Journal of Clinical Case Reports

Case Report Open Access

Primary Hyperoxaluria Type 1: A Case Report and Family Study

Julaina AJ[1]*, Tan SL[2], Nur-Jannah A[3], Yusnita Y[3] and Zabedah MY[1]

[1]*Inborn Errors of Metabolism and Genetic Unit, Department of Nutrition, Metabolic and Cardiovascular Centre, Institute for Medical Research, Ministry of Health Malaysia, Jalan Setia Murni U13/52 Setia Alam, 40170 Shah Alam, Selangor, Malaysia*

[2]*Department of Pediatrics, Sarawak General Hospital, Ministry of Health Malaysia, Jalan Hospital 93586 Kuching, Sarawak, Malaysia*

[3]*Molecular Diagnostic and Protein Unit, Specialised Diagnostic Centre, Institute for Medical Research, Ministry of Health Malaysia, Jalan Pahang 50588 Kuala Lumpur, Malaysia*

Abstract

Primary hyperoxaluria (PH) is a rare disorder that can cause renal failure due to accumulation of oxalate crystals. This study reports an eight-year-old female, product of consanguineous marriage, with strong family history of renal calculi, who presented with acute on chronic renal failure. Imaging revealed bilateral staghorn calculi and renal cortical nephrocalcinosis. Molecular studies confirmed primary hyperoxaluria type 1 in the patient, and carrier status in her parents. Patient ultimately required renal replacement therapy with hemodialysis. Organ transplantation has not yet been explored.

Keywords: Primary hyperoxaluria; Nephrocalcinosis; Renal failure; Oxalate; *AGXT* gene

Introduction

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder due to deficiency in *Alanine-Glycoxylate Aminotransferase (AGT)* enzyme. It is characterized by recurrent kidney and bladder stones resulting from buildup of oxalate. The level of this substance in urine is abnormally high as it is filtered and excreted as a waste. Oxalate can combine with calcium during its excretion forming calcium oxalate. When viewed under polarized light, the crystalline deposits were strongly birefringent, typical of calcium oxalate crystals. Calcium oxalate deposits can cause damage mainly to the kidneys and also other organs. Some calcium oxalate crystals in the interstitium were associated with foreign-body-type giant cells.

Early presentations in patients with primary hyperoxaluria are urolithiasis and nephrocalcinosis which will progress to chronic kidney disease and end-stage renal disease if left untreated. There are three types of primary hyperoxaluria; primary hyperoxaluria type 1, type 2 and type 3. Primary hyperoxaluria type 1 (PH1) has been reported to be the most common type with the estimated prevalence of 1 to 3 cases per 1 million population and an incidence rate of approximately 1 case per 120,000 live births per year in Europe [1,2].

PH1 is a result from mutations in *AGXT* gene which encodes *AGT*. There are more than 200 documented mutations throughout the 11 exons of the gene [3]. In this study, we performed a molecular genetic analysis of the *AGXT* gene in a patient with PH1 and her immediate family members. This case is the first family in Malaysia being used to analyze the mutation causing PH1.

Case Presentation

An eight-year-old Malay girl with no known medical illness was referred from a district hospital for bilateral renal calculi. She presented with a one-week history of facial puffiness, anorexia and lethargy. Ten months prior to that, she complained of two episodes of dysuria, suprapubic pain and low-grade fever. Otherwise there was no gross hematuria or change in the amount and quality of her urine. Parents sought treatment at the health clinic, and on both occasions, child was given symptomatic treatment with mist potassium citrate. No urine cultures or blood investigations were done. No antibiotics were prescribed either. Five months later, she passed out stones in her urine thrice, and was given symptomatic treatment at the same health clinic. No stone analysis or further investigations was done. She was then apparently well until she presented with uremic symptoms for one week.

She is the product of a consanguineous marriage and the youngest of four siblings. Mother had a miscarriage during her fourth pregnancy. The child's elder sister passed away at the age of nine years due to renal failure. The remaining two older siblings (one sister and one brother), and both parents are well. Patient's paternal uncle was noted to have renal stones at 18 years of age but is currently well. Family tree of this patient is shown in Figure 1.

Physical examination revealed a small-for-age girl with weight 19.1

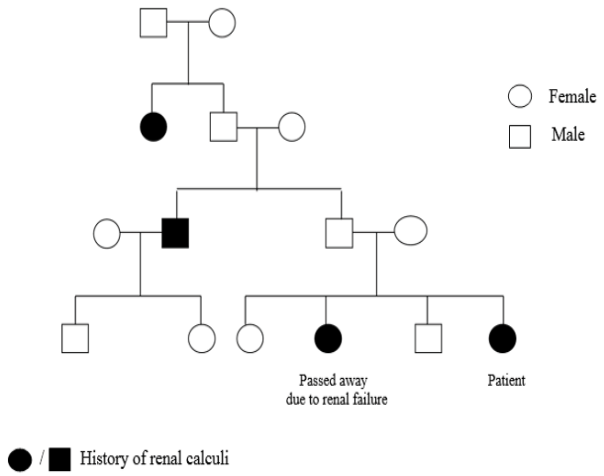

Figure 1: Patient's family tree shows strong family history of renal calculi.

***Corresponding author:** Julaina AJ, Inborn Errors of Metabolism & Genetic Unit, Department of Nutrition, Metabolic and Cardiovascular Centre, Institute for Medical Research, Ministry of Health Malaysia, Jalan Setia Murni U13/52 Setia Alam, 40170 Shah Alam, Selangor, Malaysia, Tel: +60163389679; E-mail: julaina@imr.gov.my

Received July 26, 2019; **Accepted** August 12, 2019; **Published** August 19, 2019

Citation: Julaina AJ, Tan SL, Nur-Jannah A, Yusnita Y, Zabedah MY (2019) Primary Hyperoxaluria Type 1: A Case Report and Family Study. J Clin Case Rep 9: 1269.

kg (<3rd centile) and height 126 cm (between 25-50th centile). Apart from having hypertension with BP 124/82 mmHg, the vital signs were stable. She was pale and sallow. There was facial puffiness, but no edema detected elsewhere. Abdominal palpation revealed some left flank tenderness, otherwise it was soft, with no ballotable kidneys. Cardiovascular and respiratory examination was unremarkable.

Initial investigations showed urea 42.6 mmol/L, creatinine 1510 µmol/L, sodium 125 mmol/L, potassium 5.6 mmol/L, chloride 98 mmol/L, calcium 1.5 mmol/L, phosphate 3.15 mmol/L, magnesium 1.02 mmol/L, uric acid 523 µmol/L, and iPTH 55.8 pmol/L (1.6-6.9). She had severe normocytic normochromic anemia with hemoglobin 5.3 g/dL, total white count 6,300 /µL and platelet 200,000 /µL. Blood gas revealed severe metabolic acidosis with pH 7.183, HCO_3^- 9.7, BE -16.9, pCO_2 26.5. Urine examination showed pH 6, leucocytes 3+, blood 4+, protein 1+, ketone 2+, nitrite negative, but culture was negative. Plain CTU showed bilateral staghorn calculi and renal cortical nephrocalcinosis but no hydronephrosis or hydroureter. Urinary bladder was distended with no wall thickening or bladder stones.

Screening for systemic oxalosis was also performed for the child. Eye examination did not reveal any crystalline ocular deposits. Echocardiography showed mild left ventricular hypertrophy with ejection fraction 60%, otherwise heart was structurally normal. Bone marrow examination was not done.

The patient remained oliguric with no recovery of renal function. Glomerular Filtration Rate (GFR) at presentation was 3 ml/min/1.73 m^2. Peritoneal dialysis was commenced; however, it was complicated by recurrent episodes of catheter-related peritonitis requiring multiple courses of intraperitoneal, intravenous and oral antibiotics. As a result of the poor extraction via peritoneal dialysis, she developed two episodes of hypertensive encephalopathy requiring intravenous labetolol and non-invasive ventilatory support. Patient was ultimately converted to three times per week hemodialysis via a permcath and transferred back to her district hometown about four months later. Oral medications upon discharge were frusemide, spironolactone, enalapril, losartan, prazosin, nifedipine, calcium carbonate, calcitriol, and hematinics. Organ transplant had not been explored. At time of writing, child is still alive on regular hemodialysis.

The urine organic acids results showed mild increase in excretion of glycolate with normal excretion of oxalate. Patient was diagnosed to have PH1. Figure 2 shows chromatogram results of urine organic acid. The molecular analysis was done for patient, both of her parents, her elder brother and younger sister. She also had an adopted sister who was not included in this study. Polymerase Chain Reaction (PCR) and direct sequencing were performed on 11 coding exons and flanking introns of *AGXT* gene for the patient. The patient's molecular analysis showed that she has homozygous frameshift deletion at c.33delC; p. (Lys12Argfs*34) in exon 1 of the *AGXT* gene. Both of her parents' results revealed heterozygous deletion at similar position. The molecular results are shown in Figures 3 and 4. Molecular analyses of her elder brother and sister were both normal.

Discussion

In this report, we described a pediatric patient who was referred for management of bilateral renal calculi. She presented earlier with urinary tract infection (UTI) symptoms and passing out stones however was not further investigated until she came in with uremic symptoms. Patient also has a very strong family history of kidney stones. PH is a rare disease therefore it was not suspected as a primary cause in this patient. A nephrologist or a urologist themselves may encounter none

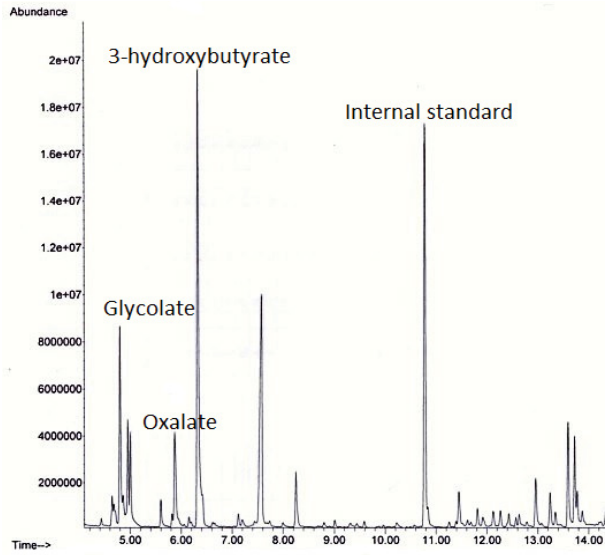

Figure 2: Chromatogram results of urine organic acids showed elevated glycolic acid.

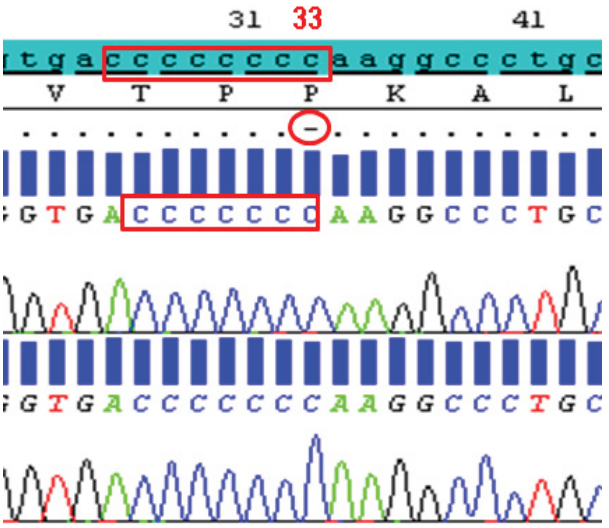

Figure 3: A homozygous deletion at c.33delC; p. (Lys12Argfs*34) in Exon 1 seen in this patient.

to only a few patients with PH during their practicing lifetime. Patients were commonly undiagnosed for more than 5 years [4].

Timely and accurate diagnosis will allow early intervention and appropriate long-term management of PH1. Early treatment can reduce formation of urinary calculi, better renal function protection, and lower the risk of systemic oxalosis when renal failure occurs [4]. An algorithm can assist clinicians in identifying patients who may have PH and conducting appropriate diagnostic tests in order to efficiently arrive at a correct diagnosis [5].

This patient's urine was reported to have oxalate of within acceptable range. However, the glycolate level was increased. Not all patients with PH will have elevated urine oxalate, but with suggestive symptoms, additional investigations should be considered. Measurement of glycolate is found to be supportive. Levels of glycolate are reported to

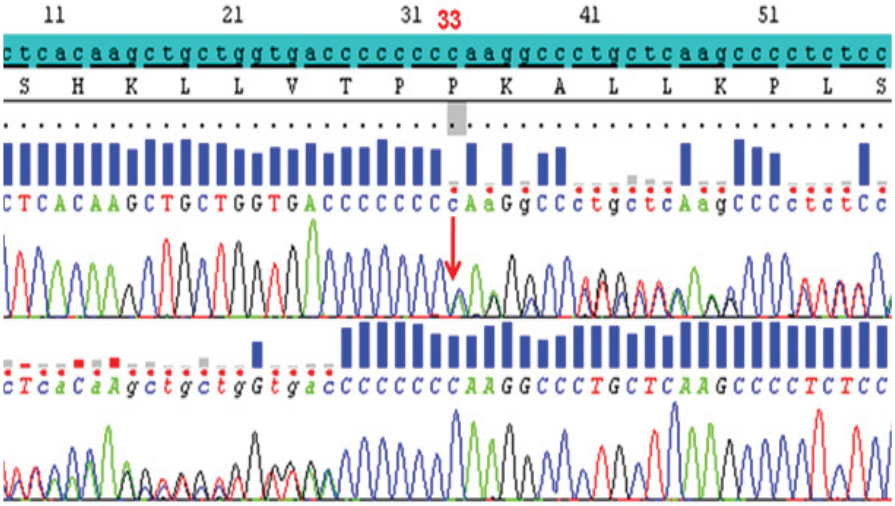

Figure 4: Both parents showed heterozygous deletion at c.33delC; p. (Lys12Argfs*34) in Exon 1.

be elevated in two thirds of patients with PH1 and may also be elevated in patients with type 3 [6].

In a patient with suggestive clinical signs, symptoms and laboratory findings, a definitive diagnosis of PH is by genetic testing. It is reasonable to pledge molecular analysis for type 1, as it accounts for approximately 80% of cases of PH [7]. The *AGXT* gene analysis in this patient showed homozygous frameshift deletion at c.33delC; p. (Lys12Argfs*34) in Exon 1 which has been previously reported in different studies [8-11]. The liver AGT activity caused by this mutation has been reported to be 6% which is consistent with the diagnosis of PH1 [11]. This patient also has a strong family history of kidney stones. Samples were also taken from parents for carrier testing. In this patient, her parents were confirmed to be carriers for the mutation as each of them carry one copy of the mutant allele respectively.

PH1 is treated conservatively. Patients are given supportive treatment including hydration, crystallization and pyridoxine (in patients with Gly170Arg (also known as G70R) or the Phe152Ile mutation [11]. As this patient presented late with end-stage renal failure, she required regular hemodialysis. In future, there may be a need for exploration of kidney transplant in this patient. However, the possibility of recurrence of urolithiasis or nephrocalcinosis caused by oxalate precipitation in the graft kidney should be taken into consideration before decision is made.

Conclusion

In conclusion, PH shall be a differential diagnosis in any patients with recurrent nephrocalcinosis and strong similar family history. Molecular diagnosis may provide as an accurate means for the diagnosis of PH1 in suspected pre-symptomatic and asymptomatic individuals. Supportive treatment should be initiated aggressively once diagnosis is confirmed. If kidney function deteriorates, organ transplantation strategy should follow.

Acknowledgement

The authors would like to thank the Director General of Health Malaysia for permission to publish this paper. We would also like to acknowledge our laboratory staff for reagents preparation and sample processing.

References

1. Cochat P, Deloraine A, Rotily M, Olive F, Liponski I, et al. (1995) Epidemiology of primary hyperoxaluria type 1. Nephrol Dial Transplant 8: 3-7.
2. Van Woerden CS, Groothoff JW, Wanders RJ, Davin JC, Wijburg FA (2003) Primary hyperoxaluria type 1 in the Netherlands: Prevalence and outcome. Nephrol Dial Transplant 18: 273-279.
3. Stenson PD, Mort M, Ball EV, Evans K, Hayden M, et al. (2017) The human gene mutation database: Towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next generation sequencing studies. Hum Genet 136: 665-677.
4. Milliner DS (2005) The primary hyperoxalurias: An algorithm for diagnosis. Am J Nephrol 25: 154-160.
5. Cochat P, Rumsby G (2013) Primary hyperoxaluria. New Eng J Med 369: 649-658.
6. Hoppe B (2012) An update on primary hyperoxaluria. Nat Rev Nephrol 8: 467-475.
7. Amoroso A, Pirulli D, Puzzer, D, Ferri L, Crovella S, et al. (1999) Gene symbol: AGXT, disease: Primary hyperoxaluria type I. Hum Genet 104: 441.
8. Coulter-Mackie MB, Lian Q, Applegarth D, Toone J (2005) The major allele of the alanine: Glyoxylate aminotransferase gene: Nine novel mutations and polymorphisms associated with primary hyperoxaluria type 1. Mol Genet Metab 86: 172-178.
9. Hoppe B, Beck B, Gatter N, Von Unruh G, Tischer A, et al. (2006) Oxalobacter formigenes: A potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int 70: 1305-1311.
10. Williams E, Rumsby G (2007) Selected exonic sequencing of the agxt gene provides a genetic diagnosis in 50% of patients with primary hyperoxaluria type 1. Clin Chem 53: 1216-1221.
11. Boualla L, Tajir M, Oulahiane N (2015) *AGXT* gene mutations and prevalence of primary hyperoxaluria in moroccan population. Genet Test Mol Biomark 19: 1-6.