Importance of Assessing Compliance with Conservative Treatment of Primary Hyperoxaluria Type 1: A Case Report of a Patient with I244T/c.969-3C>G Mutation

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INTRODUCTION

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inherited disorder of glyoxylate metabolism caused by a deficiency of the vitamin B6-dependent liver-specific enzyme L-alanine:glyoxylate aminotransferase (AGT), which is encoded by the AGT gene, alanine:glyoxylate and serine:pyruvate aminotransferase (AGXT).1,2

The reported prevalence of PH1 in Europe ranges from 1 to 3 cases per 1,000,000 population. Its incidence is approximately 1 case per 120,000 live births per year.3 Pathophysiologically, PH1 is characterized by overproduction and excessive urinary excretion of oxalate, causing recurrent urolithiasis, nephrocalcinosis, and a progressive decline in renal function.2,5 PH1 accounts for 1% to 2% of pediatric cases of end-stage renal disease (ESRD).3 As the glomerular filtration rate (GFR) declines, the accumulation of calcium oxalate in extrarenal tissues causes end-organ damage. PH1 particularly affects the bones, joints, retina, skin, bone marrow, heart, and the central nervous system.1,3,4

The PH1 diagnosis is based on clinical, ultrasonographic, and laboratory findings and is confirmed with DNA analysis or enzymology.1,3 More than 190 pathologic AGXT mutations have been documented thus far.7 Most are missense mutations, such as c.969-3C>G, are less frequent and are associated with a complete lack of AGT protein.2 Some genotype-phenotype correlations have been reported. For example, neonatal onset is common to all patients with I244T/null mutations, as reported by the largest European registry, OxlAeurope by the European Hyperoxaluria Consortium.2

Independent of mutation type, early vigorous treatment is essential for maintaining or possibly improving long-term renal function.1,8 The conservative approach involves maintaining a high urine output, minimizing calcium oxide deposition, and continuing pyridoxine treatment if the patient is responsive to this therapy.1 Combined liver–kidney transplant should be considered in patients with stage 4 or 5 chronic kidney disease.9 Preemptive isolated liver transplant might be an option for selected patients.1 Several therapies currently under investigation, such as hepatocyte transplant and gene modification therapies, could also be available for the treatment of PH1 in the future.7,8

We report a case involving an 18-year follow-up of a patient with PH1 with an early-stage diagnosis despite having an asymptomatic debut and no consanguinity history. The patient received conservative treatment. Moreover, she was heterozygous, carrying a splice-site (null) mutation in intron 8, c.969-3C>G, a condition that had been reported in only 3 other, unrelated patients.3,10

As far as we know, this is a unique case of a patient with I244T/null mutation diagnosed after the neonatal period and with normal renal function, who remained asymptomatic during an 18-year follow-up. This case is also unique because of the long-term therapeutic success.

Discussion: Physicians need a high level of suspicion to diagnose this rare disease. It has been previously demonstrated that early conservative treatment improves long-term outcomes, averting preemptive transplant during childhood. This case report emphasizes the importance of encouraging compliance with this approach, reinforces the need for good physician-patient communication, and raises awareness of the problems that might arise during conservative PH1 treatment.

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disruption in compliance and worsening of renal outcome. This case follows CARE (Case Report) guidelines.  

**CASE PRESENTATION**

**Presenting Concerns**

A 5-month-old Spanish female infant was referred to our Pediatric Nephrology Department by her general pediatrician for the evaluation of bilateral nephrocalcinosis discovered after a renal ultrasonogram (Figure 1), which was prompted by recurrent episodes of asymptomatic leukocyturia. The infant was born at 37 weeks of gestation, without illness or failure to thrive. No history of consanguineous parents, familial cases of renal stone disease, or previous illness was noted. No relevant findings were found on the physical examination.

Results of a renal ultrasonogram showed normal-sized kidneys, both with multiple hyperechogenic images over all renal parenchyma and some shaded images on the right upper kidney pole, also shown on abdominal radiographs. Initial laboratory blood test results revealed an estimated GFR by a creatinine level of 80 mL/min per body surface area of 1.73 m². Urinalysis showed a calcium/creatinine ratio of 0.06 mg/mg and an oxalate/creatinine ratio of 0.77 mmol/mmol (reference range = 0.028–0.411 mmol/mmol). The elevated concentration of urinary oxalate/creatinine as well as images compatible with nephrocalcinosis and nephrolithiasis without other symptoms led to the suspicion of primary hyperoxaluria. We performed a 24-hour urinalysis, in which, using full metabolic assessment by split injection-mass spectrometry, we found an oxalic acid excretion 5 times higher than the normal range (3 mmol/d/1.73 m²), a glycolic acid excretion of 0.93 mmol/d/1.73 m² (reference range < 1 mmol/d/1.73 m²), and a 7 mmol/mmol glyceric acid/creatinine ratio (reference range = 0–10 mmol/mmol).

Serum oxalic acid was less than 1 mg/dL (reference range < 7.1 mg/dL), determined by an enzymatic test.

Genetic analysis exhibited a heterozygous mutation (I244T in exon 7 and 969-3C>G in intron 8). This genetic testing was not available in Spain, so it was contracted out to a laboratory abroad. However, the results were obtained when the patient was 6 months old.

The patient’s diagnosis was supported by findings of a hepatic biopsy performed at the age of 2 years, confirming no AGT activity.

**Therapeutic Intervention and Treatment**

With the information about the genetic mutation, the patient’s parents were informed that she might need a combined liver and kidney transplant in the future. The patient was started on a conservative treatment regimen of 150 mg of pyridoxine once daily (23 mg/kg/d), potassium citrate at a dosage of 2.5 g daily divided into 4 doses, and magnesium supplements of 5 to 10 mEq/1.73 m² 3 times per day. Her parents firmly decided that she would maintain a daily fluid intake of 5 to 10 mEq/1.73 m²/3 times daily. Thus, a low-dose thiazide regimen was started as treatment of hypercalciuria of 6-year duration.

![Figure 1. Ultrasonograms of the right (A) and left (B) kidneys showing bilateral nephrocalcinosis.](image)

**Table 1. Laboratory findings during 18-year follow-up**

<table>
<thead>
<tr>
<th>Year</th>
<th>Serum creatinine (Cr), mg/dL</th>
<th>eGFR, mL/min/1.73 m²</th>
<th>Urinary calcium/Cr ratio, mg/mg</th>
<th>Urinary oxalate excretion, mmol/d/1.73 m²</th>
<th>Urinary oxalate/Cr ratio, mmol/mmol</th>
<th>Urinary pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>0.49</td>
<td>80</td>
<td>0.06</td>
<td>3.00 (normal &lt; 0.6)</td>
<td>0.77</td>
<td>6.5</td>
</tr>
<tr>
<td>2002</td>
<td>0.30</td>
<td>170</td>
<td>0.03</td>
<td>0.20</td>
<td>0.41</td>
<td>7.0</td>
</tr>
<tr>
<td>2003</td>
<td>0.50</td>
<td>110</td>
<td>0.10</td>
<td>0.42</td>
<td>0.08</td>
<td>7.0</td>
</tr>
<tr>
<td>2006</td>
<td>0.30</td>
<td>225</td>
<td>0.31</td>
<td>1.15</td>
<td>0.53</td>
<td>7.0</td>
</tr>
<tr>
<td>2009</td>
<td>0.50</td>
<td>120</td>
<td>0.25</td>
<td>1.46</td>
<td>0.19</td>
<td>6.5</td>
</tr>
<tr>
<td>2012</td>
<td>0.54</td>
<td>161</td>
<td>0.06</td>
<td>3.50</td>
<td>0.16</td>
<td>7.0</td>
</tr>
<tr>
<td>2015</td>
<td>0.65</td>
<td>144</td>
<td>0.05</td>
<td>1.50</td>
<td>0.11</td>
<td>7.0</td>
</tr>
<tr>
<td>2018</td>
<td>0.68</td>
<td>104</td>
<td>0.04</td>
<td>2.14</td>
<td>0.14</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* Values may be misestimated because of low urine output.  
eGFR = estimated glomerular filtration rate.
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Follow-up and Outcomes

We performed 24-hour urinalyses, renal function tests, and ultrasonography every 3 to 4 months for the first 8 years and every 6 to 8 months thereafter. Two years after diagnosis, the nephrocalcinosis and nephrolithiasis were resolved on ultrasonographic examination, and results of a noncontrast-enhanced computed tomography scan showed that she maintained normal renal function. Hence, the possibility of a preemptive liver transplant was abandoned. In addition, her retinal examination findings and her echocardiogram results showed no evidence of oxalate deposits.

At adolescence, the patient began to produce less urine to be periodically tested. For this reason, we reinforced the physician-patient relationship to emphasize the importance of maintaining a high fluid intake. She still preferred using an alarm during the night to maintain fluid intake rather than using a nasogastric tube or gastrostomy. She had secondary polyuria but not enuresis and had no need for extra psychological support. There were no other signs of noncompliance during her follow-up. We also informed her about the necessity of intravenous fluid treatment in case of fever, vomiting, or diarrhea.

Her 18-year follow-up data are shown in Table 1. The patient reached the 90th to 97th percentile of height according to a normal densitometric test result. At her final follow-up, she had a GFR of 104 mL/min/1.73 m², no urolithiasis on her ultrasonogram (Figure 2), and an excellent commitment to her treatment. A timeline of the case appears in Figure 3.

DISCUSSION

Recognizing PH1 can sometimes be a challenge, particularly when the patient remains asymptomatic. Nevertheless, our patient fulfilled several radiologic and laboratory features in the absence of secondary causes of hyperoxaluria, which permitted a prompt diagnosis at an early stage. It also allowed initiation of proper conservative treatment while the patient still had normal renal function, as recommended by Mandrile et al. Despite diffuse nephrocalcinosis appearing on her renal ultrasonogram, the patient experienced exceptional maintenance of normal renal function. Complete resolution of nephrolithiasis and nephrocalcinosis shown on images makes this case exceptional among various cases previously reviewed. Her good compliance with treatment also contrasts with that in other adolescent cases reported.

In relation to the clinical presentation, our case suggests that nephrocalcinosis is the most frequent symptom at onset, as described by Mandrile et al., and diffuse nephrocalcinosis is the characteristic infant pattern of PH1 according to Milliner et al.. However, Cochat et al. associated diffuse cortical nephrocalcinosis with ESRD in patients, whereas our patient had normal renal function at presentation. Otherwise, her age at diagnosis was less than the median of 8 years (range = 2.6-22.2 years) reported by OxalEurope. Compared with the 4 patients with I244T/null mutations previously described, she had no neonatal diagnosis.

Milliner et al noted that PH1 displays a heterogeneous phenotype, with various clinical presentations and onsets. Therefore, a high suspicion of this disease was the clue in this case of asymptomatic nephrocalcinosis and nephrolithiasis.

Urinalysis reveals increased oxalate excretion in patients with PH1. In the literature, normal oxalate excretion ranges between 0.5 and 0.7 mmol/d/1.73 m²; in our case, the oxalate excretion was 5 times above the reference range. The PH1 appeared combined with hyperglycolic aciduria, as in two-thirds of patients with PH1; however, glycolic aciduria can also be elevated in patients with primary hyperoxaluria type 3. Plasma oxalic levels are unhelpful for diagnosis if renal function remains normal. Although they were measured once, these levels appeared normal in our patient, as expected.

Low urinary calcium levels were initially present in our patient, as is typical in PH1 and type 2. These levels increased during her follow-up, however, which occurs more frequently in primary hyperoxaluria type 3, in which urinary calcium levels can vary.

Results of genetic testing revealed a causative mutation. Thus, a liver biopsy would not have been necessary. However, given that Cochat et al. defined measurement of AGT enzyme activity as the gold-standard diagnosis, in this case both tests were performed. Additionally, DNA analysis was requested of the patient’s brother and her parents. AGT enzyme activity has been associated with responsiveness to pyridoxine therapy and clinical severity. Both associations are controversial in this case with no enzyme activity.

Informing the parents of this 5-month-old patient about her prognosis with confirmed PH1 was an arduous task. First, we informed them of the currently limited understanding of the natural history of PH1. Most studies are from Europe and North America. Studies with higher consanguinity have reported a cumulative incidence of ESRD by the age of 3 years in 50% of affected infants and by 20 years in 85%, as described by Hambart et al. Nevertheless, they also reported that most patients with a normal GFR at the time of diagnosis had not developed ESRD during follow-up. On the other hand, European and American studies report a cumulative renal survival of 76% at 20 years and report 24 years as the median age at ESRD diagnosis.
Considering genotype-phenotype associations with prognoses, the median age at ESRD diagnosis was found to be 11.5 years for 42 patients with heterozygous missense/null mutations in the OxalEurope Registry. Among the 4 patients with p.Ile244Thr/null compound heterozygotes, 3 still retained renal function, with a median of 6.7-year follow-up (range = 1-17 years), whereas ESRD developed in 1 patient in the first months after birth. Leflot et al described a heterozygous patient carrying a c.969-3C>G mutation and another undescribed mutation, who also grew up with preserved renal function but with recurrent episodes of nephrolithiasis. Contrary to the literature, our patient preserved complete renal function throughout 18 years of follow-up. Thus, we have insufficient evidence to date to define the effect of the mutation analysis on the prognosis.

Cochat et al have emphasized that early initiation of an aggressive conservative treatment contributes to maintaining renal function in treatment-adherent individuals. Therefore, once the diagnosis of PH1 was considered, we initiated Cochat and colleagues’ recommended therapeutic measures. We informed the patient’s parents that her long-term adherence to conservative treatment could slow her progression to ESRD. Initially, we proposed preemptive liver transplant as a possible therapy, given that this treatment had been reported by various groups, with a pretransplant GFR between 27 and 98 mL/min/1.73 m². However, once a response to conservative treatment was observed, we decided not to perform preemptive transplant. Currently, following the suggestions by Cochat et al, we only recommend planning preemptive combined liver-kidney transplant at chronic kidney disease stage 3b to avoid systemic oxalosis and its complications. Pyridoxine therapeutic responsiveness in our patient was initially observed, as oxalate excretion decreased more than 30% with the maximum dose. Even though Fargue et al reported various mechanisms of action for pyridoxine, further investigation is needed to understand its metabolic bases in a patient with 0% enzyme activity. This fact also reinforces the recommendation of initiating vitamin B₆ in all patients regardless of their mutation or AGT activity.

Difficulty with compliance with conservative treatment of PH1 could have emerged when the patient reached adolescence, as with the cases described by Leflot et al. For this reason, our patient was trained to take charge of her treatment during personal interviews. Besides regular annual monitoring of kidney function, we more frequently checked her urinary output through 24-hour urine collection. As the urine amount collected decreased, her compliance was more closely supervised, from age 8 years. The physician–patient relationship was also reinforced. During every personal interview we reemphasized the demonstrated
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CONCLUSION

Physicians should suspect PH1 in infants and children with nephrocalcinosis or after a first nephrolithiasis appears, even if they are asymptomatic. Informing relatives and patients of the diagnosis and prognosis is a challenging issue that should be conducted by experienced physicians. Prompt initiation of conservative treatment has been demonstrated to improve long-term outcomes, preventing the need for preemptive liver-kidney transplant during childhood, regardless of mutation type. We advise patients with PH1 to achieve a high fluid intake and to avoid dehydration when concurrent illness appears. We encourage physicians to pay attention to all the described inconveniences to which the conservative treatment approach can lead, and we emphasize the crucial requirement of monitoring patients’ compliance with lifetime conservative treatment, especially during adolescence. ∗

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References


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