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ORIGINAL ARTICLE

Nine novel HOGA1 gene mutations identified in primary hyperoxaluria type 3 and distinct clinical and biochemical characteristics in Chinese children

Xiaoliang Fang[1,2] · Lei He[1,2] · Guofeng Xu[1,2] · Houwei Lin[1,2] · Maosheng Xu[1,2] · Hongquan Geng[1,2]

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Abstract

Background Primary hyperoxaluria type 3 (PH3) is characterized by mutations in the 4-hydroxy-2-oxoglutarate aldolase (HOGA1) gene. PH3 patients are thought to present with a less severe phenotype than PH1 and PH2 patients. However, the clinical characteristics of PH3 patients have yet to be defined in sufficient detail. The aims of this study were to report HOGA1 mutations of PH3 in Chinese children, and to analyze the genotype and clinical characteristics of these PH3 patients.

Methods Genetic analysis (targeted gene panel-based and/or whole-exome sequencing) of HOGA1 was performed in 52 patients with a high suspicion of PH3, and DNA was obtained from the patient and both the parents. The clinical, biochemical, and genetic data of these 12 patients identified with HOGA1 mutations were subsequently retrospectively reviewed.

Results These 12 patients were identified with HOGA1 mutation. The median onset of clinical symptoms was 18.25 (range 5–38) months. In total, 14 different mutations were identified including 9 novel mutations in these 12 patients with PH3. All of these 12 patients initially presented with urolithiasis, and 3 patients among them comorbid urinary tract infection (UTI) as another initial symptom. Ten patients experienced hyperoxaluria (average oxalate 0.77 mmol/1.73 m^2/24h). In contrast, urine calcium excretion was normal in 8 patients and 2 patients with hypercalciuria (urine calcium > 4 mg/kg/24 h). At the time of diagnosis, estimated GFR was 155.6 ml/min per 1.73 m^2, and at last follow-up time (17.3 months later from diagnosis on average), estimated GFR was 157.5 ml/min per 1.73 m^2. To date, none of the patients has impaired renal function based on and progressed to ESRD.

Conclusions We found that PH3 was significantly diagnosed in our urolithiasis patients during childhood. Nine novel HOGA1 mutations were identified in association with PH3, which provide a first-line investigation in Chinese PH3 patients. The eGFR was normal in all children with PH3. This finding is in contrast to the early impairment of renal function in PH1 and PH2.

Keywords Primary hyperoxaluria type 3 · Pediatrics · HOGA1 · Chronic kidney disease

Abbreviations

PH	Primary hyperoxaluria
AGXT	Alanine–glyoxylate aminotransferase
ESRD	End-stage renal disease
GRHPR	Glyoxylate reductase–hydroxypyruvate reductase
HOGA1	4-Hydroxy-2-oxoglutarate aldolase
eGFR	Estimated glomerular filtration rate
UTI	Urinary tract infection
CaOx	Calcium oxalate
CaPhos	Calcium phosphate

Xiaoliang Fang and Lei He contributed equally to this work and should be regarded as joint first authors.

✉ Hongquan Geng
genghongquan@xinhuamed.com.cn

[1] Department of Pediatric Urology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 1665 KongJiang Road, Shanghai 200092, China

[2] Children's Stone Treatment Center of National Health and Family Planning Commission of the People's Republic of China, 1665 KongJiang Road, Shanghai 200092, China

Introduction

Nephrolithiasis is a major public health predicament with diverse and convoluted etiology. In China, the incidence of urinary stones in children has been increasing in the last decade. Many factors can induce nephrolithiasis, and these encompass

extremes of urinary pH, dehydration, hypercalciuria, particular medications, hyperoxaluria, and hereditary disorders [1]. Hyperoxaluria is either acquired or inherited. Primary hyperoxalurias (PHs) are rare inborn errors of metabolism that are inherited in an autosomal recessive manner. They are the result of monogenic disorders of glyoxylate metabolism and lead to increased endogenous oxalate production by the liver and the formation of calcium oxalate kidney stones [1, 2].

To date, three distinct genetic forms of PH have been defined: PH1–3. PH1 (MIM# 259900), the most common and the most severe form, is due to the mutation in the alanine–glyoxylate aminotransferase gene (AGXT), and patients typically progress to end-stage renal disease (ESRD) [3]. PH2 (MIM# 260000) is due to a mutation in the glyoxylate reductase–hydroxypyruvate reductase (GRHPR); 20% of patients develop ESRD [3, 4]. PH3 (MIM# 613616) is due to the mutation in the recently identified 4-hydroxy-2-oxoglutarate aldolase (HOGA1) gene; it does not develop ESRD generally [5]. Compared with PH1 and PH2, PH3 might be the least severe form with a milder phenotype with good preservation of kidney function in most patients [6]. This often leads to delay in diagnosis. Up to the present time, most of the literatures focus on PH1 and PH2. However, few PH3 patients among Asians have been reported, but the clinical features and renal outcomes of patients with PH3 are not sufficiently characterized, especially in Chinese children. In this article, we report a series of 12 PH3 children with clinical manifestations ranging from asymptomatic nephrolithiasis to acute kidney injury (AKI) in whom genetic analysis was done. The aims of this study were to report HOGA1 mutations with PH3 in Chinese children, and to describe the genotype and the clinical characteristics of these PH3 patients.

Patients and methods

Patients

From routine inquiries and referrals to the clinic center, we first selected for HOGA1 screening patients who met the clinical criteria for primary hyperoxaluria (urine oxalate > 0.5 mmol/1.73 m^2/24 h in the absence of gastrointestinal disease or other identifiable secondary causes), in whom ultrasonography of the urinary system revealed nephrolithiasis in kidneys and/or urethral stones, nephrocalcinosis included; 52 patients with urolithiasis were enrolled in this study. Urinary oxalate was analyzed only once before diagnosis. Informed consent was given for a genetic analysis to be performed on the patients, their family members, and healthy controls to confirm the diagnosis. Each patient was informed about the aims of the study, and the consent to genetic testing was obtained. After an initial survey of HOGA1 gene mutations responsible for PH3, gene sequencing was performed on all patients with a high clinical and biological suspicion of PH at our clinic center. From this group of patients, we identified 12 patients (23%), aging from 5 to 38 months, from different regions of East China with HOGA1 mutations: six male patients and six female patients. The median age of onset of clinical symptoms was 18.25 (range 5–38) months.

The diagnosis of PH was based on clinical findings (urolithiasis, nephrocalcinosis, and end-stage renal failure), elevated plasma oxalate, and urinalysis (raised oxalate) in combination with spectrophotometric analysis of the calculi. Demographic characteristics, serum creatinine, blood electrolytes, urinary oxalate, and calcium were assessed. We tried many methods to detect plasma oxalate but all failed, so the data on this cannot be provided in this paper. The estimated glomerular filtration rate (eGFR) in children was estimated by Schwartz equation [7]. Clinical, biochemical, and genetic data were reviewed retrospectively by the referring physicians and centralized by one investigator (LA). Results were compared to age-related reference ranges.

Study design This is an observational study conducted in Department of Pediatric Urology, during the period January 2016 to December 2017. This clinical study was evaluated and approved by the Institutional Ethics Committee on Human Studies at Xinhua Hospital.

Molecular approach

Blood and DNA samples from patients and both the parents with suspected PH were received for analysis by Shanghai Institute for Pediatric Research. Genomic DNA was extracted from peripheral blood leukocytes using guanidinium chloride standard procedures. All the samples were subjected to exome sequencing using the SureSelect Human All Exon V5 probe (Agilent, Santa Clara, CA, USA). Part of the patient samples were subjected to targeted gene panel-based and others were subjected to whole-exome sequencing. Sanger sequencing was used to examine the cosegregation of the candidate variants. Amplified fragments were sequenced by Applied Biosystems 96-capillary 3730XL system. Mutations have been identified in various populations (refer to the Human Gene Mutation Database, HGMD professional 2018.3, http://www.hgmd.org/).

Results

First, we sequenced the entire HOGA1 coding region in 52 unrelated hyperoxaluric patients meeting the criteria of marked hyperoxaluria. No patient had nephrocalcinosis. Fourteen different mutations in HOGA1 were detected including 9 novel changes in 12 patients with PH3; no specific mutations of PH were found among these parents. Five

mutations, c.769 T > G, c.834G > A, c.715G > A, c.208C > T, and c.834_834 + 1GG > TT, have been reported previously. Nine novel mutations, c.290G > A, c.554C > T, c.110G > A, c.812G > A, c.841C > T, c.811C > T, c.70delG, c.406G > C, and c.418C > T, were not reported previously. A summary of genotype and the clinical and biochemical characteristics of these PH3 patients are presented in Table 1.

One mutation was a successive 2-nucleotide substitution at the last position of exon 6 and the first position of intron 6, respectively (c.834_834 + 1GG > TT), including the change of classical donor splicing site (GT → TT) combined with the alteration of its upstream close neighbor nucleotide; both sites may play an important role as a splicing modulator. Seven patients were heterozygous for this mutation. The second variant found in the patient was a guanine to adenine substitution of the last nucleotide of exon 6 (c.834G > A), which results in a synonymous mutation (p.Ala278Ala). We found that the father carried the heterozygous c.834G > A variant, while the mother carried the heterozygous c.834_834 + 1GG > TT mutation in 3 patients. The in-frame c.70delG (p.V24Sfs*19) mutation was detected in a heterozygous state in one patient. Seven missense mutations were found also: the previously documented c.769 T > G (p.CyS257Gly) and c.715G > A (p.Val239Ile) mutations; and five novel c.110G > A (p.Gly37Asp), c.290G > A (p.Arg97His), c.554C > T (p.Thr185Met), c.812G > A (p.Arg271His), and c.841C > T (p.R281W) mutation. Moreover, we found two patients with a missense mutation (c.290G > A p.Arg97His and c.715G > A p.V239I, respectively) inherited from the father. PolyPhen-2 (available at http://genetics.bwh.harvard.edu/pph2) analysis predicted that this variant is "benign." Another patient was heterozygote for one novel nonsense mutation within exon 1: c.208C > T (p.Arg70X), which led to premature termination.

Table 1 Clinical and biochemical characteristics of PH3

Patient number	Age of onset (months)	Presenting symptoms	Stone type	Urine oxalate (mmol/1.73 m^2/24 h)	Urine calcium (mg/kg/24 h)	Plasma creatinine (μmol/l)	eGFR (ml/min/1.73 m^2)	Genotype
1	38	Bilateral stones	CaOx	0.93	3.63	30	153	c.769 T > G p.Cys257Gly c.834_834 + 1GG > TT
2	23	Bilateral stones	CaOx	0.67	4.52	20	204	c.290G > A p.Arg97His c.554C > T p.Thr185Met
3	22	Bilateral stones and hematuria	n.a	0.52	2.46	19	232	c.834G > A p.Ala278Ala c.715G > A p.Val239Ile
4	8	Bilateral stones and UTI	CaOx	0.95	4.95	28	104	c.834G > A p.Ala278Ala c.834_834 + 1GG > TT
5	12	Bilateral stones and UTI, anuria	CaOx CaPhos	0.65	3.59	36	100	c.110G > A p.Gly37Asp c.834_834 + 1GG > TT
6	24	Unilateral stone	CaOx	0.59	3.89	25	177	c.208C > T p.Arg70 c.554C > T p.Thr185Met
7	26	Bilateral stones and hematuria	n.a	1.66	n.a	20	218	c.812G > A p.Arg271His c.834_834 + 1GG > TT
8	9	Bilateral stones and abdominal pain	CaOx	0.84	2.63	25	125	c.841C > T p.R281W c.811C > T p.R271C
9	20	Bilateral stones and hematuria	CaOx	0.91	0.77	25	154	c.70delG p.V24Sfs*19 c.834_834 + 1GG > TT
10	24	Bilateral stones	n.a	n.a	n.a	30	141	c.834G > A p.Ala278Ala c.834_834 + 1GG > TT
11	8	Bilateral stones and hematuria	n.a	n.a	1.93	24	125	c.406G > C p.Gly136Arg c.418C > T p.Arg140Cys
12	5	Bilateral stones and UTI	CaOx	0.52	1.73	21	134	c.834G > A p.Ala278Ala c.834_834 + 1GG > TT

n.a, not available; *CaOx*, calcium oxalate; *CaPhos*, calcium phosphate; *UTI*, urinary tract infection

Most PH3 patients did not have a positive family history for urolithiasis. All PH3 patients presented with urolithiasis, but the clinical symptoms of the PH3 are different; 3 patients first suffered from urinary tract infection (UTI) leading to a further diagnosis of bilateral kidney stones, and one of them had anuria caused by acute kidney injury (AKI), 4 patients had hematuria, 1 patient presented with abdominal pain, and 4 patients had no symptoms. Eleven patients presented with bilateral stones; only one patient had a unilateral stone. An average level of urinary oxalate excretion was detected in 10 patients with hyperoxaluria according to age-related local values (average urine oxalate 0.77 mmol/1.73 m^2/24 h, normal < 0.5 mmol/1.73 m^2/24 h), and was not detected in time in 2 other patients with bilateral multiple urinary calculi with a high suspicion of PH, due to machine failure. During follow-up, we reexamined the urinary oxalate of the 2 patients with values of 0.57 mmol/1.73 m^2/24 h and 0.65 mmol/1.73 m^2/24 h. Urine calcium excretion was determined in 10 patients with levels observed above the reference range in 2 patients with hypercalciuria (urine calcium > 4 mg/kg/24 h). Most of the cases in Chinese children were found to have normal urine calcium excretion.

All patients received supportive therapy, based on high fluid intake and oral citrate, as recommended by international guidelines [8]. Most patients can remove urinary stone by less traumatic surgical methods (such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, retrograde intrarenal surgery (RIRS)), thus avoiding percutaneous nephrolithotomy and open surgery, thereby reducing the damage to the kidney of the stone removal procedure itself. The outcomes of 12 patients with PH3 are presented in Table 2. Two of the children with hypercalciuria were also given oral hydrochlorothiazide, and another child received antibiotic prophylaxis for UTI. The urinary stones in 5 patients were completely removed; none recurred, but in 2 patients were recurred during follow-up. Five other patients had residual stone; one of them was an insignificant residual stone. Stone analysis showed predominantly calcium oxalate monohydrate. At diagnosis, estimated GFR was 155.6 ml/min per 1.73 m^2, and at last follow-up (median 17.3 months from diagnosis), estimated GFR was 157.5 ml/min per 1.73 m^2. To date, all patients have normal renal function; none of the patients has displayed impaired renal function and progressed to ESRD.

Discussion

The estimated prevalence of PH is around 1–3 per million of the population. Phenotypic heterogeneity and non-availability of mutational analysis universally have led to its underdiagnosis. Short of mutational analysis, other investigations such as plasma and urine oxalate levels are not confirmatory. The molecular mechanisms of PH1 and PH2 were identified in 1988 and 1999, respectively [4, 9]. PH1 is the most severe form, accounting for 80% of all the cases. PH2 shows a less severe phenotype with the absence of infantile oxalosis and ESRD occurring in about 20% of patients. However, the association of PH3 and mutations in HOGA1 gene was not established until 2010 [6]. Both PH2 and PH3 may have similar prevalence of about 10% of total genetically characterized PH cases [10]. Four other publications have focused on this disease, leading to the description of a total of 60 cases [5, 6, 11–13]; PH3 was first described in Ashkenazi Jewish pedigrees [6], then in Caucasians. Up to now, most of the described PH3 mutations came from the population of European Americans and rarely in the Chinese population [14, 15].

Table 2 Outcome of 12 patients with PH3

Patient number	Gender	Procedures (number)	Clinical outcome	Follow-up (months)	Plasma creatinine (μmol/l)	eGFR (ml/min/1.73 m^2)
1	Female	ESWL, Ureteroscopy (3) JJ	Recurrent urolithiasis	26	31	166
2	Male	Ureteroscopy JJ RIRS	None	26	28	168
3	Female	ESWL (3)	Stone residue	20	23	202
4	Male	ESWL Ureteroscopy JJ RIRS	Insignificant residual stone	17	32	134
5	Male	JJ Ureteroscopy	None	15	38	111
6	Male	ESWL Ureteroscopy JJ	None	16	28	170
7	Male	ESWL	None	17	23	205
8	Female	Ureteroscopy JJ ESWL	None	16	27	155
9	Female	Ureteroscopy (2) JJ ESWL	Stone residue	20	27	160
10	Female	Ureteroscopy (2) JJ	Stone residue	13	33	132
11	Male	ESWL (2)	Recurrent urolithiasis	11	28	141
12	Female	ESWL Ureteroscopy JJ RIRS	Stone residue	11	27	146

JJ, double-J ureteric stenting; *ESWL*, extra-corporeal shock wave lithotripsy; *RIRS*, retrograde intrarenal surgery

To date, more than 200 mutations have been described in PH patients, including 26 variants in PH3 with the 2 most common alleles (c.700 + 5G > T and p.E315del) accounting for more than 70% of the total [5, 11, 16]. Fourteen different HOGA1 gene mutations were detected in 12 patients with PH3. However, the most common alleles had not been detected in our study. We detect the mutation of c.834_834 + 1GG > TT is most common in the Chinese population, which accounts for 50% of the total. This result was different from the previously reported common mutations. The reason for this difference in results may be that most PH3 mutations previously reported came from the population of European Americans. So, a relationship between HOGA1 and ethnic distribution may be suspected. Different ethnic groups may have different genetic mutations. With the mutations being population specific, sequencing of the entire gene rather than targeted analysis will be required.

We investigate a series of children with clinical manifestations ranging from nephrolithiasis to infantile oxalosis in whom genetic analysis was done. The results of the genetic analysis confirmed PH1 in six children, PH2 in one children, and PH3 in 12 children [17]. According to the study by Hopp et al. [16], the overall carrier frequency of PH is approximately 1:70, and the inferred prevalence is approximately 1:58,000. Surprisingly, the frequency of PH3 in our clinic center is higher than PH1 and PH2; however, the difference between the expected and observed prevalences for PH3 may be due to the underdiagnosis of this disease which has overall milder phenotypes, is usually asymptomatic, and is much less likely than PH1 to result in ESRD [16]. Additionally, Monico et al. [12] found that some HOGA1 carriers present with mild hyperoxaluria or idiopathic urinary stone disease; they suppose this may be related to haploinsufficiency. Therefore, gene analysis of HOGA1 is informative to the diagnoses of PH3 cases who have idiopathic calcium oxalate urolithiasis or PH phenocopies [18, 19].

To further characterize the PH3 phenotype, we pooled our clinical experience, assembling patients from 12 unrelated families. Genetic analysis is invaluable in deciding the appropriate management, prognostication, prenatal diagnostic testing, and sibling screening. Bilateral multiple renal stones were found in a majority of PH3 children with normal renal function followed by serum creatinine and echogenic kidneys on ultrasound examination. Hence, children with multiple renal stones, especially bilateral, should be thoroughly investigated for PH. The urine oxalate was higher at presentation in PH3 patients compared with locally established reference values, and PH3 patients displayed persistent hyperoxaluria at examination, as previously reported [5, 20]. The urinary oxalate levels of the 10 Chinese children were higher in our clinic center and were elevated: the mean value being 0.77 mmol/1.73 m^2/24h. These patients presented hyperoxaluria according to international reference values. Hypercalciuria was found in half of published cases [6, 11, 21], but only 2 patients from our series presented with this abnormality. The excretion of 4-hydroxyglutamate—a potential biomarker for PH3—was not investigated in our patients, which is known to be relatively unstable [20, 22] and is metabolized either enzymatically or non-enzymatically to glyoxylate and/or oxalate. Stone analysis showed predominantly calcium oxalate monohydrate. All patients with PH3 described in previous studies displayed a normal eGFR during follow-up consistent to these previous data reporting a favorable outcome in PH3 patients. No patient experienced impaired eGFR in our study. However, the PH3 patient with ESRD was recently reported [14, 23, 24], suggesting that PH3 may not be as clinically benign as previously thought. These studies have reported that the GFR was significantly impaired in some patients with PH3 diagnosed during childhood. This finding is in contrast to the early impairment of renal function in PH1 and PH2 patients and appears to refute preliminary reassuring data on renal function in PH3. However, the underlying reason of the decline in kidney function remains unclear. They analyzed that the severity of PH3 in their series was also demonstrated by a high rate of urological procedures, with some patients even requiring open surgery to remove stones. Speculatively speaking, it may not be hyperoxaluria or urolithiasis per se but the repeated stone removal procedures [14, 16]. Therefore, we suggest that each stone removal procedure should be carefully evaluated and discussed to avoid potential additional damage. All of these urological procedures may have hampered renal function. However, it is impossible to determine whether the renal impairment seen in patients is secondary to PH3 itself, to kidney damage secondary to urological procedures, or to both possibilities. These data reinforce the need for long-term renal function follow-up of patients with PH3, and show that PH3 should no longer be regarded as a benign condition. We showed the stone removal procedures in the 12 patients in Table 2. Obviously, there were few stone removal procedures, so that this should be commented a little better, as with regard to kidney function over time. In order to better understand the prognosis of PH3, we plan to follow these PH3 patients prospectively through a registry or some other mechanism.

The information derived from our detailed analysis (i.e., genetic, clinical, and biochemical analyses) of this series of 12 patients with PH3 starting during childhood includes (1) the first report of a series of HOGA1 gene mutation in 12 Chinese children patients with PH3. Fourteen different mutations were identified including nine novel mutations. The mutation of c.834_834 + 1GG > TT is most common in this Chinese population, which accounts for 50% of the total. (2) Most patients presented with bilateral stones. Patients presented with hyperoxaluria according to age-related local values, and urine calcium excretion was normal for most. There was no significant impairment of eGFR in all patients; none of the patients developed ESRD. (4) The diagnostic procedure we

would recommend in patients to examine for primary hyperoxaluria is that every child with urolithiasis should have a complete metabolic assessment, and if the urinary oxalate level is higher or multiple urolithiasis is on both sides, then we recommend genetic analysis for these patients.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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