

Case Report

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Primary hyperoxaluria as an indication of liver and kidney transplantation: Case report and literature review**Anastasiya Chekhovych; Jolanta Gozdowska*; Magdalena Durlik**

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Abbreviations: AGXT: Alanine-Glyoxylate Amino-transferase; Caox: Calcium Oxalate; DAC: Daclizumab; GRHPR: Glyoxylate And Hydroxypyruvate Reductase; HOGA: 4-Hydroxy-2-Oxoglutarate Aldolase; HD: Hemodialysis; HCV: Hepatitis C Virus; KTX: Kidney Transplantation; LKTX: Liver-Kidney Transplantation; MMF: Mycophenolate Mofetil (MMF); NC: Nephrocalcinosis; Pox: Plasma Oxalate; PD: Peritoneal Dialysis; PJP: Pneumocystis Jirovecii Pneumonia; Scr: Serum Creatinine; Tac: Tacrolimus; TCMR: T Cell-Mediated Rejection; Uox: Urinary Oxalate; ZHIB: Zero-Hour Implantation Biopsy.

Abstract

Primary Hyperoxaluria (PH) is a metabolic liver disease that results in oxalate overproduction that cannot be metabolized by the liver [1]. PH is caused by mutations in one of three genes that encode enzymes involved in glyoxylate metabolism. As oxalate is primarily excreted in the urine, the kidney is the prime target for oxalate deposition, which leads to end-stage kidney disease [2].

A patient named MN with Nephrocalcinosis (NC) was referred to the Children's Memorial Health Institute of Warsaw in early childhood. The patient was diagnosed with PH type 1. PH type 1 is caused by mutations in a gene called AGXT that encodes alanine-glyoxylate aminotransferase. This enzyme is found in hepatic peroxisomes. It converts a compound called glyoxylate to the amino acid glycine [3].

In 02.12.1996, at the age of 13 the patient received a first kidney transplant from family member. In 16/09/1998 graftectomy was performed due to rapidly progressive kidney failure, nephrocalcinosis and infections. The patient had to return to hemodialysis after renal allograft loss. Also the patient was diagnosed with chronic HCV genotype 4 infection in 1998. In 08.11.2002, at the age of 19, the patient was qualified for a simultaneous liver and second kidney transplantation due to primary hyperoxaluria. The patient was treated with combination of: Daclizumab, steroid, tacrolimus, mycophenolate mofetil. Since October, 2015 the patient had been treating with combination of ombitasvir, paritaprevir, ribavirin and ritonavir. Hepatitis C Virus (HCV) was successfully eliminated.

Patients with kidney failure from primary hyperoxaluria type 1 should not undergo kidney transplantation alone due to the very high risk of recurrence. Combined liver and kidney transplantation is the treatment of choice [4].

Keywords: Primary hyperoxaluria; kidney insufficiency; kidney transplantation; combined liver; kidney transplantation.

Introduction

Primary Hyperoxaluria (PH) is a metabolic liver disease that results in oxalate overproduction that cannot be metabolized by the liver [1]. PH is caused by mutations in one of three genes that encode enzymes involved in glyoxylate metabolism [2]. There are three types: PH type 1 is caused by mutations in the gene called AGXT, PH type 2– in the GRHPR gene, PH type 3– in the HOGA1 gene. The patient was diagnosed with PH type 1. The AGXT gene encodes alanine-glyoxylate aminotransferase. This enzyme is found in hepatic peroxisomes. It converts a compound called glyoxylate to the amino acid glycine. AGXT gene mutations result in an accumulation of glyoxylate, which is then converted to oxalate for removal from the body as a waste product. Oxalate that is not excreted from the body combines with calcium to form calcium oxalate deposits, which can damage the kidneys and other organs [3]. In this report, we describe a case of PH type 1 in a female, who first underwent only kidney transplantation, then due to rapidly increasing kidney insufficiency - combined liver and kidney transplantation.

Case report

A Female Patient (MD), born in 1983, was referred for the first time to the Infant Jesus Teaching Hospital from to the Children's Memorial Health Institute of Warsaw in December 2005 due to continuation of nephrology care.

In early childhood, a patient was diagnosed with PH type 1. From birth, patient was reporting recurrent urinary tract infections due to calcium oxalate depositions. Later she developed end stage renal disease and was performed with peritoneal dialysis till the first kidney transplantation, 1996. Also patient gave a history of minor ventricular septal defect, left ventricular and septal hypertrophy, sinus tachycardia treated pharmacologically and HCV (diagnosed in 1998).

In 02.12.1996, at the age of 13 the patient received a first kidney transplant from family member. In 16/09/1998 graftectomy was performed due to rapidly progressive kidney failure, nephrocalcinosis and infections. The patient had to restart hemodialysis after renal allograft loss.

In 1998 the patient was diagnosed with chronic HCV genotype 4 infection.

In 08.11.2002, at the age of 19, the patient was qualified for a simultaneous liver and second kidney transplantation due to primary hyperoxaluria. Post-operative infection was treated according to antibiotic sensitivity. On the 17th day after surgery decline in transplanted kidney function was observed. Methylprednisolone was administered 3 pulses and the patient was scheduled for biopsy. The biopsy revealed presence of calcium oxalate deposition and no rejection. The hemodialysis catheter was inserted for decreasing a blood oxalate concentration, after 9 days of hemodialysis the catheter was successfully removed. On the 42th day after surgery, liver rejection signs came up. Methylprednisolone was administered 3 pulses until test results were normal. The patient was discharged home in general good condition. The patient was treated with combination of: Daclizumab (DAC), Steroid, Tacrolimus (TAC), Mycophenolate Mofetil (MMF).

Hepatitis C virus relapsed in transplanted liver. In 2005, the patient underwent liver biopsy due to chronic HCV. There were no liver fibrosis, cholestasis. There were minor neutrophil and lymphocytic infiltration in 1-2 portal triads. In USG there weren't any abnormalities.

Patient was admitted to the hospital with deterioration in renal function of the second transplanted kidney (SCr elevated from 2.5 mg/dl to 4.21 mg/dl). 01/09/2015, biopsy due to kidney failure of the second kidney graft revealed extensive interstitial fibrosis and tubular atrophy (IF/TA 3 grade), atherosclerosis with considerable artery lumen diameter reduction, thickening of the tunica media due to hypertension, furthermore excluded acute cellular rejection of transplanted kidney.

From 10.2015 to 15.02.2016 the patient was being treated with combination of ombitasvir, paritaprevir, ribavirin and ritonavir. Hepatitis C Virus (HCV) was successfully eliminated.

On 17.02.2016 the patient with HCV posthepatic cirrhosis was admitted to hospital due to rapidly progressive hepatic failure during treatment. On 01.03.2016 temporal catheter was implanted into right jugular vein and dialysis was initiated. Despite intensive pharmacological treatment, due to the rapidly progressing failure of the transplanted liver, the patient was being prepared for retransplantation of both organs. Unfortunately, the patient died before retransplantation.

Discussion

Primary hyperoxaluria type 1 is a rare disorder that is inherited in an autosomal recessive manner [5]. The onset of the disease in childhood and adolescence is often characterized by recurrent kidney stones (with or without nephrocalcinosis) and progressive renal failure [6].

Late-onset form of disease is mainly characterized by an occasional deposition in kidney and onset in adulthood, but acute renal failure may also occur caused by bilateral renal obstruction by calcium oxalate deposits. Other symptoms include urinary tract infections, painful urination, and hematuria. Ongoing systemic oxalosis may result in the following clinical symptoms: conduction disorders, vascular calcification with necrosis of the distal parts of the limbs, visual impairment, specific brown-colored deposits in the retina, skin nodules, joint involvement, and bone diseases that lead to fractures in long-term dialysed patients [6].

Diagnosis is based on clinical signs, the composition of the deposits and molecular genetic testing. The activity of the enzyme AGXT may be considered. However, due to wide availability of genetic testing, liver biopsy to obtain tissue for enzymatic activity is now rarely performed. For pregnant women at risk and families with history of PH, prenatal genetic testing and preimplantation genetic diagnosis are recommended [7].

In 2002, Riksen was the first, who reported a patient diagnosed with PH1 only after failure of his second kidney graft due to the late onset of end-stage renal disease [8]. Retrospectively, his vascular problems, skeletal abnormalities and cardiac arrhythmias fit the picture of severe systemic oxalosis. Diagnosis was based on biochemical urine analysis, which revealed elevated excretion rates of oxalate and glycolate, whereas no

L-glycerate was present. At that time after diagnosis the patient was treated only conservatively with a high fluid intake, avoidance of high oxalate foods, a thiazide diuretic, and pyridoxine [9].

In case report presented patient was consulted by cardiologist due to oxalosis developed cardiovascular problems (left concentric ventricular hypertrophy, impaired left ventricular relaxation, hyperkinetic left ventricle, fibrosis of mitral and aortic valves) and sinus tachycardia.

In 2019, Cai and Lin reported 3 cases of PH diagnosed after renal graft loss, what confirms that the treatment scheme with the combined Liver-Kidney transplantation is the treatment of choice. Three different patients underwent isolated kidney transplantation with a deceased kidney donors, performed with routine Zero-Hour Implantation Biopsy (ZHIB), as part of the routine renal transplant procedure. In all cases ZHIB of the renal allograft showed no crystals. The patients received standard triple immunosuppression. Patient 1, 2, 3 were admitted to hospital due to the delayed graft function on post-operative day 46, 38, 75 respectively. Renal graft biopsy revealed acute T Cell-Mediated Rejection (TCMR) and extensive deposits of CaOx crystals in the interstitial tubule.

Patient 1 reentered to the maintenance hemodialysis in the clinic and looked forward to a chance of combined liver and kidney transplantation in the future. Patient 2 returned to the maintenance hemodialysis and was investigated for the overall decline in health due to the severe anemia. Patient 3 also returned to the maintenance hemodialysis. *P. jirovecii* was confirmed by fiberoptic bronchoscopic biopsy and patient died of severe pneumonia caused by PJP [9].

Presented patient also had to restart hemodialysis 2 years after her first kidney transplantation from family member. In 1998 graftectomy was performed due to rapidly progressive kidney failure, nephrocalcinosis and infections. After 4 years of HD patient underwent simultaneous liver and kidney transplantation due to primary hyperoxaluria.

Early intensive treatment is essential to maintain kidney function. Treatment is based on minimization of the deposition of calcium oxalate as protection from advanced renal failure by maintaining high diuresis, vitamin B6 (pyridoxine) use and calcium oxalate crystallization inhibitors (citrate, pyrophosphate and magnesium). In case, medication and lifestyle changes don't help, oxalate should be removed with dialysis [6]. Oxalate removal is much more effective with hemodialysis than peritoneal dialysis. For that reason, peritoneal dialysis should not be suggested [7].

As dialysis cannot prevent systemic oxalosis in an individual, organ transplantation is the preferred option for treatment. The percentage of survivors after liver-kidney transplant is higher than the percentage of survivors after isolated kidney transplant: Adult five-year survival percentage for individuals after kidney vs combined liver and kidney transplantation are 45% vs 67% and those for children are 14% vs 76%. After kidney- and/or liver-transplant period, daily hemodialysis should be performed until the renal clearance of oxalate maintains oxalate in plasma below 30 $\mu\text{mol/L}$, in order to minimize risk of oxalate nephropathy [7].

Isolated renal transplantation in PH-1 with established ESRF offers only a temporary solution as oxalate deposition results in recurrent disease and renal graft failure, with a 3-year graft

survival of only 17-45%. Liver being the only organ responsible for glyoxylate detoxification by the enzyme AGT, PH-1 can only be cured by replacing the deficient host liver with an unaffected liver. Isolated liver transplant is an attractive treatment option in selected patients before established advanced chronic renal failure [10]. Isolated liver transplant may be considered in an individual with significant residual renal function ($\text{GFR} > 60 \text{ mL/min/1.73 m}^2$), because single organ transplant will withhold decline in renal function [7]. Combined LKTX has developed to the point where it has been accepted as a valuable treatment option for patients with PH-1 with good long-term results and also combined transplantation of liver and kidney from the same donor protects the kidney from rejection and improves kidney graft survival [10,11]. A study from the UK retrospectively reviewed six children who underwent LKTX for PH-1. Overall, the patient survival was four out of six, with poor outcome in two infants with PH-1 and severe systemic oxalosis, and the other four children keeping well after a follow-up of six months to seven years [11,12].

There are 3 cases of patients at different age with good long-term results confirming the advantage of LKTX over KTX.

The patient is a male child born on August 10, 1992 with no family history of any renal disease. He was diagnosed to have PH-1 during childhood and progressed to severe renal failure at the age of 4 and started hemodialysis (HD for one year. He underwent a combined LKT from a deceased donor on April 15, 1997 and was on triple immunosuppression with steroid, MMF (mycophenolate mofetil) and Tac (tacrolimus). In February 2004 he restarted HD due to dysfunction of the renal allograft. He had a second renal transplant on August 25, 2004, from his mother, and received immunosuppression with Dac (daclizumab), prednisolone, MMF (mycophenolate mofetil) and Tac (tacrolimus). In February 2008, he underwent left native nephrectomy for renal cell carcinoma and subsequently he was treated with reduced immunosuppression, in view of the history of malignancy, his treatment was modified by replacing tacrolimus with rapamycin. In 2011 he was 17 years old, had normal hepatic graft function, normal renal graft function and had no evidence of any recurrence of oxalosis or of renal cell carcinoma [11].

The patient is a male born on February 8, 2001 with no family history of any renal disease. At the age of one year he was diagnosed with PH-1 following liver biopsy. His renal function steadily worsened in the ensuing years and he was kept on HD for about 14 months before he underwent a cadaver LKTX on October 23, 2005. In 2011 he continued to remain stable with normal hepatic and renal graft, normal plasma oxalate (1.7 $\mu\text{mol/L}$) and 24-h urine oxalate excretion. He was on triple immunosuppression with steroid, MMF (mycophenolate mofetil) and Tac (tacrolimus) [11].

Patient is a 26-year-old female with ESRD due to genetic confirmed PH-1 (homozygous mutation p.I244T). She was on HD for three years. She underwent sequential LKTX. First, she underwent a cadaver LTX. She was kept on intermittent HD 4 times a week and her plasma oxalate levels were measured sequentially in order to evaluate the best timing for sequential kidney transplant. Four months after the liver transplant, she underwent a KTX from a deceased donor. The post-operative period was uneventful and she was discharged without performing any dialysis session. One year post-transplant, she has stable with no signs of recurrent oxalosis [13].

Conclusion

The prognosis is poor if primary hyperoxaluria type 1 is untreated. Patients with kidney failure from primary hyperoxaluria type 1 should not undergo kidney transplantation alone due to the very high risk of recurrence. Combined liver and kidney transplantation or isolated liver transplantation is the treatment of choice to suspend decline in renal function [4].

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