Pediatr Nephrol (2010) 25:2359–2362
DOI 10.1007/s00467-010-1593-z

BRIEF REPORT

Excellent renal function and reversal of nephrocalcinosis 8 years after isolated liver transplantation in an infant with primary hyperoxaluria type 1

Mónica Galanti · Angélica Contreras

Received: 24 May 2009 / Revised: 9 June 2010 / Accepted: 10 June 2010 / Published online: 14 July 2010

Abstract Primary hyperoxaluria type 1 (PH-1) is a rare autosomal recessive disease caused by the absence or deficiency of the liver-specific intermediary metabolic enzyme alanine glyoxylate aminotransferase. The prognosis of this metabolic disease is poor. Theoretically, the primary metabolic defect can be cured by liver transplantation. However, controversy exists around the age and stage of the disease that liver transplantation should be performed. We report on a patient who presented at the early age of 2 months with nephrocalcinosis. Isolated liver transplantation was performed at the age of 21 months. Eight years later, the estimated glomerular filtration rate was 85 ml/min/1.73 m^2, and imaging studies did not reveal nephrocalcinosis. This case report supports the strategy of early isolated liver transplantation in patients with PH-1.

Keywords Primary hyperoxaluria · Alanine glyoxylate aminotransferase · Oxalosis · Epidemiology · Transplantation · Treatment · Timing · Perioperative care

M. Galanti · A. Contreras
Pediatric Nephrology, Roberto del Río Hospital,
Santiago, Chile

M. Galanti (✉)
Unidad de Nefrourología, Servicio de Pediatría,
Hospital Roberto del Río,
Santiago, Chile
e-mail: monicagalanti@gmail.com

Introduction

Hyperoxalurias are a group of metabolic disorders of oxalate metabolism that lead to renal and systemic damage through the deposition of oxalate crystals into tissues. They can be classified, according to etiology, into genetic or primary hyperoxalurias (PH) and secondary or acquired hyperoxalurias. PH can further be classified into type I (PH-1) and type II (PH-2), according to the enzyme affected [1–3]. In PH-1, the disorder is due to the absence, deficiency, or mistargeting of liver alanine glyoxylate aminotransferase (AGT), and in PH-2, the disorder is caused by deficiency of glyoxylate reductase/hydroxypyruvate reductase (GR/GDH) [3–5]. There is also a group of patients that present with clinical features of hyperoxaluria in whom hepatic AGT and GR/GDH are normal, and pyridoxine deficiency and malabsorption are excluded, suggesting the existence of at least one more type of PH, not 1 or 2, with the familial pattern of an inherited disorder [3, 5].

The clinical spectrum of PH-1 is very large, ranging from early nephrocalcinosis and severe renal failure in infancy during the first year of life to occasional urolithiasis. The infantile form often presents as a life-threatening condition because of rapid progression to end-stage renal disease (ESRD) before the age of 5 years [2, 3, 5, 6].

Early diagnosis and treatment are essential to prevent renal failure and general oxalosis [3, 5, 7–9], with early transplantation being—theoretically—the best cure. However, because of the operative risk and questionable long-term results [3, 5, 10], this strategy is still controversial.

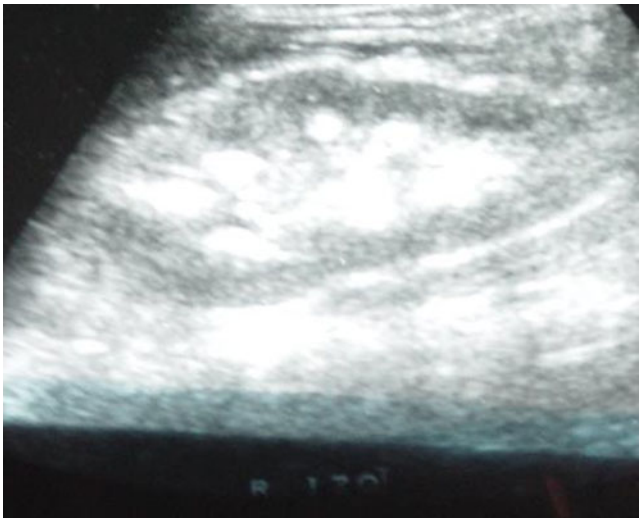

Fig. 1 Ultrasonography at 2 months of life

Here, we describe our long-term observation of an infant with PH-1 who presented with nephrocalcinosis at the age of 2 months and in whom preemptive liver transplantation was performed at the age of 21 months and at an estimated glomerular filtration rate (GFR) of 61 ml/min/1.73 m^2.

Case report

Pre-transplant course

The patient was a male born to consanguineous parents. A sister had died at the age of 8 months from acute renal failure secondary to diarrhea. Post-mortem examination demonstrated nephrocalcinosis and systemic signs of oxalosis, which then raised the possibility of primary hyperoxaluria. Because of the family history, a sonographic study was performed on our patient at age 2 months, which revealed bilateral nephrocalcinosis (Fig. 1).

PH-1 was confirmed in the Mayo Clinic by increased 24-h urinary oxalate (166 mg/1.73 m^2), glycerate 25 μg/mg (normal value<19 μg/mg), and glycolate 201 μg/mg (normal value<70 μg/mg). Testing of a 24-h urine collection reveal oxaluria at 7.7 mg/dl (0.55 mg/kg) and an oxalate/creatinine ratio of 0.4 (normal value 0.02–0.04). Plasma creatinine and nitrogen levels were 0.4 and 4 mg/dl, respectively. Clearance creatinine calculated with the Schwartz formula was 65 ml/min/1.73 m^2 at the age of 2 months [11]. There was slight microhematuria, and the calcium/creatinine ratio was 0.002. Uric acid, plasma bicarbonate, electrolytes, and hepatic function were normal. Following diagnosis, the infant was started on fluid therapy with 2–3 l/m^2, which was fortunately well-tolerated. Infectious diseases required intravenous fluid therapy several times. Therapy to inhibit calcium crystallization was started right from the beginning with sodium citrate 0.15 g/kg per day and magnesium 500 mg/m^2/day. The patient also received pyridoxine 300 mg/m^2/day. After 3 weeks of pyridoxine, the 24-h oxaluria was 351 mg/1.73 m^2, and the pyridoxine dose was adjusted to 400 mg/m^2/day. After 3 months of treatment, an accident occurred with urethra catheterization, and we were unable to obtain the urine collection. Pyridoxine was discontinued with the elevation of the 24-h oxaluria from 166 to 351 mg/1.73 m^2.

Post-transplant course

The patient underwent a liver transplantation at the age of 21 months and a serum creatinine of 0.6 mg/dl, an estimated clearance of 61 ml/min/1.73 m^2, and bilateral nephrocalcinosis. Segment II and III from a deceased donor liver were transplanted. Immunosuppressive therapy consisted of cyclosporine A, azathioprine, prednisone, and anti-CD25 as induction. Five days after transplantation, the patient experienced liver dysfunction, and liver biopsy showed acute allograft rejection, which responded well to a change in the immunosuppressive therapy to tacrolimus and mycofenolate. Sodium citrate and fluid therapy were maintained. After transplantation, urinary oxalate excretion was normalized within 3 months, and the oxalate/creatinine ratio decreased from 0.4 to 0.07 ng/mg. Twelve-months post-transplantation, the oxalate/creatinine ratio was 0.022. We did not have possibility for follow-up.

Radiological and ultrasound follow-up of the kidneys revealed a progressive reduction of nephrocalcinosis, showing normal kidneys without nephrocalcinosis 8 years after transplantation (Fig. 2). At the age of 7 years, the patient was hospitalized twice because of two episodes of

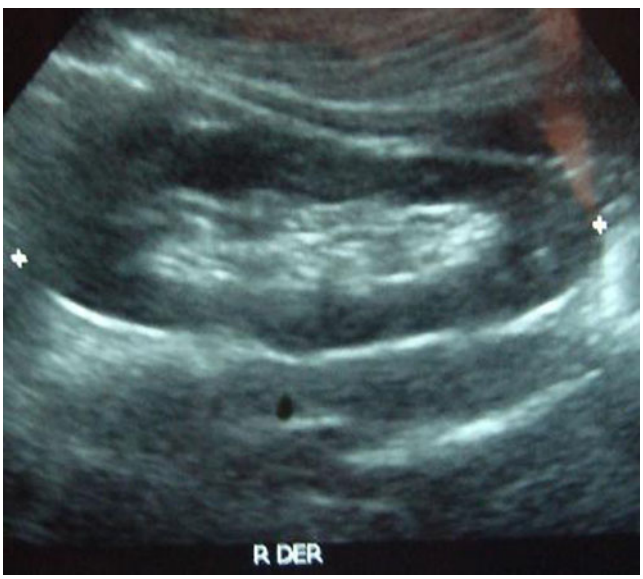

Fig. 2 Right and left kidney 8 years after transplant

febrile dehydration following pleuroneumonia and diarrhea. On these occasions, the serum creatinine was temporally elevated up to 1.5 mg/dl, but normalized after intravenous rehydration. Eight years after transplantation, his renal function has been maintained, with a calculated clearance of 85 ml/min/1.73 m^2 and with serum creatinine of 0.9 mg/dl. There were no signs of nephrocalcinosis at that time, and no evidence of extra renal involvement, with normal growth and psychomotor development. Liver function and liver ultrasonography results have been excellent throughout the intervening years.

Discussion

PH-1 is the most common form of PH inherited with an autosomal recessive pattern. In this disorder, the liver enzyme AGT is either absent or inactive, leading to the accumulation of oxalate, which is excreted by the kidneys, and to nephrolithiasis, nephrocalcinosis, ESRD, and oxalate accumulation in other organs.

The recommended therapy to prevent these manifestations is the maintenance of high fluid intake, pyridoxine supplements in those who are pyridoxine responsive [3, 12, 13], and the use of potassium or sodium citrate or neutral orthophosphate. Organ transplantation as either preemptive liver transplantation or combined liver/kidney transplantation provides a chance to 'heal' the genetic defect. It is still controversial whether, and if so, when an isolated liver transplantation or a combined liver/kidney transplantation should be performed [3, 5, 14–20]. When the GFR falls below 30–50 ml/min/1.73 m^2, plasma oxalate reaches the critical saturation point, resulting in oxalate deposition in different organs (a feature named systemic oxalosis) [3, 5, 7, 21]. With this in mind, early isolated liver transplantation should be the treatment of choice in PH-1. However, the operative risk of transplantation [3, 5, 22] as well as disappointing long-term results [3, 23] have been used as arguments against early liver transplantation.

The timing and strategy of transplantation depends upon local availability, balance of risk, and patient choice. It is accepted that combined kidney/liver transplantation is the optimal treatment if the kidney disorder is already advanced. The European experience is the best documented [24]. Transplantation is most successful, even in infants, when performed before generalized oxalosis [3, 5, 10, 22, 23].

Although isolated liver transplantation before stage 3 of chronic kidney disease is an attractive alternative, it is not practiced more frequently despite its recommendation because of the lack of suitable patients with sufficiently conserved renal function at the time of diagnosis.

Our patient received an isolated liver transplantation at an early state of chronic kidney disease (CKD) due to testing at an early age because of a sister who previously presented the disease and, consequently, an early diagnosis. He received a pediatric liver transplant at the age of 21 months, at which time he had a creatinine clearance of 61 ml/min/1.73 $m^2$and no signs of general oxalosis. During the long-term post-transplantation follow-up—8 years—we documented a regression of nephrolcalcinosis and stable, good renal function. His current serum creatinine of 0.9 mg/dl and an estimated GFR of 85 ml/min/1.73 m^2 do not exclude CKD stage 1; however, the long-term improvement in renal function despite severe episodes of dehydration and the disappearance of nephrocalcinosis, as evidenced in the imaging controls, demonstrates the ongoing preventive and healing potential of early liver transplantation. The quick normalization of oxalate excretion also demonstrates that liver transplantation had been performed before generalized oxalosis, which may be why our long-term results are better than those sometimes reported in children with more advanced CKD [3, 10, 22, 23]. The patient's liver function 8 years after transplantation is characterized by normal serum bilirubin and liver enzyme levels. At the last control, gamma-glutamyltranspeptidase and the transaminases glutamyl oxaloacetic and glutamyl pyruvic were 11, 33, and 18 IU, respectively; alkaline phosphatase was 229 IU. Serum albumin and prothrombin were 4.6 and 104%; normal blood lipids and serum ammonia were 57.2 μmol/l. The patient currently receives tacrolimus 3 mg every 12 h as monotherapy.

In conclusion, the ethical decision to perform preemptive liver transplantation can only be made on a case to case basis. Timing and strategy depends on the parents/patients wish, local availability, and a balancing of risks. Our experience supports the strategy of very early preemptive liver transplantation if the family agrees and optimal conditions for organ transplantation are present.

References

1. Danpure CJ, Purde PE (1995) Primary hyperoxaluria. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular basis of inherited disease. McGraw-Hill, New York
2. Hoppe B, Beck BB, Milliner DS (2009) The primary hyperoxalurias. Kidney Int 75:1264–1271
3. Leumann E (1999) Fifth Workshop on Primary Hyperoxaluria. Nephrol Dial Transplant 14:2784–2789
4. Johnson SA, Rumsby G, Cregeen D, Hulton SA (2002) Primary hyperoxaluria type 2 in children. Pediatr Nephrol 17:597–601
5. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO (2006) Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol 21:1075–1081
6. Khoo JJ, Pee S, Kamaludin DP (2006) Infantile primary hyperoxaluria type 1 with end stage renal failure. Pathology 38:371–374

7. Bobrowski AE, Langman CB (2006) Hyperoxaluria and systemic oxalosis: current therapy and future directions. Expert Opin Pharmacother 7:1887–1896
8. Leumann E, Hoppe B, Neuhaus T, Blau N (1995) Efficacy of oral citrate administration in primary hyperoxaluria. Nephrol Dial Transplant 10[Suppl 8]:14–16
9. Munir WM, Sharma MC, Li T, Dealba F, Goldstein DA (2004) Retinal oxalosis in primary hyperoxaluria type 1. Retina 24:974–976
10. Brinkert F, Ganschow R, Helmke K, Harps E, Fischer L, Nashan B, Hoppe B, Kulke S, Muller-Wiefel DE, Kemper MJ (2009) Transplantation procedures in children with primary hyperoxaluria type 1: outcome and longitudinal growth. Transplantation 87:1415–1421
11. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
12. Monico CG, Rossetti S, Olson JB, Milliner DS (2005) Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int 67:1704–1709
13. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH (1994) Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med 331:1553–1558
14. Ellis SR, Hulton SA, McKiernan PJ, de Ville de Goyet J, Kelly DA (2001) Combined liver-kidney transplantation for primary hyperoxaluria type 1 in young children. Nephrol Dial Transplant 16:348-354
15. Millan MT, Berquist WE, So SK, Sarwal MM, Wayman KI, Cox KL, Filler G, Salvatierra O Jr, Esquivel CO (2003) One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria: A single-centre experience. Transplantation 76:1458–1463
16. Kavukçu S, Türkmen M, Soylu A, Kasap B, Oztürk Y, Karademir S, Bora S, Astarcioğlu I, Gülay H (2008) Combined liver-kidney transplantation and follow-up in primary hyperoxaluria treatment: Report of three cases. Transplant Proc 40:316–319
17. Grewal HP, Brady L, Cronin DC 2nd, Loss GE, Siegel CT, Oswald K, Fisher JS, Bruce DS, Aronson AJ, Woodle ES, Millis JM, Thistlethwaite JR, Newell KA (2000) Combined liver and kidney transplantation in children. Transplantation 70:100–105
18. Gagnadoux MF, Lacaille F, Niaudet P, Revillon Y, Jouvet P, Jan D, Guest G, Charbit M, Broyer M (2001) Long term results of liver-kidney transplantation in children with primary hyperoxaluria. Pediatr Nephrol 16:946–950
19. Rosenblatt GS, Jenkins RD, Barry JM (2006) Treatment of primary hyperoxaluria type 1 with sequential liver and kidney transplants from the same living donor. Urology 68:e7–e8
20. Nissel R, Latta K, Gagnadoux MF, Kelly D, Hulton S, Kemper MJ, Ruder H, Söderdahl G, Otte JB, Cochat P, Roquet O, Jamieson NV, Haffner D (2006) Body growth after combined liver-kidney transplantation in children with primary hyperoxaluria type 1. Transplantation 82:48–54
21. Broyer M, Jouvet P, Niaudet P, Daudon M, Revillon Y (1996) Management of oxalosis. Kidney Int Suppl 53:S93–S98
22. Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben-Ari Z, Bar-Nathan N, Zehavi I, Dinari G, Mor E (2001) Primary hyperoxaluria type 1: Improved outcome with timely liver transplantation: A single-center report of 36 children. Transplantation 72:428–432
23. Nolkemper D, Kemper MJ, Burdelski M, Vaismann I, Rogiers X, Broelsch CE, Ganschow R, Müller-Wiefel DE (2000) Long-term results of pre-emptive liver transplantation in primary hyperoxaluria type 1. Pediatr Transplant 4:177–181
24. Jamieson NV, European PHI Transplantation Study Group (2005) A 20-year experience of combined liver/kidney transplantation for primary hyperoxaluria (PH1): the European PH1 transplant registry experience 1984-2004. Am J Nephrol 25:282–289