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WORD COUNT	2641	TIME SUBMITTED	27-DEC-2022 11:14AM
		PAPER ID	94400993

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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 79465

Manuscript Type: CASE REPORT

Effect of liver transplantation with primary hyperoxaluria type 1: Five case reports and review of literature

Wang XY *et al*. LT's effect in PH1

Abstract

BACKGROUND

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disease stemming from a deficiency in liver-specific alanine-glyoxylate aminotransferase, resulting in increased endogenous oxalate deposition and end-stage renal disease (ESRD). Organ transplantation is the only effective treatment, however, its approach and timing remain controversial.

CASE SUMMARY

We retrospectively analyzed 5 patients diagnosed with PH1 from the Liver Transplant Center of the Beijing Friendship Hospital from March 2017 to December 2020. Our cohort included 5 patients (4 males and 1 female). The median age at onset was 4.0 years (range: 1.0-5.0), age at diagnosis was 12.2 years (range: 6.7-23.5), age at liver transplantation (LT) was 12.2 years (range 7.0-25.1), and the follow-up time was 26.3 mo (range: 12.8-40.1). All patients had delayed diagnosis and three had progressed into ESRD by the time they were diagnosed. Two patients received preemptive LT (pre-LT); their estimated glomerular filtration rate (eGFR) was maintained > 120 mL/min/1.73 m^2, indicating a better prognosis. Three patients received sequential liver and kidney transplantation. After transplantation, serum and urinary oxalate decreased, and liver function recovered. At the last follow-up, the eGFRs of the latter three patients were 179, 52, and 21 mL/min/1.73 m^2.

CONCLUSION

Different transplantation strategies should be adopted for patients based on their renal function stage. Pre-LT offers a good therapeutic approach for PH1.

Key Words: Primary Hyperoxaluria type 1; Liver transplantation; Combined liver and kidney transplantation; Sequential liver and kidney transplantation; Renal calculi; End-stage renal disease; Case reports

Wang XY, Zeng ZG, Zhu ZJ, Wei L, Qu W, Liu Y, Tan YL, Wang J, Zhang HM, Shi W, Sun LY. Effect of liver transplantation with primary hyperoxaluria type 1: Five case reports and review of literature. *World J Clin Cases* 2022; In press

Core Tip: Primary hyperoxaluria type 1(PH1) is a rare autosomal recessive disease, resulting in increased endogenous oxalate deposition and end-stage renal disease. Organ transplantation is the only effective treatment, however the approach and timing are controversial. To investigate the effect and timing of liver transplantation (LT) for PH1, we retrospectively analysed 5 patients. The conclusion is LT can treat PH1, different transplantation strategies should be adopted for patients with different renal function stages. Pre-LT is a more appropriate treatment.

INTRODUCTION

Primary hyperoxaluria (PH) is a rare autosomal recessive disease with three subtypes. A deficiency of liver-specific alanine-glyoxylate aminotransferase (AGT), resulting in increased endogenous oxalate deposition, resulting in hyperoxaluria[1,2]. Because of the rarity and high rate of misdiagnosis of this condition, most patients present with existing end-stage renal disease (ESRD). Based on existing literature, organ transplantation is the only effective treatment for PH[3]. Liver transplantation (LT), as one of the treatments for genetic metabolic diseases, can result in partial or full remission, and prevent metabolic crises[4]. Since 2013, more than 200 cases of genetic metabolic diseases have been treated at our LT center. Some of these diseases included abnormal organic acid metabolism[5], urea cycle disorder, and PH. The surgeries performed included living donor LT, post-mortem organ donation and cross-auxiliary LT[6,7]. The following is a experience in the Beijing Friendship Hospital liver transplantation center of five cases with PH1 seen from 2017 to 2020. In this report, we provide data on quantified oxalic acid (OA) concentrations in serum and urine, which

have been rarely reported in the literature, and discuss the timing and effects of transplantation.

CASE PRESENTATION

Chief complaints

Case 1: Bilateral renal calculi for 2 years, and PH1 diagnosis for 7 mo.

Case 2: Bilateral renal calculi for 22 years, nausea and vomiting for 1 year, and PH1 diagnosis for 7 mo.

Case 3: Bilateral renal calculi for 15 years and PH1 diagnosis for 2 mo.

Case 4: Bilateral renal calculi for 11 years.

Case 5: Bilateral renal calculi for 5 years and decreased urine output for 16 d.

History of present illness

Case 1: Two years ago, bilateral renal calculi were identified by physical examination; there were no specific symptoms and no treatment was prescribed. One month ago, the patient visited our hospital for analysis of gout/calculus factor in urine which suggested oxaluria; genetic testing suggested PH1.

Case 2: Bilateral renal calculi were identified on a physical examination 22 years ago. The patient was prescribed medication to assist the passage of the calculi, but this failed; no further diagnosis or treatment was provided. Over a year ago, she developed anorexia, nausea, and vomiting without obvious cause and the symptoms gradually worsened. Hemoglobin (HGB) was tested at 85 g/L, blood urea nitrogen (BUN) 36.8 mmol/L, and creatinine (Cr) 1262.4 μmol/L in the other hospital. A bilateral renal

ultrasound showed bilateral renal atrophy and multiple diffuse multiple renal calculi bilaterally. PH1 was diagnosed by genetic testing. The patient was put on hemodialysis.

Case 3: No obvious cause was identified for abdominal pain, nausea, and vomiting over 15 years. There were no other symptoms. The local hospital conducted an abdominal ultrasound which identified renal calculi. The study of a stone technique in a local hospital. After repeated detection of stones and repeated gravel. Nausea and vomiting were repeated before 6 mo, and blood Cr was 1465.7 mmol/L and BUN 36 mmol/L. Genetic testing suggested PH1. The patient was commenced on hemodialysis.

Case 4: Diagnosed with two renal calculi 11 years ago. There was no extraordinary discomfort and no treatment was provided. Genetic testing suggested PH1 for 2 mo.

Case 5: Diagnosed with two renal calculi five years ago, without symptoms or treatment. One month ago, they experienced pain in the right side of the abdomen, nausea, and vomiting. The treatment of the hospital and the right ureteral calculi, the right ureteral calculi, the right terteral stone. There was no obvious cause of the reduced urine output (< 500 mL/d), light blood was noted in the urine, Scr was 1300 μmol/L, and an abdominal ultrasound showed bilateral chronic kidney damage. Genetic testing suggested PH1 and the patient was commenced on hemodialysis.

History of past illness

Case 1: Myocarditis.

Cases 2 and 3: Hypertension.

Cases 4 and 5: None noted.

Personal and family history

All cases: No abnormalities detected.

Physical examination

All cases: No abnormalities detected.

Laboratory examinations

All cases were diagnosed as PH by genetic testing.

Case 1: HGB 139 g/L, scr81 μmol/L, estimated glomerular filtration rate (eGFR) 55.1 mL/min/ m^2, the gout/calculus factor in urine suggested oxaluria.

Case 2: HGB 85 g/L, scr 766 μmol/L, eGFR 5.8 mL/min/m^2.

Case 3: HGB 71 g/L, scr 1541 μmol/L, eGFR 5.7 mL/min/m^2.

Case 4: HGB 127 g/L, scr 80 μmol/L, eGFR 71.0 mL/min/m^2.

Case 5: HGB 64 g/L, scr 967.9 μmol/L, eGFR 6.4 mL/min/m^2.

Imaging examinations

Cases 1, 2 and 4: Urinary system ultrasonography identified multiple calculi bilaterally.

Case 3: Urinary system ultrasonography identified nephrocalcalgia.

Case 5: Urinary system ultrasonography identified right ureteral calculus.

FINAL DIAGNOSIS

All cases: PH1, multiple calculi in both kidneys.

Case 1: Chronic kidney damage [chronic kidney disease (CKD)3].

Case 2: Renal anemia, chronic kidney damage (CKD3).

Case 3: Nephrocalcalgia, renal anemia, chronic kidney damage (CKD5).

Case 4: Chronic kidney damage (CKD3).

Case 5: Right ureteral calculus, renal anemia, chronic kidney damage (CKD5).

TREATMENT

All cases: Symptomatic treatment.

Case 1, 2, and 4: Pre-LT.

Cases 3 and 5: Lithotomy, estimated glomerular filtration rate (SLKT), hemodialysis (HD).

OUTCOME AND FOLLOW-UP

General information and clinical manifestations

Between January 2017 and December 2020, 5 patients were diagnosed with PH1 by identifying mutations of the AGXT gene. There were four males and one female. The median age of onset (the first time that patient's relatives first noticed the relevant clinical manifestations) was at 4.0 years (range 1.0-5.0), the median age at diagnosis was 11.9 years old (range 6.7-23.5), and the median age at LTx was 12.2 years old (range 7.0-25.1), and the median follow-up time was 26.3 mo (range 12.8-40.1 mo). All cases had urolithiasis and/or nephrocalcinosis. ESRD occurred in three cases. All five had a delayed diagnosis.

Laboratory examination

Biochemical blood and urine indices are shown in Table 1. HGB was 97.2 ± 30.2 g/L, serum K^+ 4.8 ± 0.7 mmol/L, Na^+ 141.0 ± 1.1 mmol/L, and Ca^{2+} 2.4 ± 0.1 mmol/L. eGFR was 28.8 ± 28.4 mL/min/1.73 m^2 and urine OA (UOA)/Cr was 748.2 ± 153.6 μg/mg Cr.

Molecular biology

Nine heterozygous mutations were identified in the five cases (Figure 1). The mutations included c.28_c.29delCCinsA, c815_c.816insGA, c.32C>G, c.346G>A, c.33_34insC, c.824_825insAG, c.26dupC, and c.473C>T, c.145A>C. None were identified to be novel. Two patients produced a c.32C>G mutation and two a c.824_825insAG mutation.

Operative and postoperative data

Among the five cases, two received pre-LT and three SLKT [LT and kidney transplantation (KT) were performed as separate procedures]. Four donors were mothers and one was a donor after cardiac death (DCD). The median interval between LT and KT of cases 2, 3, and 5 was 4.3 mo (range: 2.3-9.8); cases 1 and 4 received an LT only. Serum OA (SOA) of cases 3 and 5 before LT were 134.0 and 233.6, while those of cases 2 and 3 before KT were 452.0 and 142.5. Cases 1, 2, and 4 did not have recorded values before the LT, and case 5 did not have a recorded value before the KT. The median intensive care unit stay after LT was 5 d (range: 3-18). Renal function improved postoperatively in all cases. Table 2 shows the details of the surgical procedure and relevant data. All cases were followed-up to 2020-12-16, showing 100% survival at a median follow-up time of 26.3 mo (range: 12.8-40.1).

The normal plasma oxalate (POx) concentration was 10 umol/L, which should be controlled below 50 μmol/L during dialysis. The normal 24-h urinary oxalate concentration was less than 45 mg(< 0.5 mmol/24 h/1.73 m^2). The normal value of urinary oxalate/creatinine is related to age: 5-12 year, 47-119 μg/mg (60–150 μmol/mmol) and > 12 year 1.6-63.7 μg/mg (2-80 μmol/mmol)[8]. We used the Oxalic Acid Colorimetric Assay Kit (Sigma-Aldrich, MAK179) to test the SOA, and the UOA in our cases. The longitudinal data are shown in Figures 2A and 2B. The monitoring of these indices was not uniform due to patient compliance, issues with transportation, and other problems.

As seen in Figure 2A, case 4 with pre-LT showed some improvement in SOA after surgery, whereas case 1 could not be evaluated due to incomplete data; all three SLKT cases (2, 3 and 5) showed postoperative improvements. Pre-LT case 4 showed improved UOA postoperatively, whereas patient 1 could not be evaluated due to incomplete data. In SLKT patients, case 5 showed improvement postoperatively, while cases 2 and 3 had poor postoperative results (Figure 2B). Cases 1 and 4 with pre-LT and case 5 with SLKT showed a return to normal eGFR postoperatively; cases 2 and 3 showed improvement. In terms of renal function, LT significantly improved renal function in cases 1 and 4 who underwent pre-LT. However, SLKT cases 2, 3, and 5 had little improvement of renal function at the LT stage, but improved renal function after KT; case 5 was the only one to regain normal function.

DISCUSSION

PH is a rare autosomal recessive metabolic disease[9], stemming from a deficiency in liver-specific AGT, which then results in endogenous oxalate production, urinary calculi, and even lead to renal dysfunction[10,11]. Of the three types of PH, PH1 is the most common, accounting for about 80% of all cases[8,12]. Study from Europe and North America report an annual incidence rate of 0.1-0.2/100 million and a prevalence rate of 0.8-2.9/100 million[8]. Due to the rarity of PH1, its diagnosis is often delayed or completely missed[13]. The median age of disease onset is 5.5 years old or younger; around 90% of these patients have calculi and 20%-50% have developed ESRD by the time that a PH1 diagnosis is made[14].

Oxalate deposition is the critical saturation point of POx when GFR reduces below 60 mL/min/1.73 m^2. Systemic oxalosis occurs in many sites, including bone, heart, *etc.*[11,15], the immediate institution of hemodialysis is recommended. However, dialysis alone cannot overcome the continuous production of oxalate[16,17], leaving organ transplantation as the only effective therapy. However, transplantation strategies need to be tailored to individual patients[18-21]. Pre-LT should be performed in all patient's in stage 3b of CKD (eGFR is 30-60 mL/min/1.73 m^2), combined liver and KT (CLKT)

should be performed when the patient is an infant or in CKD stage 4 (eGFR is 15-29 mL/min/1.73 m^2). SLKT is more suitable for patients with at CKD stage 5 (eGFR < 15 mL/min/1.73 m^2, ESRD).

CLKT involves the implantation of a whole or partial transplanted liver and kidney from the same donor and during the same surgical procedure[22-24]. Continuous hyperhydration and hemodialysis are necessary[22,25-27]. However, dialysis cannot completely remove POx, and oxalation is often present in dialysis patients[19]. SLKT involves two stages: A single LT is performed followed by KT[23]. With this procedure, hemodialysis is maintained after LT until normal levels of oxalate are achieved, then the KT can proceed[17,21,28,29]. In our cases, deceased donors were used for case 2, while case 3 and 5 received their livers from a living donor and kidney from a deceased donor, with all three surviving at the last follow-up assessment. Following LT, the oxalate accumulates in the kidney, resulting in kidney disease. Therefore, intensive dialysis should be employed before KT to reduce POx below saturation levels[21]. As it is difficult to quantify the total oxalate load *in vivo*, there is no consensus on the optimal interval between liver and KT[19,21]. The normal ranges of plasma OA have been determined using different methods. Elgstoen[30] reported normal POA at 3-11 μmol/L (n = 67), while in their three PH patients these levels ranged 50-170 μmol/L. In that study, OA was tested using the Oxalic Acid Colorimetric Assay Kit (Sigma-Aldrich, MAK179). To obtain control SOA levels in our study, we collected morning urine samples from seven non-PH individuals and found that in those individuals, urinary OA ranged from 69.7-208.0 μmol/L. Due to problems regarding patient compliance, family economic conditions, limited medical resources, *etc*. Our three cases opted for conventional hemodialysis. The timing of the DCD kidney donation was uncontrollable, and SOA did not decrease to normal before KT in 3 cases. The postoperative recovery of SLKT case 5 was superior to cases 2 and 3 based on renal function and UOA; this may be related to the shorter duration between ESRD development and transplantation (0.2 year in case 5 *vs* 2.9 year in case 2 and 0.6 year in case 3). In addition, case 5 received their organ from a living doner.

Pre-LT is an effective method for avoiding hepatic or renal failure[16,17,19]. There is no unified standard for conducting pre-LT when no obvious renal dysfunction is present[12]. Based on the recommendations of the Oxal Europe Expert Group[8], a pre-LT should be considered in patients with CKD3b. Pre-operative eGFRs in cases 1 and 4 were 55.1 and 71.0 mL/min/1.73 m^2, respectively, and both were staged as CKD3. Their livers showed a good postoperative recovery. With regard to their calculi, case 1 remained relatively unchanged but case 4 showed an improvement; their latest eGFRs were 127.4 mL/min/1.73 m^2 and 157.0 mL/min/1.73 m^2, respectively, indicating a trend towards normal.

CONCLUSION

PH1 has a high rate of misdiagnosis, and high heterogeneity in terms of the clinical phenotype and genotype. Most patients develop ESRD by the time of their PH1 diagnosis. Each transplantation method has its advantages, which should be comprehensively considered as part of a tailored approach to treating the patient's condition, and based on the abilities of the transplantation center and relevant economic factors. Both pre-LT and SLKT can be safely performed and provide encouraging results for patients with PH1. We believe that LT should be performed as early as possible to avoid further organ damage and to maximize postoperative recovery.

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