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Recovery From Dialysis in Patients With Primary Hyperoxaluria Type 1 Treated With Pyridoxine: A Report of 3 Cases

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Abstract

Primary hyperoxaluria type 1 (PH1) is a genetic disorder characterized by overproduction of oxalate and eventual kidney failure. Kidney failure is usually irreversible in PH1. However, in PH1 patients homozygous for the G170R mutation, pyridoxine is an enzyme co-factor and decreases urine oxalate excretion (UOx) by reducing hepatic oxalate production. We report recovery from dialysis in three PH1 patients homozygous for the G170R mutation in response to pharmacologic dose pyridoxine treatment. Median age at initiation or resumption of pyridoxine treatment was 37 years (range 20–53), and pyridoxine dose was 8.8 mg/kg/d (range 6.8–14.0 mg/kg/d). Duration of hemodialysis prior to renal recovery was 10 months (range 5–19). POx improved after recovery of renal function. At a median of 3 months (range 2–46) following discontinuation of hemodialysis, estimated glomerular filtration rate (eGFR) was 34 ml/min/1.73 m² (range 23–52), plasma oxalate concentration (POx) was 8.8 μmol/L (4.6–11.3), and UOx was 0.93 mmol/24 hours (0.47–1.03). Kidney function was maintained during a median of 3.2 yrs (range 1.3–3.8) of follow-up. These observations suggest that kidney failure may be reversible in a subset of PH1 patients homozygous for the G170R mutation treated with pharmacologic dose pyridoxine.

INTRODUCTION

The primary hyperoxalurias constitute a group of rare autosomal recessive disorders characterized by aberrant metabolism of glyoxylate into oxalate. PH1 is the most common and severe form and accounts for 80% of cases.¹ PH1 is caused by mutations in the *AGXT* gene which encodes the liver-specific peroxisomal enzyme alanine/glyoxylate aminotransferase (AGT). AGT normally converts glyoxylate into glycine within liver peroxisomes. When the enzyme is defective or deficient, glyoxylate is aberrantly converted into oxalate which is eliminated in the urine.² Excessive UOx can lead to nephrolithiasis, nephrocalcinosis, and progressive chronic kidney disease (CKD).^{3,4}

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Once PH1 patients initiate maintenance dialysis, their kidney failure is generally considered irreversible and combined liver and kidney transplantation is the preferred treatment. However, a subset of PH1 patients homozygous for the G170R mutation has a more treatable phenotype in which AGT remains functional but mislocated. Pyridoxine (vitamin B6) is a chemical chaperone for AGT, increasing its activity through peroxisomal targeting.⁵⁻⁷ Thus treating patients with pharmacologic doses of pyridoxine (5–8 mg/kg/day) significantly reduces UOx in heterozygous patients and may even normalize UOx in homozygous patients.^{8,9} Approximately 9% of PH1 patients are homozygous for the G170R mutation.¹⁰ The value of reducing hepatic oxalate production with pyridoxine in patients with advanced CKD is unknown. We here report three G170R homozygous patients with kidney failure who experienced renal recovery allowing dialysis discontinuation after pharmacologic dose pyridoxine treatment. These observations suggest that reducing hepatic oxalate production even in PH1 patients with advanced CKD may be beneficial.

CASE REPORTS

We reviewed patients enrolled in the Rare Kidney Stone Consortium (RKSC) PH Registry, an observational registry involving consented patients under approval of the Mayo Clinic IRB. Among the 41 G170R homozygous PH1 patients in the registry, 23 progressed to kidney failure, of whom 12 were treated with pyridoxine. Pyridoxine was started in 2 patients after more than one year of dialysis and in 8 patients within 3 months of dialysis initiation (including the 3 patients in this series). Subtherapeutic doses of pyridoxine were started prior to ESKD in the remaining 2 patients but did not prevent progression to kidney failure. The 3 patients reported in our series were the only patients to recover sufficient kidney function to stop dialysis. Baseline characteristics of these 3 patients are shown in the Table, and the relationship among pyridoxine treatment, eGFR, POx, and time on dialysis is depicted in Figure 1.

Case 1:

A woman developed nephrolithiasis at age 25. At age 37, she presented to an outside institution with a creatinine of 14 mg/dL. Kidney biopsy showed acute tubular injury, calcium oxalate crystals within the tubules and interstitium, and interstitial fibrosis involving 50% of the sample. UOx was 1.32 mmol/24 hrs. She was started on thrice weekly hemodialysis and referred to our institution three months later for transplant evaluation. On presentation to our institution, her pre-dialysis POx was 47.2 $\mu\text{mol/L}$ (normal < 1.8 $\mu\text{mol/L}$) and UOx was 0.95 mmol/24 hr (normal < 0.46 mmol/24 hr). *AGXT* genetic testing revealed homozygosity for the G170R mutation. Three months after initiation of hemodialysis, she was started on pyridoxine therapy (14 mg/k/d).

Approximately 20 months after initiation of hemodialysis (17 months after initiation of pyridoxine) hemodialysis was discontinued. Three months after discontinuation of hemodialysis, the patient had a creatinine of 2.5 mg/dL (eGFR 23 ml/min/1.73 m²). POx was 11.3 $\mu\text{mol/L}$, and Uox was 1.03 mmol/24 hr. After 4.6 years on pyridoxine (3.2 years after dialysis discontinuation), her creatinine remained 2.3 mg/dl.

Case 2:

A 2.5-year-old girl presented to an outside institution with bilateral nephrolithiasis. A diagnosis of PH was presumed due to an elevated UOx. She was started on pyridoxine (2.5 mg/kg/d) but self-discontinued the medication at age 16. At the age of 20, she presented with a creatinine of 5.2 mg/dL. CT imaging showed bilateral nephrolithiasis without obstruction. Kidney biopsy showed acute tubular injury, oxalate crystals within the tubules, and interstitial fibrosis involving 75% of the interstitium. POx was not measured, and UOx was 2.34 mmol/24 hrs/1.73m². She was started on thrice weekly hemodialysis, and pyridoxine was resumed.

One month after starting dialysis, she was referred to our institution for transplant evaluation. *AGXT* genetic testing revealed G170R homozygosity. POx obtained 6 weeks after starting hemodialysis was 26.6 μmol/L. Her pyridoxine dose was increased to 6.8 mg/kg/day. Five months after starting pyridoxine, dialysis was reduced to twice weekly and eventually discontinued 11 months after starting pyridoxine. Her creatinine remained stable at 1.8 mg/dl (eGFR 34 ml/min/1.73 m²) 3.8 years after dialysis discontinuation, with POx was 8.8 μmol/L, and UOx was 0.93 mmol/day. Following an obstructive stone episode complicated by acute kidney injury, she experienced a decline in kidney function and resumed hemodialysis 6.5 years after it was originally discontinued.

Case 3:

A 33-year-old woman developed renal failure of unclear etiology and was initiated on hemodialysis. After 3 months of hemodialysis, she received a living donor kidney transplant (KT) elsewhere which failed within 5 years due to oxalate nephropathy. Five months after KT failure, she presented to our institution on peritoneal dialysis. *AGXT* genetic testing revealed homozygosity for the G170R mutation, and she was started on pyridoxine (7.8 mg/kg/d). Ten months later, she received a second living donor KT elsewhere. Post-transplant, she was continued on pyridoxine. Thirteen years after her second KT, she had an iothalamate clearance of 59 ml/min/1.73 m², POx of 4.2 μmol/L, and a UOx of 0.51 mmol/24 hr. She subsequently developed septic shock and acute kidney injury in the setting of a perforated cecal ulcer attributed to lymphoma. She was initiated on continuous hemodialysis and transitioned to intermittent hemodialysis every 4–5 days. Pyridoxine was temporarily held due to her inability to tolerate oral intake but resumed approximately one week after dialysis initiation. Seven weeks after dialysis initiation, she was transferred to our facility. On presentation, POx was 66.8 μmol/L, and UOx was 1.87 mmol/24 hr. Hemodialysis was increased to 6 days per week. A renal allograft biopsy showed acute tubular injury with associated calcium oxalate crystals and interstitial fibrosis involving 40% of the sample. Subsequently, dialysis was tapered to twice weekly. Due to recovery of kidney function, dialysis was able to be stopped 6 months after it started. Two months after dialysis discontinuation, the patient had stable renal allograft function with an eGFR of 52 ml/min/1.73m², POx of 4.6 μmol/L, and UOx of 0.47 mmol/1.73 m²/24 hr. Pyridoxine was continued at 10 mg/kg/d. After five months off dialysis, eGFR was 47 ml/min/1.73m² and urine oxalate 0.46 mmol/24 hrs. Renal allograft function was maintained until her death due more than a year after discontinuing dialysis.

DISCUSSION

This case series demonstrates that kidney failure secondary to oxalate nephropathy in PH1 can be reversible following reduction in hepatic oxalate production. We report three patients homozygous for the G170R mutation with severe oxalate nephropathy who experienced renal recovery allowing dialysis discontinuation after treatment with pyridoxine 8.8 mg/kg/d (range 6.8–14.0). Median duration of dialysis prior to renal recovery was 10 months (range 5–19). Renal recovery was sustained for a median of 3.2 years (range 1.3–6.5). Our findings challenge the conventional wisdom that kidney failure in PH1 is always irreversible. Rather, even advanced CKD can be reversed if hepatic production of oxalate can be reduced. We speculate that the prompt initiation of pyridoxine within months after kidney failure, before kidney damage becomes irreversible, accounts for the improved outcome in these patients. Overall, 3/8 patients (38%) started on pharmacologic dose pyridoxine within 3 months of dialysis initiation experienced renal recovery, a much higher rate of renal recovery than that seen in the general population (1.0–2.4%).^{11,12} Pyridoxine is a co-factor for AGT and other enzymes involved in amino acid metabolism. Specifically, pyridoxine is involved in neurotransmitter synthesis, homocysteine regulation, and gluconeogenesis.¹³ The G170R mutation results in functional but mistargeted AGT, with the potential for enhanced enzyme activity when sufficient pyridoxine is present. By contrast, most other mutations result in nonfunctional or deficient enzymes.^{5–7,14} Thus patients with G170R mutations are more likely to experience renal recovery when treated with pyridoxine. Another method of reducing hepatic oxalate production in PH1 patients regardless of genotype is siRNA therapy.¹⁵ In PH1, use of siRNA technology targeting the hepatic enzyme GO has been proposed. GO is responsible for converting glycolate to glyoxylate, the immediate precursor to oxalate. Thus inhibiting GO reduces the primary substrate necessary for oxalate formation and knocking out GO in AGT-deficient mice results in significantly lower UOx.¹⁶ A clinical trial of siRNA inhibition of GO has shown promising reductions in UOx in PH1 patients with preserved kidney function.^{17,18} Another potential target of siRNA technology in PH is the hepatic isoform of LDH (LDHa) which catalyzes the final step from glyoxylate to oxalate. siRNA therapy targeting LDH in mice has been shown to reduce oxalate production, and clinical trials of LDH inhibition using siRNA technology are currently underway.^{19,20}

Our series suggests that reducing hepatic oxalate production may be of benefit even in PH1 patients with advanced CKD. Thus new or emerging treatments may allow for recovery of kidney function in a subset, even after kidney failure ensues.

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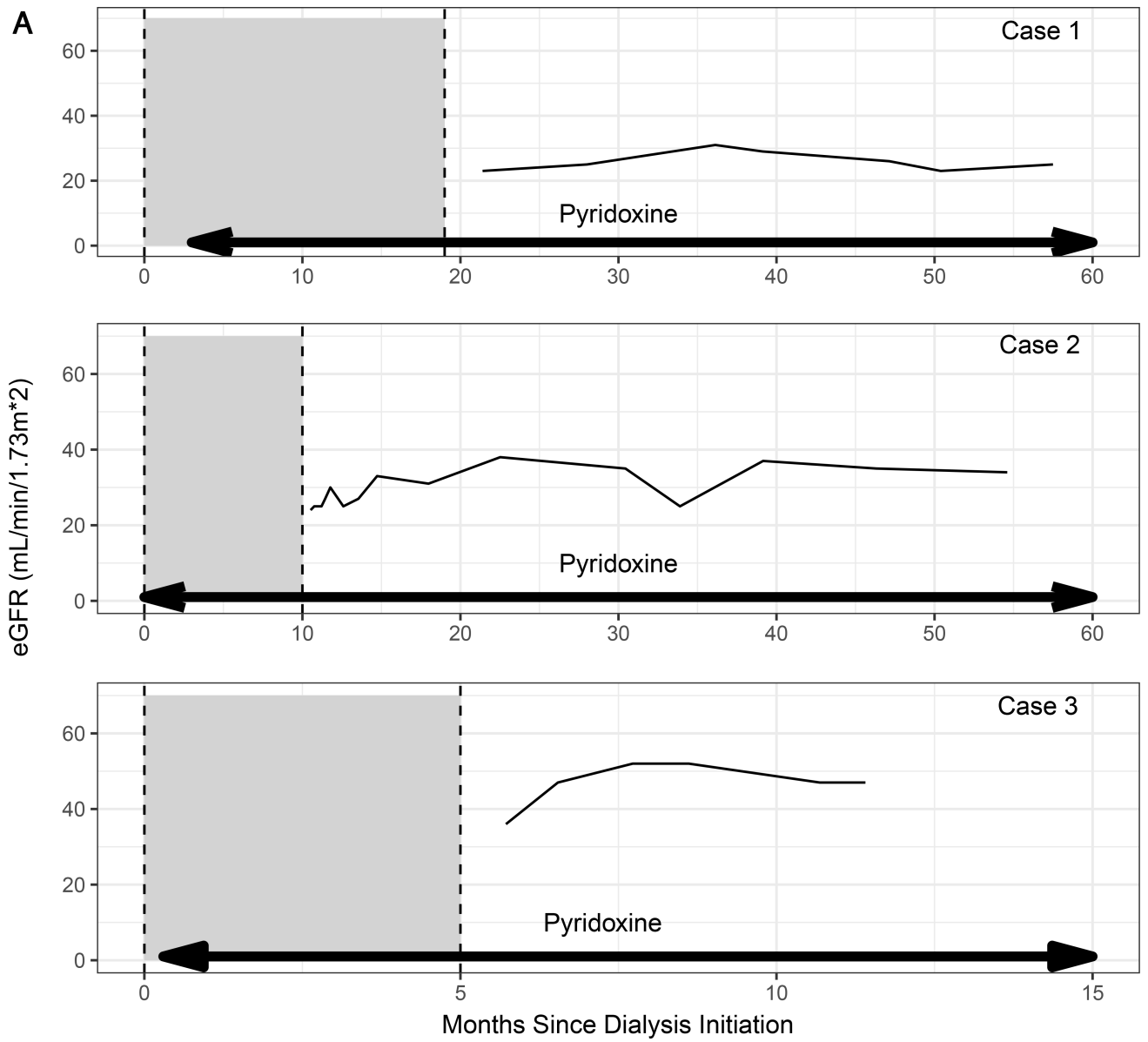
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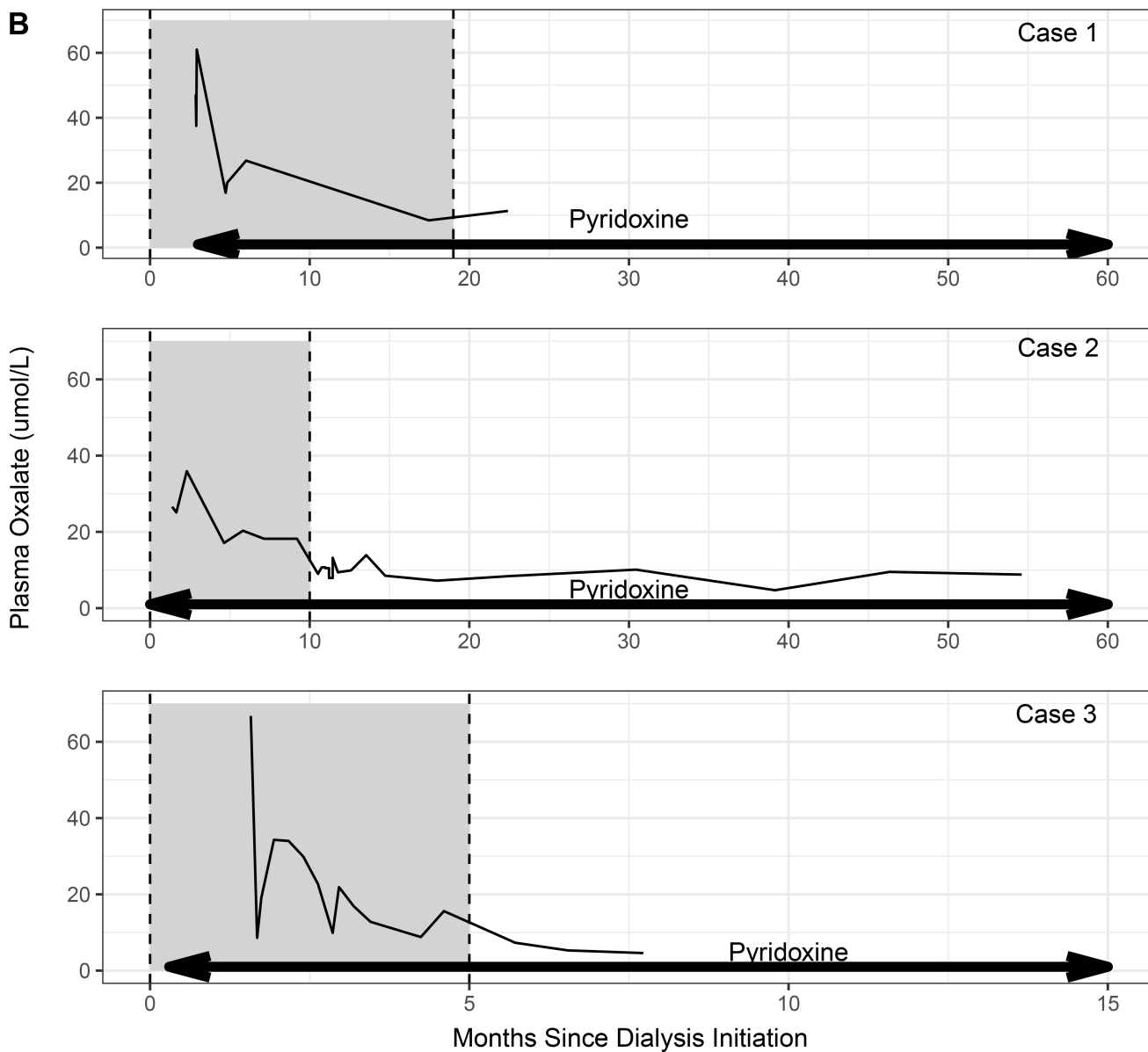


Figure 1. (A) Estimated glomerular filtration rate (eGFR) and (B) plasma oxalate levels in relation to pyridoxine initiation (arrows). Time on dialysis is shown as the shaded area between dotted lines.

Table 1.

Baseline clinical and laboratory characteristics of G170R homozygous PH1 patients followed at Mayo Clinic who recovered renal function after treatment with pharmacologic dose pyridoxine

Patient	Age at PH1 symptom ¹ onset (years)	Age at dialysis initiation (years)	Timing of pyridoxine initiation or resumption	Initial POx ³ (μmol/L)	UOx ² before pyridoxine initiation (mmol/24 hrs)
1	25	37	3 months after dialysis initiation	47.2 on dialysis, prior to pyridoxine initiation	0.95
2	2.5	20	At time of dialysis initiation	26.6 on dialysis, 6 weeks after pyridoxine initiation	2.34
3	33	53	Within 1 week after dialysis initiation	67.9 on dialysis, 6 weeks after pyridoxine resumption	1.87 ⁴

¹Symptoms = nephrolithiasis or development of chronic kidney disease

²normal Uox = 0.46 mmol/24 hrs

³normal Pox < 1.8 μmol/L, level obtained immediately prior to dialysis session

⁴2 months after pyridoxine started.