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Article in *Urolithiasis* · June 2017

DOI: 10.1007/s00240-017-0996-8

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# Primary hyperoxaluria in populations of Pakistan origin: results from a literature review and two major registries

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Received: 29 November 2016 / Accepted: 18 June 2017  
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**Abstract** Primary hyperoxalurias (PH) are devastating, autosomal recessive diseases causing renal stones. Undifferentiated hyperoxaluria is seen in up to 43% of Pakistani paediatric stone patients. High rates of consanguinity in Pakistan suggest significant local prevalence. There is no detailed information regarding number of cases, clinical features, and genetics in Pakistan-origin (P-o) patients. We reviewed available information on P-o PH patients recorded in the literature as well as from two major PH registries (the Rare Kidney Stone Consortium PH Registry (RKSCPHR) and the OxalEurope PH Registry (OxER);

and the Aga Khan University Hospital in Pakistan. After excluding overlaps, we noted 217 P-o PH subjects (42 in OxER and 4 in RKSCPHR). Presentations were protean. Details of mutations were available for 94 patients of 201 who had genetic analyses. Unique mutations were noted. Mutation [c.508G>A (p. Gly170Arg)] (present in up to 25% in the West) was reported in only one case. In one series, only 30% had mutations on exons 1,4,7 of AGXT. Of 42 P-o patients in OxER, 52.4% were PH1, 45.2% PH2, and 2.4% PH3. Of concern is that diagnosis was made after renal transplant rejection (four cases) and on bone-marrow

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aspiration (in five). Lack of consideration of PH as a diagnosis, late diagnosis, and loss of transplanted kidneys mandates that PH be searched for diligently. Mutation analysis will need to extend to all exons and include PH 1,2,3. There is a need to spread awareness and identify patients through a scoring or screening system that alerts physicians to consider a diagnosis of PH.

**Keywords** Primary hyperoxaluria · Consanguinity · Oxalate stones · Oxalosis · End-stage renal disease · Pakistan origin · Oxalate crystals · Mutation analysis

The primary hyperoxalurias (PH) are associated with oxalate urinary tract stones, early onset renal impairment particularly in PH1, and tissue oxalate crystal deposition. Because presentation may be so diverse, ranging from asymptomatic patients to those with failure to thrive, haematuria, pyuria, recurrent urinary tract infection, nephrocalcinosis, or anaemia, this disease may escape detection.

A rare autosomal recessive disease, PH, is infrequently reported from Pakistan. This may be from failure to estimate urinary oxalate concentrations especially in paediatric patients and the lack of awareness of some of the characteristics of the disease, which include nephrocalcinosis, pure calcium oxalate monohydrate stones, variable but often early age at onset and early onset renal impairment with associated anaemia.

We believe that a large hidden burden of disease exists in Pakistan, as increasing prevalence of urinary stones is noted in children, [1], 72% of which are now in the upper urinary tract [2]. A significant number of stones may be attributed to PH, particularly in children under 6 months of age. Of 2618 paediatric urolithiasis patients, 24.3% have oxalate crystalluria; ~6% recur after clearance; and 18% have renal failure at presentation and 40–43% hyperoxaluria [2]. The presence of (undiagnosed) PH in adults is suspected, possible as 1.1% (of 449) stones from across Pakistan analysed by Fourier Transformation Infra-Red spectroscopy (FTIR) (June–October 2015) at the Aga Khan University clinical laboratory were pure calcium monohydrate stones (unpublished data from Dr Aysha Habib, clinical Laboratories, AKU). The incidence of PH in children born to P-o parents in West Midlands, UK, is higher than in those born to Western European parents [3]. Pakistan has a high consanguinity rate [4, 5] which makes it likely that this autosomal recessive disease has a high prevalence, as in countries such as Tunisia and in the Middle East [6]. Cochat has noted that 44% of the 78 PH patients in his series had Muslim parents [7].

We sought to review information on the incidence and prevalence of the disorder in those of Pakistani origin to highlight the need for early detection and therapy.

## Objectives

To document the existing burden of PH in Pakistan-origin (P-o) populations.

## Methods

We reviewed medical literature, data from two international PH registries and obtained information from the Aga Khan University hospital, listing all cases of PH in Pakistan-origin (P-o) populations, their clinical presentations, and genetic mutations.

The term Pakistan origin refers to those in whom a parent or both parents were of documented Pakistani origin, in either expatriate or native populations. Genetic documentation, strong clinical data to support a diagnosis of PH, proven hepatic alanine:glyoxalate transaminase (AGT), glyoxylate reductase/hydroxypyruvate reductase (GRHPR) or 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1) enzyme deficiency, or evidence of systemic oxalosis served as inclusion for a diagnosis of PH.

Relevant publications and cases were identified by literature review in Pubmed<sup>®</sup> and Google Scholar<sup>®</sup> and Google<sup>®</sup> search. The Aga Khan University Hospital [AKUH] admission database was analysed and both urology and paediatric surgical colleagues at AKUH were asked to identify if they had treated any cases of PH. Data on P-o patients were reviewed from two recognized data bases—that of Rare Kidney Stone Consortium PH Registry (RKSCPHR) and the OxalEurope PH Registry (OxER). Cases were examined for possible duplication and excluded as appropriate.

## Findings

### Pakistan-origin patients with PH

The initial overall count showed 260 patients. The PH registries yielded 46 patients (42 in OxER, four in RKSCPHR). There were no admissions with PH documented in the AKUH inpatient database. AKUH faculty yielded one ambulatory patient. Most (213) cases were identified using the web-based searches after cross checking with inclusion in the registries (see Table 1).

After exclusion of all potential overlaps, we noted a total of 217 patients in P-o population. Overlaps between cases documented in the Sindh Institute of Urology and Transplantation by Rizvi [2] and Khaliq's [8] report is very likely; hence, 40 patients were eliminated from the final list. For 44 out of these 150, results from their genetic analysis were available, confirming PH1. For all 42 patients included in OxER, either genetic analysis ( $n = 41$ ) or hepatic enzyme study ( $n = 1$ ) was available.

**Table 1** Cases of primary hyperoxaluria in Pakistan-origin patients

Cohort #	Total <i>n</i> of P-o PH patients	Description of probands	Were sibs affected?	Source
1	40	40 PH patients, all in ESRD; in a cohort of 15,093 paediatric stone patients (1998–2012)	Not known	Rizvi [34]
2	150	Possible overlap with cohort #1 [34]	Not known	Khaliq [8]
3	1	Renal transplant failure in adult led to diagnosis of PH. Patient went from Greece/Macedonia to Pakistan for renal transplant	Not known	Spasovski [4]
4	1	9-month-old Pakistani boy with pyuria died at 11 months. No history of renal calculi or hematuria. Renal biopsy demonstrated deposits of calcium oxalate in the tubules and fibrosis of interstitial tissue. There was complete absence of AGT catalytic activity on liver biopsy. Died before transplant	One subsequent sib not affected. Fetal liver biopsy in the mother's subsequent pregnancy showed normal enzymatic activity	Ilium [11]
5	42	P-o in the OxalEurope [OxER] group. 41 were confirmed by genetic analysis and one by liver enzyme studies	Not determined	Courtesy Sally-Anne Hulton and Sander F. Garrelfs
6	1	31-year-old male. Early unrelated-donor-allograft renal failure, led to discovery of increased cortical echogenicity. Demonstration of oxalate on renal biopsy	Not known	Alsuwaida [35]
7	3	2 unrelated persons, Pakistani origin. Presented with PH1 at 4 months and 3 years of age, with the younger patient failing to thrive and progressing to early renal failure, the older one following a relatively benign course with urolithiasis. Absent catalytic activity on liver biopsy. Maternal grandfather and paternal grandmother were sibs. Prenatal diagnosis offered for the subsequent pregnancy after first—it was refused	One brother of one of these patients was also homozygous	Von Schnakenberg [15]
8	1	Oxalate crystals reported in bone marrow in a native Pakistani, one of five such cases in this series, the others being numbers 12, 13, 19	Not known	Hassan [36]
9	1	11-year-old girl from Pakistan with a 5-month history of fever, bilateral loin pain, and progressive weight loss; then dysuria and vomiting. Had passed a stone at 3 years, no investigations done. Bilateral renal stones on ultrasound. Bone and joint pains were from osteodystrophy, an undisplaced subcapital fracture of the left hip and bilateral stress fractures of both lower femurs. Bone biopsy demonstrated oxalate crystals. Ur. Oxalate, 0.67 mmol/l; and glycolate, 0.40 mmol/l. Parents were cousins	Four sisters and a brother were normal.	Cochat [7]
10	(1)	At least one patient probably with HOGA-1 deficit, PH 3, from Pakistan ref by a Pakistani physician	Not known	Monico, Milliner et al. [12]
11	1	Pakistani female girl child 11 years; parents consanguineous. Reported from Hong Kong, with Renal staghorn stone, nephrocalcinosis in the opposite kidney; and musculoskeletal abnormalities. First presented with UTI at age 4 years. 24-h urine oxalate measured 1930 mmol/day. 24-h urine calcium level was normal. Musculoskeletal abnormalities included: osteodystrophy and diffuse osteosclerosis, multifocal intra-osseous lytic lesions and bilateral pathological fracture of femoral neck and proximal humeral diaphyses. Metaphyseal abnormalities were evident over bilateral knees and ankles	Younger sister not affected	Chu [16]
12	1	Detected by oxalate crystals in bone marrow: 37-year-old female, with pancytopenia. 3-day history of migratory arthralgias, fever, vomiting and mouth ulcers, in ESRD from obstructive uropathy and with chronic liver disease for 4 years. Cushingoid facies and right inguinal lymphadenopathy. She was drowsy and had a temperature of 39 °C. Blood film showed pancytopenia with anisocytosis, target cells, polychromasia and nucleated red cells. Crystals of COM found in bone marrow. Diagnosed at AKUH (native Pakistani)	Not known	Sajid [9]

**Table 1** continued

Cohort #	Total <i>n</i> of P-o PH patients	Description of probands	Were sibs affected?	Source
13	1	Oxalate crystals reported in bone marrow (native Pakistani)	Not known	Raza [39]
14	4	From the Mayo Clinic Hyperoxaluria Center and Rare Diseases Consortium	Not known	Milliner (personal communication)
15	1	18-month-old child, [from Koth, West Punjab (Pakistan)]; failure to thrive, polyuria, and polydipsia for 4 months back; first in birth order; non-consanguineous marriage, no significant family history"	Not known	Chanchlani [13]
16	1	At least one patient from the series in this study is from Pakistan Overlap with the 4 patients from RKSCPHR confirmed	Not known	Tang et al. [37]
17	1	Unpublished: one case of proven PH requesting hepatic transplantation (Native Pakistani)	Not known	AKU faculty
18	4	Four members of one P-o family, consanguineous parents: (i) a girl (Kidney transplanted elsewhere, failed); and (ii and iii) her twin brothers, and (iv) a younger brother (all three brothers had liver transplants). All PH type 1. Presented as failure to thrive, with high plasma and urinary oxalate. Pre-transplant, all three showed homogenous medullary nephrocalcinosis. AGT 4 $\mu\text{mol/h/mg}$ (normal 19.1–47.9) in the two in whom it was tested	Yes	Perera [17]
19	2	Oxalate crystals found in bone marrow and on renal biopsy	Not known	Ehsan [38]
20	(3)	Genetic analysis, proven PH2 (these are included in OxalEurope group)	All 3 are of one family	Johnson [10]

Consolidated listing of sources after exclusion of any possible overlap

Number of index patients	Source
150	Khaliq (considered inclusive of 40 patients from Rizvi's cohort 2)
42	OxER (includes the three patients in Johnson's paper [10])
04	RKSCPHR
02	Aga Khan University (one reported in literature)
19	Others
217	Total

Four P-o patients were noted in the RKSCPH Registry. Overlaps between RKSCPHR and two reported cases in the literature (cases #10 and #16 in Table 1) were confirmed by correspondence and excluded. One unreported case of PH (case #17 Table 1) was worked up in a Northern hospital and approached AKU for liver transplantation. The other case from AKUH (case #12 Table 1) was detected after a bone-marrow biopsy for anaemia showed oxalate crystals [9]. Although neither had genetic analysis nor had hepatic enzyme analysis to prove the diagnosis, all presented with the clinical features of PH.

### Clinical spectrum and diagnostic pathway

The majority were children at time of diagnosis. The age of patients was not available in some publications. The youngest presented at 4 months (#7, Table 1). In the subset of 150

native Pakistanis [8], who underwent genetic analysis, the range of age of onset was 1–15 years, with rapid progression to renal failure at adolescence. In the three patients with PH2 in Johnson's series, the age at diagnosis was 0.8–1.8 years, and the age at first stone was 0.8 years [10].

Adult diagnosis is documented. Four patients (one each in cohorts #2, #3, #6, and #18) were diagnosed after renal transplant failure. Five presented as adults with anaemia secondary to oxalate crystals noted in bone-marrow aspirate (#8, #12, #13, and two in #19). One additional patient underwent a bone biopsy (#10), which showed crystals of oxalate in bone. One patient died whilst awaiting transplant in Europe (#4) [11].

Most patients presented with renal calculi; some with pyuria (#4), UTI (#11); or failure to thrive (especially in younger patients—one each in #7, #15, and #18). Median age at first stone in PH2 in a South Asian cohort was

39 months. With a median follow-up of 4 years, only 1 of 13 had a significant decline in renal function [10].

### Confirmation of diagnosis

Hepatic enzyme studies had been done in patient #4, in two siblings of the index case in #18, and in one case from the OxER cohort. All other patients were diagnosed either by genetic analysis or clinical evidence of oxalosis.

### Genetic analysis

Genetic analyses were available on 201 patients—150 by Khaliq, 41 from OxER and 10 from others. Results of detailed analysis beyond exon 1, 4 and 7 in Khaliq's [8] series are still awaited.

Table 2 lists the genetic mutations and the related amino acid code, referenced according to the cohorts, as shown in Table 1.

With analysis limited to exons 1, 4, and 7, Khaliq noted 17 mutations in 44 of 150 patients (29% of their cohort). In the OxER data, 41/42 patients had confirmed genetic analysis. Combining results from genetic and enzyme analysis, 22 (52.4%) have PH1, 19 (45.2%) PH2, and 1 (2.4%) PH 3. Johnson [10], adding 13 cases to the list of known PH2, noted that all but one were from South Asia, three (from one family) of them P-o; the rest were Afghans. In the paper by Monico [12], at least one case of PH3 is included.

Mutations noted in different cohorts varied. c.1049G>A (p.G350D), accounted for 24% ( $n = 10$ ) of all mutations (and 47.6% of the mutations specifically amongst PH1) in OxER data, cohort #5; and 8% of Khaliq's cohort (#2) [8].

c.798–802 del insACAATCTCAG was seen in 4 of 21 (19%) PH1 patients (in OxER). Khaliq noted c.568G>C [p.G190R] in 7 of 44 (16%) PH1 cases and c.33dupC in 5 of 44 (11.3%) [8].

c. 245 G>A [p.G82E] was reported on exon 2 [7] and noted in 2% (cohort #2) [8] to 4.9% (cohort #5) of all mutations. 'Three novel mutations, one splice-site, four index and twelve missense mutations' have been noted without further description [8].

Noticeable was the absence of the most common mutation in Western Europe, and c.508G-A (p.G170R) noted only in one heterozygous patient [4], where it occurred with c.33\_34InsC.

Other mutations unique to Pakistanis were noted in exon 2 (PH1), where Chanchlani [13] (case #15) noted a missense mutation PH1, with substitution of thymidine with cytosine at nucleotide 302 (c.302T>C). On exon 8 PH1, Schnakenberg [14, 15] describes "Nucleotides 920–924 (CATCA) deleted and replaced by ACAATCTCAG,

leading to a shift in the reading frame and the introduction of a stop codon, with a loss of 119 amino acids at the C terminal". This change was noted in only 2.5% of their total PH1 cohort; but occurred in two unrelated P-o families.

Other Pakistan specific mutations have been observed. As an example, Chu [16] noted a novel missense mutation 364 C>T R122X mutation, for the AGXT gene and Perera a c.653C>T (p.Ser 218Leu) mutation [17].

The commonest mutation on GRHPR (Table 2) was c.[403\_404 + 2delAAGT] seen in 15 of 19 (80%) OxER patients, among which two patients had a combination of the c.[403\_404 + 2delAAGT] and c.[540 del T] mutation, and two had c.[494G>A]G165N mutation.

Documentation of mutations in HOGA1 is available for one patient from OxER with c.134C > T.

### Data on estimates of disease burden

Hyperoxaluria in 40–43% of paediatric stone patients [2] is indicative of a potentially high incidence of PH.

### Discussion

This is the first attempt at description of PH in P-o patients. We have included 217 PH cases with documented clinical evidence, hepatic enzyme studies, or confirmed genetic analysis. Possible duplicates were excluded. We have not obtained information by questionnaire or established registry in Pakistan in this preliminary exploration. There are some additional shortcomings to our study: this survey was limited to recorded literature as we have yet to evaluate physician knowledge of the disease, its milder variants, delayed presentation, and existence without hyperoxaluria. We need to survey all hospitals, contact all nephrologists and urologists by questionnaire, and seek information from stone databases. We have not sought information on conservative treatment (e.g., supplementation with pyridoxine) in the reported patient groups.

Information on genetic mutations in this cohort of PH P-o patients was incomplete, but our consolidated series from multiple sources is valuable. Mutations noted in this cohort differ from those generally seen in Caucasian and perhaps the Japanese populations. Mutations were found on exons 1, 4, or 7 of AGXT in only 30% [8] as compared to 77% [17] noted in Caucasian populations. In PH2, the Exon4/Intron 4 missplicing c.[403\_404 + 2delAAGT] were seen in ~80% of P-o patients in OxER and in 37.8% of PH2 patients in Takayama's [18] series (where 78%–7/9 of those with this mutation were from the Indian subcontinent).

**Table 2** Mutations seen in AGXT gene in P-o patients

Genetic	Protein (Single Letter Code)	Cases with this mutation N (% of proven PH1 in that cohort) [references]	Cross reference to cohort/patient # in Table 1
c.1049G < A	p.G350D	8 (18%) of 44 known P-o PH1 with mutations on 1,4,7 exons in cohort 2) [8]	2
		10 (48% of 21 P-o PH1) [from OxER data]	5
AGT-Mi allele		12 of 44 (27%) [8] occurred in combination with p.G350D	2
c.568G>C	p.G190R	7 of 44 (16%) [8]	2
c.245G>A	p.G82E (p.Gly82glu)	1 [7]	9
		2 of 21 P-o patients with PH1 [OxER data]	5
		3 of 44 (7%) [8]	2
c.508G>A	p.G170R p.Gly170Arg	0 of 44 [8]	2
		1 case reported [4] (Spasovski)	3
c.33dupC		5 (11.3% of 44 known PH1, 3.3% of 150 patients) [8]	2
c.33_34InsC		1 [4]	3
c.245G>A		2 of 21 (9.5%) [OxER data]	5
c.798-802 delinsACAATCTCAG		4 of 21 (19%) [OxER data]	5
c.653C>T	p.S218L (p.Serine218Leucine)	1 of 21 [OxER data]	5
c.653C>T	p.S218L (p.Serine218Leucine)	Seen in a patient, her (twin) brothers and another brother [17]	18
c.302T>C	p.L101P (HGMD ID CM093792)	2 of 21 [OxER data]	5
c.302T>C	p.L101P (HGMD ID CM093792)	1 [13] This patient had a PTH level of 788 pg/ml	15
c.922C>T	p.Gln308Ter	1 of 21 [OxER data]	5
Combined deletion and insertion in exon 8		3 (in two Pakistani families in which one additional sib was homozygous) [14]	7
c.364 C>T R122X		1 [16]	11

The terms ‘Asian origin’ and ‘Indian subcontinent’ are vague and misleading. Asia is composed of many genetically distinct populations. The word Indian subcontinent should be replaced by the term South Asia, which includes Afghanistan, India, Pakistan, Sri Lanka, Bangladesh, Nepal, and Bhutan. It includes populations in which the current mtDNA represents the original invasions of the ‘mother’ mtDNA (and who are mainly in the Deccan peninsula) as well as those in the northern areas of South Asia, which have been subject to many invasions of fresh mtDNA from the North-Western corridors.

For the AGXT gene, a comprehensive genetic analysis of all 11 exons is required, because (i) the >150 known mutations in PH occur across all 11 exons [19] and (ii) mutations have been noted in P-o patients on other exons: on Exon 2 by Cochat [3] Chanchlani [13] and on Exon8 (von Schnakenburg) [15]. Limiting the analysis to exons 1, 4, 7 (PH1) will miss other unique mutations reported in P-o

persons. Some will question the use of gene wide screening of all exons, but it is well known that some genetic variations are ethnically determined, and would be missed by limited screening [20].

In addition, GRHPR and HOGA1 should also be considered, after initial screening the urine for glyceric acid for PH2 and HOG, DHG, and 4-OH-Glu metabolites for PH3. We know from Monico’s report [12] that at least one of the patients with HOGA1 mutation was from Pakistan, and the OxER documents a significant number of patients with PH2. Johnson [10] reports on additional cases with PH2, all but one originated from South Asian region, from Pakistan (three patients), and Afghanistan.

In Mandrile’s [21] analysis of 410 patients (from the OxER) with documented AGXT genotype, nearly, 10% of patients were from ‘other countries’, which included a very wide swathe of countries inclusive of Afghanistan and Pakistan. Our data from the OxER pertains to those

registered as Asians in whom ethnicity was attributed to Pakistan and who had genetic or liver enzyme study confirmation of the disease.

We suggest that genetic analysis algorithms will need to be modified. Alternatives of whole genome sequencing and testing for a panel of genes will need to be considered for P-o patients. This would provide important knowledge that will help to better understand the PH spectrum in Pakistan.

### The ‘missing’ genetic mutations

Coulter-Mackie [22] draws attention to the fact that some genetic mutations such as c.508G>A (p.G170Arg) and 33\_34insC show no obvious ethnic associations and have been found in a variety of populations. Danpure [23] has shown that c.508G>A (p.Gly170Arg) allows significant residual catalytic activity, and is found in 20–40% of patients in the West. Only one patient in this series had this mutation.

This has ominous portents: If p.Gly170Arg (c.508G>A) mutation or the Phe152Ile (c.454T>C; p.F152I) mutations are indeed absent, and not unreported, then the P-o population will be unresponsive to pyridoxine therapy, and will develop end-stage renal disease earlier. Harambat reports that patients with p.Gly170Arg (allelic frequency 21.5%) show a delayed onset of renal failure (at a median age of 47 years for homozygotes, 35 years for heterozygotes compared with 21 years for PH without this mutation) [20]. On the other hand, c.33dupC (12% allele frequency in Caucasians) that leads to protein truncation was found in only 3.3% P-o patients.

### Variance in phenotypic expression of genotype

Whilst the ultimate diagnosis of PH rests on genetic analysis, there is considerable variation in phenotypic expression [17]. Population analysis by Hopp [24] suggests that PH is more common than determined from clinical cohorts. This might be because milder forms of PH, in which suspicion of the disease is not raised, result in missed diagnosis. The genetic mutations influencing all three PH enzymes AGT, GRHPR, and HOGA1 will need to be studied, as Beck [25] notes that multi-allelic inheritance might be responsible for the phenotypic variation.

### Ignorance regarding PH and possible missed diagnosis in Pakistanis

As many patients in the OxalEurope registry OxER are of P-o, we suggest that Pakistan could harbour a larger load of PH than we record, and it is worth determining the actual disease burden as this is a devastating disease. Our inability to find more cases might arise from reporting failure,

insufficient awareness, milder forms of disease, and late onset (masquerading as idiopathic stone disease).

### Prediction of future total PH burden in Pakistan

Estimates of disease burden are difficult. Hutchesson, noted an incidence of 1 in 14,552 P-o births in Birmingham [26], an immense number as compared to the estimated incidence rate (1 in 201,777) in NW European new-borns in the same region. This was the finding in a small community isolated from home, in which the gene frequency could have been enhanced beyond that in the parent country (Pakistan). This is likely, because the rate of first cousin marriages (55%) in the Pakistani origin parents is higher than that in the new-born’s maternal grandmothers (33%) [27]. PH incidence in Pakistan might be predicted to be as high as found in the P-o population in Birmingham, because similar rates of consanguinity, ‘biraderi’, and endogamy exist in Pakistan (ranging between 50% [27] and 76%) [3]. This could well increase allele frequency to significantly impact on the incidence of PH [28]. In addition, though an autosomal recessive disorder, there is evidence that in some of the families, more than 25% of the siblings are affected.

Extrapolation of Western incidence such as the prevalence rates from North American data in the RKSCPHR (which suggests a prevalence of 1 in 58,000 and carrier rate 1 in 70), to Pakistani population would be erroneous, as the population demographics are different. In Pakistan, 33% are under 15 years of age, whilst in the UK, this group only represents 17.3%. Age standardized rates are not available. Nevertheless, based on Western data, we would have 24–62 patients a year and a total existing PH burden ranging between 40 and 2897.

In Pakistan, high consanguinity rates increase the chances for manifestation of this autosomal recessive disorder. One could argue that continuous intermarriage would eventually eliminate deleterious recessive genes, especially in a fatal condition such as PH. However, reproductive compensation occurs in these groups to maintain a level of persistence of the disease [29], and thus, we need to draw attention to the importance of considering a diagnosis of PH in this population.

More insight into the disease burden in Pakistan is pivotal to improve therapeutic strategies for this devastating disease, especially with new promising therapeutic modalities under development [30, 31]. There are options for genetic counselling and chorionic villus biopsy in subsequent pregnancies. Loss of kidney transplants in undiagnosed cases can be avoided and screening must be considered appropriately in transplant recipients [32]. Focused effort is needed to detect all patients. Cases will continue to be missed because of lack of awareness and



failure to estimate urinary metabolites; glycolate, glycinate, 4-hydroxy-2-oxoglutarate (HOG), and 2,4-dihydroxyglutarate (DHG) (which are raised in PH1, 2 and 3, respectively) [33]. Better understanding of the PH spectrum in Pakistan (including its common mutations) will help to set up a cost-effective, first-line investigation pathway to diagnose PH in an earlier stage of the disease course.

## Conclusion

1. This preliminary survey suggests high numbers of P-o patients in Pakistan.
2. Information on PH needs to be disseminated to all urological units in Pakistan, and a PH risk *score card* developed to alert the need for detailed diagnostic evaluation.
3. Methods for chemical analysis and normal ranges of 24-h urines and spot samples for oxalate: creatinine ratio should be standardized across Pakistan. Physicians need to be urged to investigate urinary excretion of oxalate and other metabolites.
4. Genetic analysis for diagnosis of PH will need to include investigation of AGXT (all exons), GRHPR, and HOGA1 as appropriate.
5. All children presenting with renal stones, and adults presenting with recurrent stones should be evaluated with at least one urinary oxalate and possibly a glyceric acid excretion screen.
6. A registry of urinary tract stone disorders needs to be initiated in Pakistan to contribute data and provide valuable information for physicians nationally and internationally.

**Acknowledgements** We acknowledge the support and valued critique of earlier drafts of this paper by Professor Dawn S Milliner, Director, Rare Kidney Stone Consortium, and principal investigator, Primary Hyperoxaluria group, Mayo Clinic Hyperoxaluria Center, Rochester. We acknowledge with gratitude the contribution of data from the OxalEurope registry (see <http://www.oxaleurope.com>) and the sharing of laboratory data by Farooq Ghani, M.B.B.S., M.S., Ph.D., FACB, Diplomate American Board, Service Chief & Director Clinical Laboratories, Associate Professor, Department of Pathology, Aga Khan University.

## Compliance with ethical standards

**Conflict of interest** All authors have declared that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Funding** This study has not received any grant funding.

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