23: 1462–1465
39. Cochat P, Faure JL, Divry P, Danpure CJ, Descos B, Wright C, Takvorian P, Floret D (1989) Liver transplantation in primary hyperoxaluria type 1. Lancet I: 1142–1143
40. Schürmann G, Schärer K, Wingen AM, Otto G, Herfarth C (1990) Early liver transplantation for primary hyperoxaluria type 1 in an infant with chronic renal failure. Nephrol Dial Transplant 5: 825–827
41. Watts RWE (1990) Treatment of renal failure in the primary hyperoxalurias. Nephron 56: 1–5
42. Scheinman JI (1991) Primary hyperoxaluria: therapeutic strategies for the 90's. Kidney Int 40: 389–399
43. Ellis D, Avner ED, Starzl TE (1986) Renal failure in children with hepatic failure undergoing liver transplantation. J pediatr 108: 393–398
44. Bonsel GJ, Essink-Bot ML, Klompmaker IJ, Sloof MJH (1992) Assessment of the quality of life before and following liver transplantation. Transplantation 53: 796–800

Comment

The idea of correcting the metabolic defect in primary hyperoxaluria type 1 (PH1) by liver transplantation, *before* renal failure has occurred, is tempting. Indeed, if sufficient organs were available and liver transplantation was a safe procedure, no one would question this approach. Performing a total hepatectomy in a paediatric patient whose liver function is normal in every respect constitutes a major decision and requires strict criteria. These are not easy to define, since renal function in patients with PH1 does *not* decline at a predictable rate. Indeed, it may remain stable over several years or even temporarily improve, but may also deteriorate abruptly following an episode of dehydration or obstruction. The authors cannot easily overcome this fundamental problem. While they consider isolated liver transplantation to represent a first choice treatment for patients prior to having reached an advanced stage of