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Original Research Article

Clinical and genetic profile of patients with primary hyperoxaluria: observation from a single centre from West India

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ABSTRACT

Background: Primary hyperoxaluria (PH) is characterized by oxalate overproduction due to glyoxylate pathway enzyme defects in the liver. Apart from heterogeneous clinical manifestations of PH, diagnosis by urinary and plasma oxalate levels or stone analysis is not always confirmatory. Mutational analysis is required for definite diagnosis. There is heterogeneity between genotype of PH patients between Western and Indian population. The aim of this study is to describe clinical and genetic profile of Indian patients, diagnosed with PH in Western India.
Methods: All clinical PH suspects in Nephrology and Paediatric Nephrology units from October 2016-September 2020, were counselled for genetic analysis for diagnostic confirmation. Cases, genetically confirmed to have PH, were included and retrospectively analysed for their clinical profile, modality of renal replacement therapy, survival/death. The mutations identified in our patients were compared with commonly prevalent mutations in world PH databases.
Results: 13 of 15 patients were identified to have genetically confirmed PH. Median age at diagnosis was 1 year (range, 4 months to 46 years) and six (46.15%) were male. Six (46.15%) infants, two (15.38%) adolescents and five (38.46%) presented in adulthood. Nine presented as ESKD, while three patients progressed to ESKD during study. Eight (61.54%) with AGXT mutation were diagnosed as PH type1, four (30.76%) GRHPR mutation while one (7.69%) female infant had PH type 3 with HOGA mutation. Out of thirteen, five (38.46%) patients expired, five (38.46%) are ESKD requiring dialysis. Two (15.38%) post-transplant patients, graft loss for one and another requiring supportive medical management for deteriorating eGFR.
Conclusions: ESKD being commonest presentation, high index of suspicion in all cases with renal stone and complete work up should be done for early diagnosis and timely intervention. National registry is required for detection of novel PH mutations in Indian population.

Keywords: Primary hyperoxaluria, End stage kidney disease, Genetic testing

INTRODUCTION

Primary hyperoxaluria (PH) is a group of autosomal recessive disorders resulting in excess of oxalate level in tissues, causing increased excretion of oxalate by kidneys. Three different types of PH are known till today, all affecting glycoxylate metabolism in the liver by different affected genes.[1] Type I from a mutation in the AGXT-gene (encoding for alanine:glyoxylate aminotransferase, AGT); type II in the GRHPR-gene (for glyoxylate reductase/hydroxypyruvate reductase) and type III the HOGA1-gene (for 4-hydroxy-2-oxoglutarate aldolase 1).[2-4]

The true prevalence of PH is unknown. Type 1 PH being the commonest, accounts for 1 to 2 percentage of cases of paediatric End Stage Kidney Disease (ESKD) according to registries from Europe, United States and Japan.[5-7] Clinical manifestations of PH are heterogeneous with respect to age, clinical presentation, severity, and rate of progression to renal insufficiency.[8] These may vary from infantile nephrocalcinosis, recurrent nephrolithiasis with or without obstructive complications to end stage kidney disease (ESKD) as first presentation in late adulthood.[9] Diagnosis by urinary and plasma oxalate levels or stone analysis is not always confirmatory. Mutational analysis is required for definite diagnosis.[1] The genetic profile helps in prognosticating outcome, guides treatment and helps in screening family members for timely intervention and prevention of early progression to ESKD.

There is heterogeneity between genotype of PH patients in the West as compared to the Indian population. Apart from anecdotal case reports.[10-12] Indian population specific database that will help in documenting hitherto unknown novel mutations of pathogenic significance are not well established. The aim of this study is to evaluate clinical and genetic profile of Indian patients, diagnosed with PH during a period of 4 years at a tertiary hospital in Western India.

METHODS

Study type

Retrospective observational study.

Study place

Place of the study was Institute of kidney diseases and research centre, Ahmedabad.

Study duration

Duration of the study was October 2016 to September 2020.

Patient selection criteria

All patients who were clinically suspected to have primary hyperoxaluria were counselled in detail regarding need for genetic analysis for diagnostic confirmation. Those who agreed for genetic testing underwent clinical exome sequencing (CES). Out of the patients whose genotyping was done, those who were found to have underlying mutations confirming PH were included in the study.

Procedure

Patients suspected to have PH based on their clinical presentation were evaluated as follows. Laboratory work up including complete blood count, renal function test, serum values for calcium, phosphorous, uric acid, magnesium, blood gas analysis and urine analysis was done. X ray and ultrasound KUB were done to identify renal calcifications due to calcium oxalate deposition. Creatinine clearance was calculated using the Modified Schwartz formula for children, while for adults the Modification of Diet in Renal Disease (MDRD) formula was employed.

For cases not progressed to ESKD with reasonable urine output, 24 hours urine metabolic work up for calcium, oxalate, citrate, uric acid, magnesium and creatinine excretion was done. If 24 hours urinary oxalate excretion exceeded the upper-limit for age, PH was the most likely diagnosis. However, normal oxalate excretion did not rule out PH in patients progressed to CKD. In patients with calculus who underwent nephrolithotomy or lithotripsy, stone analysis was performed using spectroscopy. Presence of calcium oxalate monohydrate as the predominant component strongly suggested PH. Histopathological examination of nephrectomies or renal biopsies that showed refractile, non-brown staining tubular crystals on hematoxyllin and eosin stain, with birefringence on polarized microscopy also suggested oxalate deposits characteristic of PH.

All these patients with clinico-laboratory parameters suggestive of PH were counselled to undergo genetic analysis for diagnostic confirmation. Role of genotyping in guiding further treatment, choice of dialysis modality and kidney versus combined liver kidney transplantation was discussed in detail with patients and their families. Extended benefit of genetic analysis to other asymptomatic family members in retarding progression to ESKD by timely intervention was also explained.

Clinical exome sequencing was performed for all patients who opted for genetic testing. DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >80-100X coverage on Illumina sequencing platform. The sequences obtained are aligned to human reference genome (GRCh37/hg19) using Sentieon aligner and analysed using Sentieon for removing duplicates, recalibration and re-alignment of indels. In addition to single nucleotide variants (SNVs) and small Indels, copy number variants (CNVs) were detected from targeted sequence data using the ExomeDepth (v1.1.10) method. This algorithm detects rare CNVs based on comparison of the read-depths of the test data with the matched aggregate reference dataset. Clinically relevant mutations were annotated using published variants in literature and a set of diseases databases -ClinVar, OMIM (updated on 21st November 2018), GWAS, HGMD (v2018.3) and SwissVar. Only non-synonymous and splice site variants found in the clinical exome panel consisting of 8332 genes were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region were not reported. The classification of the variations is done based on American College of Medical Genetics.[13] Patients who were thus genetically confirmed, were included in the study. Their medical records were

reviewed. Their clinical profiles and outcomes were analysed. The genotypes identified in our population were compared with the western databases.

Ethical approval

Approved on 15th October, 2020 by EC meeting.

Statistical analysis

Descriptive statistics for continuous variables is presented as mean±standard deviation. The difference in means is expressed as mean±SD with 95% confidence interval. Categorical variables are expressed as frequencies (%) with median values.

P<0.05 are considered as statistically significant.

RESULTS

Table 1 shows presenting features and clinical course of thirteen patients. Table 2 shows their genetic profile.

Table 1: Clinical and laboratory profile of study subjects.

Age	Sex	PH type	Clinical features	USG KUB	24 hr Urine ox	Stone analysis	Histopathology	Intervention	Outcome
4 months	F	3	Recurrent calculi+UTI	B/L calculi No HDN	-	Calcium oxalate monohydrate (70%)	-	ESWL Oral citrate Pyrodoxine Fluids	Normal RFT
4.5 months	M	1	Anuria Acidosis Pulmonary edema	B/L NC	-	-	-	Acute PD→ Conservative	Expiry
6 months	F	1	Anuria Edema Acidotic breathing	B/L NC	-	-	Bx:Oxalate crystals in tubules	Acute PD→ CAPD	CAPD peritonitis Expiry
6 months	F	1	Anuria Acidosis Hypertension	B/L NC	-	-	Bx: Oxalate crystals in tubules	Acute PD→ Conservative Mx	Expiry
9 months	M	1	Olig-anuria Convulsion	B/L NC	-	-	-	Acute PD→ CAPD	CAPD X 3 yrs
10 mo	F	2	Anuria Hypertension Pulmonary edema	B/L NC	-	-	-	CAPD	Expiry
12 months	F	2	Hematuria Oliguria	B/L NC	-	-	-	CAPD	CAPD X 6 mo
12 yr	M	1	Anuria Acidosis Convulsions Hypertension Hematuria	B/L contracted calcified kidneys	-	-	-	CAPD→mHD→CAPD	Systemic oxalosis Recurrent chronic pancreatitis, SVC syndrome, B/L Knee joint swelling. CAPD peritonitis. Expiry

Continued.

Age	Sex	PH type	Clinical features	USG KUB	24 hr Urine ox	Stone analysis	Histopathology	Intervention	Outcome
15 yr	M	2	Fever Turbid urine Renal colic Oliguria P/h/o renal stone	B/L HDUN with obstructive calculi	-	-	NxUx: oxalate crystals in tubules	B/L DJS→Left NxUx mHD	mHD X 2.5yrs
39 yr	F	1	Renal colic with LUTO symptoms Recurrent hematuria	B/L HDUN with obstructive calculi Graft: NC	Post Tx: Elevated excretion	-	Graft Bx: Tubular Oxalate crystals +	B/L PCND→PCNL mHD LRKT	CKD V T: CAPD X 2 yrs
40 yr	M	1	Recurrent renal calculi Gross hematuria	B/L renal stones with mild HDN with irregular renal cortical outline	-	Calcium oxalate monohydrate (65%)	-	ESWL mHD	mHD X 5 yrs
45 yr	F	2	Renal Failure of unknown etiology	B/L contracted kidneys with raised echogenicity Graft:NC	Post Tx: elevated excretion	-	-	mHD LRKT	CKD III T: Conservative Mx
46 yr	M	1	Recurrent renal calculi Gross hematuria	B/L HDUN with obstructive calculi	-	Calcium oxalate monohydrate (75%)	-	ESWL PCNL mHD	mHD X 4 yrs

Table 2: Genetic profile of study subjects.

Gene	PH type	Genetic analysis	Mutation	ACMG criteria
HOGA1	3	Exon 1c.134C>T (p.Pro45Leu)	Homozygous missense variation	Uncertain significance
AGXT	1	Exon 2, c.245G>A (p.gly8Glu)	Homozygous	Pathogenic
AGXT	1	Exon 2, c.245G>A (p.Gly82Glu)	Homozygous missense variation	Likely pathogenic
AGXT	1	Exon 2, c.302T>C (p.Leu101Pro)	Homozygous missense variation	Likely pathogenic
AGXT	1	Exon1, c.32C>G (p.Pro11Arg), c.107G>A (p.Arg36His)	Homozygous missense variation	Likely pathogenic
GRHPR	2	p.Gly165Asp)	Homozygous	Pathogenic
GRHPR	2	Exon1 c34A>G,exon4 126bp	Heterozygous	Likely pathogenic
AGXT	1	Exon 1 c.33dupC (p.Lys12GlnfsTer156), c.577dupC (p.Leu193ProfsTer32)	Heterozygous basepair duplication	Pathogenic
GRHPR	2	Exon4, c.349T>C (p.Ser117Pro)	Homozygous missense	Uncertain significance
AGXT	1	Exon1, c.33dupC (p.lys12Glnfster156)	Homozygous	Pathogenic
AGXT	1	Exon1,2c.33dupC, c.2 (p.Lys12Glnfs), Ter 156, p.Gly82Glu	Heterozygous	Pathogenic
GRHPR	2	intron 1 c.84-14_84-13del (intronic), exon 4 c.349T>C (p.ser117pro)	Heterozygous	Uncertain significance

Continued.

Gene	PH type	Genetic analysis	Mutation	ACMG criteria
AGXT	1	intron 5 c.596-2A>G(3' splice site)	Homozygous	Pathogenic

Table 3: Clinical profile of patients as per genetically diagnosed PH type.

	PH1 (n=8)	PH2 (n=4)	PH3 (n=1)
Median age at presentation	6.5 years	8 years	4 months
Male:female	5:3	1:3	0:1
Common presentation	1. Medullary nephrocalcinosis with olig-anuria 2. Recurrent renal calculi	1. Recurrent renal calculi	Recurrent UTI with multiple renal stones
Extra renal involvement	37.5%	None	None
Consanguinity	50%	25%	-
Progression to ESKD	100%	100%	none
Death	37.5%	50%	none

Total thirteen out of fifteen patients were identified to have genetically confirmed PH during study duration. Median age at diagnosis was 1 year with ages ranging from 4 months to 46 years. Out of thirteen cases, six (46.15%) were male. Six (46.15%) had infantile onset, two (15.38%) were diagnosed in adolescence and five (38.46%) presented in adulthood. Nine patients presented in end stage kidney disease (ESKD) with its sequelae, while three patients progressed to ESKD during study duration. Thus, all but one patient progressed to ESKD.

Five (38.46%) children with infantile onset had bilateral nephrocalcinosis and presented in ESKD and one (7.69%) infant presented with multiple renal calculi and recurrent UTI. Recurrent gross haematuria was a presenting feature in five (38.46%) patients, while four (30.76%) patients; three adults and one adolescent had history of recurrent renal calculi. Two (15.38%) cases presented with nephrolithiasis in graft kidney post renal transplant.

Family history of consanguinity was identified in five (38.46%) cases, two (15.38%) cases had family history of renal calculus and none had family history of renal failure or need for renal replacement therapy.

Positive findings on radiological evaluation included presence of radio-opaque stones on X-ray KUB in six (46.15%) and nephrocalcinosis in one (7.69%) case. USG KUB confirmed the X-ray findings and also identified cortico-medullary nephrocalcinosis in six (46.15%) infants with very early onset.

Tests like calcium oxalate monohydrate predominance on stone analysis (five), elevated 24 hours urinary oxalate excretion (three), histopathological evidence of refractile birefringent oxalate crystals on biopsy/nephrectomy specimen (four), helped narrow down the differentials, among our study subjects.

Genetic analysis done by CES established the diagnosis. Eight (61.54%) patients with AGXT mutation were diagnosed as PH type1, four (30.76%) patients had GRHPR mutation and hence were PH type 2 while one (7.69%) female infant, 4 months old was diagnosed as PH type 3 with HOGA mutation. Nine (69.23%) patients had homozygous and four (30.76%) had compound heterozygous mutations. As per ACMG criteria six (46.15%) mutations were classified as pathogenic, four (30.76%) as likely pathogenic and three (23.07%) as variants of uncertain significance.

Out of thirteen, five (38.46%) patients expired during study duration, five (38.46%) are ESKD requiring dialysis. Two (15.38%) post-transplant patients suffered graft dysfunction leading to graft loss for one and another requiring supportive medical management for deteriorating eGFR. One (7.69%) child has normal renal function on conservative management.

Table 3 describes clinical profile of all three types of PH patients.

PH1

Homozygous/compound heterozygous AGXT gene mutation causes alanine glyoxylate aminotransferase enzyme deficiency leading to PH1 with autosomal recessive inheritance. In our study, total eight patients were identified to have PH1 based on their genetic analysis.

Ages of PH1 study subjects ranged from 4 months to 46 years (median age 6.5 years). Male: female ratio was 5:3. AGXT was the most common mutation found in infantile onset PH, in four of six cases (66.67%). One child presented at age 12 years in ESKD with contracted calcified kidneys. Two cases aged 40 and 46 years had history of recurrent renal calculi with obstructive

complications. One patient presented post-transplant with graft recurrence.

Positive family history of consanguinity was identified in 50% cases. Extra renal involvement was present in three (23%) cases in our study, all of whom had PH1. Recurrent chronic pancreatitis, cardiovascular manifestations with superior venacava syndrome due to extensive involvement of neck veins and skeletal involvement with multiple joint swelling were present in one patient, one had retinal oxalate deposits with cardiac dysfunction, and one patient had severe skeletal manifestations with bilateral knee joint arthritis due to intra-articular calcifications. Since all patients presented in ESKD, laboratory work up was inconclusive. Confirmative diagnosis was established by genetic analysis, details of which are summarized in table 1 and 2.

All eight PH1 patients progressed to ESKD. Of these two adult patients are undergoing haemodialysis and two children are on CAPD. Three children, two with infantile onset PH1 and one adolescent expired during study duration due to RRT related complications. One patient diagnosed post-transplant, 39 year old female who underwent living related renal transplant with spouse donor, had graft loss and is presently managed on CAPD, awaiting combined liver kidney transplant under cadaver transplant program.

PH2

Four (30.76%) patients were diagnosed to have recessively inherited PH2 based on the detection of homozygous/compound heterozygous mutations of GRHPR gene encoding for glyoxylate reductase-hydroxypyruvate reductase enzyme on CES. Median age was 8 years (10mo, 45years), male:female ratio was 1:3.

Out of the four cases with PH2, two presented aged 15 and 34 years with recurrent stone disease and two patients presented in early childhood (10 months, 3.5 years) with bilateral nephrocalcinosis in end stage. Family history of parental consanguinity was present in one case and renal calculus in two cases. None had extra renal involvement.

Out of four all progressed to ESRD. 15 year old boy at present is on hemodialysis. Post living related transplantation, presently CKD Stage 3T, she is being managed conservatively. Two children with early childhood onset were initiated on CAPD but succumbed to disease severity and RRT related complications.

PH3

One (7.69%) female child, first born of non-consanguineous marriage with no significant family history, presented in early infancy at 4 months of age with multiple renal calculi, recurring after two sessions of extracorporeal shock wave lithotripsy (ESWL). She also had two episodes of culture positive UTI within 4 months of life. USG KUB showed bilateral tiny calculi (largest 7 mm) without hydronephrosis. Stone analysis was attempted on urinary gravel post ESWL session which confirmed calcium oxalate monohydrate predominance (70%). This was confirmed by CES. She had homozygous missense mutation of HOGA1 gene encoding for 4-hydroxy 2-oxoglutarate aldolase, classified as variant of unknown significance as per ACMG criteria. With the background clinical and laboratory profile she is diagnosed as PH type 3. Confirmation of mutational pathogenicity awaits parental Sanger's sequencing.

Presently three years of age, on conservative management with citrate and pyridoxine oral supplements and interval ultrasound screening, she has normal renal function and no calculus or UTI recurrence.

DISCUSSION

Primary hyperoxaluria is estimated to affect 1 in 58,000 individuals worldwide, as per NIH data.[14] Type 1 is the most common form, accounting for approximately 80% cases. Types 2 and 3 each account for about 10% of cases.[14] Being a rare disease entity, there is limited literature on varied clinical presentations of primary hyperoxaluria from Indian subcontinent. Furthermore, there is paucity of population specific genetic database. Our study is the largest Indian study on PH in both these regards, to the best of our knowledge.

PH1

Out of thirteen PH patients included in our study, eight (61.5%) had PH1, which is in accordance with PH1 being the commonest genotype. Four (50%) PH1 cases presented during infancy, one (15%) had childhood onset (5-18 years) and three (37.5%) presented in adulthood. Median age at presentation was 6.5 years, youngest patient being 4 months old and oldest 46 years old. Soliman et al15 reported 34.6% of study patients presenting in infancy, 34.6% between 1-5 years of age and 30.8% between 5-15 years of age, with median age at presentation 6 years (range 0.1-29 years). This is in agreement with extended spectrum of PH1 presentation with respect to age.

In our study, infantile PH1 presented with oliganuria, uremia and complications thereof. Adolescent and adult onset PH1 presented with history of recurrent renal calculi±chronic pyelonephritis. Those with obstructive symptoms required lithotripsy/lithotomy or diversion procedures. Comorbidities of CKD superseded, as disease activity progressed with subsequent decline in renal function.

All PH1 patients in our study had ESKD. Majority had phenotypically severe, infantile onset (37.5%) with cortico-medullary nephrocalcinosis. Past history of recurrent renal calculi with progression to ESKD was also a common presentation. This is attributable to lack of awareness regarding underlying metabolic causes of renal stone diseases, particularly among children. Low threshold

of suspicion of a rare disease like PH, improper evaluation and delayed referral precludes timely intervention which explains progression to ESKD.

Study of 26 patients of PH1 by Soliman et al had 65.4% of study subjects presenting with ESKD.[15] In a case series of seven children with PH from a tertiary center in South India, of five children with PH1 mutation, two had ESKD while three others had renal dysfunction at presentation.[12]

History of consanguinity was found in 50% of patients with PH1 in our study which corresponds with autosomal recessive inheritance pattern of the disease. Soliman et al reported a consanguinity of 76.9% in their PH1 study group which is explained by higher prevalence of inbreeding among Egyptian population.[15]

In our study extra renal involvement was identified only in patients with PH1. Three (37.5%) out of eight PH1 patients had extra renal involvement in terms of cardiovascular dysfunction (two), skeletal osteopathy (one), retinal involvement (one) and recurrent cholangitis-pancreatitis (one). In study by Soliman et al, extrarenal manifestations of oxalosis were reported in two of the study patients and did greatly impact their quality of life.[15] One patient had retinal and myocardial affections whereas the other patient had soft tissue, bone and bone marrow deposition. These systemic manifestations could have been avoided by early diagnosis and aggressive renal replacement therapy when indicated.

In our PH1 study group three (37.5%) out of eight cases expired. Infantile oxalosis had very poor outcome with two out of four patients succumbing within few months of diagnosis; one child expired due to septicaemia from CAPD peritonitis and one had complications from systemic oxalosis. One adolescent PH1 patient expired four years after diagnosis du e to systemic oxalosis related complications. Four adult patients progressed to ESKD, including one graft loss due to post transplant recurrence. They are presently on dialysis. Soliman et al15 reported mortality of >40%, Hoeven et al cohort mortality rate was 28% whereas mortality rate found by Harambat et al8 was 13%.[16] Higher mortality rate is probably explained by longer exposure to oxalate load as a result of diagnostic and therapeutic delay. This eventually leads to higher prevalence of renal insufficiency or ESRD at the time of diagnosis, with increased dialysis, transplantation or systemic oxalosis related mortality.

PH2

The second most extensively studied gene responsible for PH is GRHPR. Clinically, although classical presentation is reported as urolithiasis and obstructive complications with older age at onset and lesser severity, presentation similar to PH1 is known.[17] Progression to ESKD is well documented.[18]

In our study, four (30.76%) out of thirteen study subjects were genetically confirmed to have GRHPR mutation. Median age at presentation was 8 years. Johnson et al reported a single centre cohort with thirteen PH2 patients having median age at onset of 1.7 years.[18] This is in contrast to our study due to poor index of suspicion for rare metabolic causes in infantile nephrocalcinosis. This leads to missed opportunity for diagnosing early onset PH2.

Two (50%) out of four patients, one adolescent and one adult, presented with recurrent renal calculi and its sequelae. One infant and one child presented early, with nephrocalcinosis and ESKD. M J Kemper et al reported 71% of their cohort of 24 PH2 patients, having stone disease at presentation.[16] Johnson et al reported 38.46% cases presenting with nephrolithiasis.[18]

Two (50%) of four patients who presented with deranged renal function, subsequently progressed to ESKD. Two others had ESKD at presentation, of these one adult patient was diagnosed posttransplant following graft dysfunction due to recurrence. Johnson et al reported normal renal function for all their study subjects, but one.[18] Our study is in alignment with recent evidence by Garrelfs et al suggesting not-so-benign outcomes for patients with PH2.[19]

There was no extra renal involvement among PH2 patients in our study. This is in accordance with Kemper et al and Johnson et al.[17,18]

In our experience, both early onset cases of PH2 had poor outcomes. They were offered CAPD and expired due to disease and RRT related complications. The adolescent with PH2 is on mHD for the last two and half years listed for deceased donor transplantation. The patient with post-transplant recurrence has progressively declining graft function, on conservative management. Transplant recommendations (isolated kidney versus combined liver kidney) need more evidence based inputs for PH2 patients. Thus, PH2 is a disease with significant morbidity and mortality.[18]

PH3

It is caused by mutations in HOGA1 gene located on chromosome 10, corresponding to enzyme 4-hydroxy-2-oxoglutarate aldolase 1. Early age at onset (<3 years) with presentation as recurrent hematuria, urolithiasis and recurrent UTI have been reported in the few case series, studied so far.[20-23] Favorable outcomes with rare cases progressing to CKD due to uncontrolled hypercalciuria or complications of urolithiasis have been reported.[23]

We report single case of PH3 diagnosed in a four month old female child. This is the youngest PH3 case reported in India. Patient presented with recurrent gross hematuria and UTI, in accordance with classical presentation described in literature. Metabolic work up suggested hypercalciuria and stone analysis confirmed calcium

oxalate monohydrate (70%). Genetic analysis as per ACMG criteria13 detected HOGA1 mutation as variant of unknown significance, due to absence of similar mutation in standard databases.

Generating indigenous population specific database for genetic diseases like PH will help in diagnostic confirmation for novel gene mutations, prognosticating outcomes and guiding treatment. Furthermore, common population specific mutations can help establish local panels and facilitate financially feasible genetic testing in resource limited settings.

Median age at presentation of our study cohort is one year. Infantile onset PH with severe phenotype may be underdiagnosed and hence underreported. All cases of infantile nephrocalcinosis thereby warrant thorough evaluation including genetic analysis. Likewise, all children with stone disease should undergo meticulous metabolic work up including genetic study, where indicated. Once PH mutation is confirmed, it should be used to screen other family members. This will go a long way in identifying subclinical cases which may benefit from medical management with pyridoxine in case of select mutations (p.Gly170Arg, p.Phe152Ie). Early diagnosis will enable better RRT plan to reduce systemic oxalosis. Pre-emptive transplant strategies can be employed to reduce disease morbidity.

Genetic analysis: Our study concluded AGXT to be the most common gene mutation in PH, which corresponds with PH prevalence reported worldwide. However, the mutations identified were different from previously reported common mutations. Also PH1 mutations like p.Gly170Arg or p.Phe152Ie which respond to pharmacotherapy with pyridoxine have not been reported in our study.[24,25] This highlights need for early RRT.

Three mutations (two PH2, one PH3) were reported as uncertain significance as per ACMG criteria due to paucity of similar mutations reported in standard databases.[13] This may be due to limited genetic mutations identified for the less common PH types. Also standard reference databases used for reporting purpose are poorly representative of Indian population. Hence more genetic studies should be performed for PH patients and national registries be maintained to facilitate detection of novel PH mutations in Indian population.

Two cases of adult onset PH were diagnosed post-transplant following graft recurrence. This could be avoided with pre transplant evaluation for PH. All patients with stone disease, opting for transplant should undergo thorough metabolic work up. For ESKD patients metabolic work up cannot conclusively rule out PH. In these patients, genetic analysis plays an important role in guiding transplantation strategy and optimizing post-transplant outcomes. While PH1 cases with pyridoxine sensitive mutations may benefit from isolated kidney transplant with aggressive peri-transplant oxalate burden management and continuation of pyridoxine post-transplant, most other PH1 cases with CKD stage IV/V will require liver kidney transplant.[26] For PH2, although isolated kidney transplant has been performed for most cases, our experience of post-transplant recurrence suggests otherwise.[18]

There was no genotype phenotype correlation identified in our study, in accordance with the heterogeneous nature of PH.

However, retrospective and single centre data is major limitation of our study. For more robust data, multicentre prospective studies are required.

CONCLUSION

ESKD being commonest presentation high index of suspicion in all cases with renal stone and complete work up should be done for early diagnosis and timely intervention. National registry is required to facilitate detection of novel PH mutations in Indian population.

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