KI REPORTS
KIReports.org

Decoding Loin Pain Hematuria Syndrome: In-Depth Review of Clinical Characteristics and Family History

Bhanu Prasad[1,2], Aditi Sharma[3], Aarti Garg[3], Pouneh Dokouhaki[4] and Mathew B. Lanktree[5]

[1]Section of Nephrology, Department of Medicine, Regina General Hospital, Regina, Saskatchewan, Canada; [2]College of Medicine, University of Saskatchewan, Regina, Saskatchewan, Canada; [3]Institute for Microbial Systems and Society, University of Regina, Regina, Saskatchewan, Canada; [4]Department of Pathology and Lab Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; and [5]Division of Nephrology, St Joseph's Health Care Hamilton, Departments of Medicine and Health Research Methodology, Evidence and Impact, McMaster's University, Hamilton, Ontario, Canada

Correspondence: Bhanu Prasad, Regina General Hospital, 1440, 14th Avenue, Regina, Saskatchewan, S4P 0W5, Canada.
E-mail: bprasad@sasktel.net

Received 27 June 2023; revised 25 August 2023; accepted 29 August 2023; published online 7 September 2023

Kidney Int Rep (2023) **8,** 2826–2829; https://doi.org/10.1016/j.ekir.2023.08.040

INTRODUCTION

Hematuria is quite common and accounts for over 20% of urology evaluations.[1] In screening studies among healthy volunteers, the prevalence ranges from 2.5% to 31%.[2] Although isolated hematuria (IH) is a common occurrence, the reported prevalence of loin pain hematuria syndrome (LPHS) is 1 in 10,000. The low prevalence of LPHS is likely due to the condition being a diagnosis of exclusion and therefore being underappreciated and underdiagnosed. Patients with IH and patients with LPHS share common features such as the absence of urological disease and the presence of glomerular hematuria. For reasons that are as yet unclear, patients with LPHS experience debilitating unilateral or bilateral flank pain, originating from the kidneys.

Is LPHS an "umbrella term" for all patients with glomerular hematuria and pain with differing etiopathogenesis or is it an independent entity. Is it a kidney disorder or "renal migraine" where neurogenic stimuli lead to the release of vasoactive neuropeptides or is it a somatization disorder. As part of disentangling any unexplained illness, it is essential to perform a thorough phenotype assessment (physical characteristics, family history, and comorbidities). Phenotyping allows us to stratify patients and understand disease mechanisms. In this paper, we performed detailed phenotype assessment and pedigree analysis on patients with LPHS and compared them with patients with IH.

RESULTS

Methods are provided in a supplementary file. All the 24 patients with LPHS and 10 patients with IH agreed to participate and their demographic data is presented in Table 1. Patients with LPHS were predominantly female (87%), with median age of 41 years (interquartile range 36–48). Of the patients with LPHS, 16 (67%) had microscopic hematuria, and 8 (33.3%) reported gross hematuria with exacerbations of loin pain. Nine (37%) patients reported bilateral pain, with 83% reporting opiate use with a median dose of 19 mg (0.1–78 mg). The median creatinine was 64 μmol/l (interquartile range 54.7–69.2) with albumin-to-creatinine ratio of <2.0 mg/mmol. Thirteen of 24 (54%) patients had a preceding history of kidney stones, but none had an obstructing stone on imaging at the time. There was a lag time of 6 years between the median age at onset (30 years) and at diagnosis (36 years) (Table 1). Of the patients with LPHS, 10 of 24 and 5 of 24 were diagnosed with anxiety/depression and asthma, respectively, before the diagnosis of LPHS.

Patients with LPHS in comparison with those with IH had more irritable bowel syndrome (37% vs. 10%), depression/anxiety (58% vs. 20%), migraine (50% vs. 20%), history of frequent kidney infections (37.5% vs. 10%), and history of physical assault (29% vs. 10%). There was also a greater family history of chronic pain (21% vs. 30%), chronic fatigue syndrome (16.7% vs. 0%), and mood disorders (62.5% vs. 30%) (Table 2). We further subdivided the patients into 2 subgroups (patients with preexisting stones vs. spontaneous onset) and did not identify any notable differences (Supplementary Table S1). Analysis of the pedigree charts revealed that 2 patients with LPHS (LPHS-17 and -21) had a history of LPHS in their family. In

Table 1. Cohort characteristics

Demographic data	LPHS Cohort ($N = 24$)	IH Cohort ($N = 10$)
Sex (Female, *n* %)	21 (87%)	8 (80%)
Current age (yrs), median (IQR)	41 (36–48)	56 (51–61)
Age at diagnosis (yrs), median (IQR)	36 (27–44)	50 (48–56)
Age at onset (yrs), median (IQR)	30 (20–41)	50 (48–56)
Marital status		
Single, *n* %	10 (42%)	2 (20%)
Married, *n* %	13 (54%)	8 (80%)
Divorced, *n* %	1 (4%)	0 (0%)
Education level		
In school, *n* %	3 (12%)	0 (0%)
Completed high school and a technical/vocational program, *n* %	6 (25%)	1 (10%)
High school graduate or General Education Diploma, *n* %	5 (21%)	3 (30%)
Less than 4 years of college with an associate degree or equivalent, *n* %	4 (17%)	2 (20%)
College graduate (4- or 5-year program) or master's degree, *n* %	6 (25%)	4 (40%)
Working status		
Not working, *n* %	9 (37%)	0 (0%)
Part-time, *n* %	9 (37%)	2 (20%)
Full-time, *n* %	5 (21%)	7 (70%)
Retired, *n* %	1 (4%)	1 (10%)
Change in working status		
Quit Job, *n* %	9 (37%)	0 (0%)
Reduced hours, *n* %	10 (42%)	0 (0%)
None of the above, *n* %	5 (21%)	10 (100%)
Annual Household Income (CAD)		
Less than $20,000, *n* %	6 (25%)	0 (0%)
$20,000–$49,999, *n* %	5 (21%)	1 (10%)
$50,000–$99,999, *n* %	4 (17%)	3 (30%)
$100,000–$149,999, *n* %	2 (8%)	3 (30%)
More than $150,000, *n* %	7 (29%)	3 (30%)
Hematuria		
Microhematuria	16 (67%)	9 (90%)
Macrohematuria	8 (33%)	1 (10%)
Kidney stones (Yes), *n* %	13 (54%)	0 (0%)
Kidney stone incidence, *n* %		
Never	11 (46%)	0 (0%)
Less than 4 times	4 (17%)	0 (0%)
≥4 times	9 (37%)	0 (0%)
Kidney stone position, *n* %		
Left kidney	3 (23%)	0 (0%)
Right kidney	5 (38%)	0 (0%)
Both sides	5 (38%)	0 (0%)
Pain (Yes)	24 (100%)	0 (0%)
Pain side, *n* %		
Left	8 (33%)	0 (0%)
Right	7 (29%)	0 (0%)
Both sides	9 (37%)	0 (0%)
Opioids (Yes), *n* %	20 (83%)	0 (0%)
Opioid duration (yrs), median (IQR)	4.0 (1.00–7)	0
Morphine milligram equivalent (mg), median (IQR)	19.0 (0.1–78)	0
Diabetes, *n* %	1 (4%)	0 (0%)
Hypertension, *n* %	3 (12%)	3 (30%)
Family history of isolated hematuria (Yes), *n* %	6 (24%)	2 (20%)
Family history of kidney stones (Yes), *n* %	15 (62%)	5 (50%)

CAD, Canadian dollars; IH, isolated hematuria; IQR, interquartile range; LPHS, loin pain hematuria syndrome.

Table 2. Comorbidities and family history of diseases

Comorbidities/family history of disease (*n*, %)	LPHS ($N = 24$)	IH ($N = 10$)
Diabetes	1 (4.2%)	0 (0%)
Blood pressure	3 (12.5%)	3 (30%)
Asthma	5 (20.8%)	1 (10%)
Polycystic ovarian disease	3 (12.5%)	0 (0%)
Endometriosis	6 (25%)	1 (10%)
Kidney stone	13(54.2%)	0 (0%)
Chronic fatigue syndrome	3 (12.5%)	0 (0%)
Gastrointestinal disease/IBS	9 (37.5%)	1 (10%)
Trauma to the abdomen and back	5 (20.8%)	0 (0%)
Anxiety/depression	14 (58.3%)	2 (20%)
Migraine	12 (50%)	2 (20%)
Thyroid	4 (16.7%)	2 (20%)
Rheumatological conditions	2 (8.3%)	0 (0%)
History of frequent kidney infections	9 (37.5%)	1 (10%)
Hysterectomy	7 (29.2%)	1 (10%)
History of physical/sexual assault	7 (29.2%)	1 (10%)
A parent suffering from a chronic disease or chronic pain	5 (20.8%)	3 (30%)
Family history of kidney stones	15 (62.5%)	5 (50%)
Family history of IH	6 (24%)	2 (20%)
Family history of LPHS	2 (8.3%)	0 (0%)
Family history of hypertension	16 (66.7%)	9 (90%)
Family history of diabetes	14 (58.3%)	6 (60%)
Family history of gout	6 (25%)	3 (30%)
Family history of chronic fatigue syndrome	4 (16.7%)	0 (0%)
Family history of asthma	10 (41.7%)	3 (30%)
Family history of mood (depression/anxiety)	15 (62.5%)	3 (30%)
Family history of allergy	15 (62.5%)	5 (50%)
Painful uterine bleeding ≥7 (on a scale of 1–10)	11 (45.8%)	5 (50%)

IBS, irritable bowel syndrome; IH, isolated hematuria; LPHS, loin pain hematuria syndrome.

addition, 6 patients with LPHS (LPHS-01, -02, -04, -05, -11, and -21) and 2 patients with IH (HEMA-01 and -05) had a history of IH in their families (Figure 1).

DISCUSSION

In this paper, we present a thorough and comprehensive assessment of phenotypic characteristics and pedigree charts of 24 patients with LPHS and 10 patients with IH. To our knowledge, this is the first study to report 2 patients with LPHS with a history of LPHS in their families. In addition, 6 patients with LPHS and 2 patients with IH had a history of painless hematuria in their families. In comparison with patients with IH, patients with LPHS had greater family history of mood disorders, chronic fatigue syndrome, painful uterine bleeding, and allergies. This information, to our knowledge, has not been reported before. Similarly, patients with LPHS were likely (in comparison to IH) to have comorbidities such as anxiety/depression, migraine, irritable bowel syndrome, chronic fatigue syndrome, and prior history of physical/sexual assault.

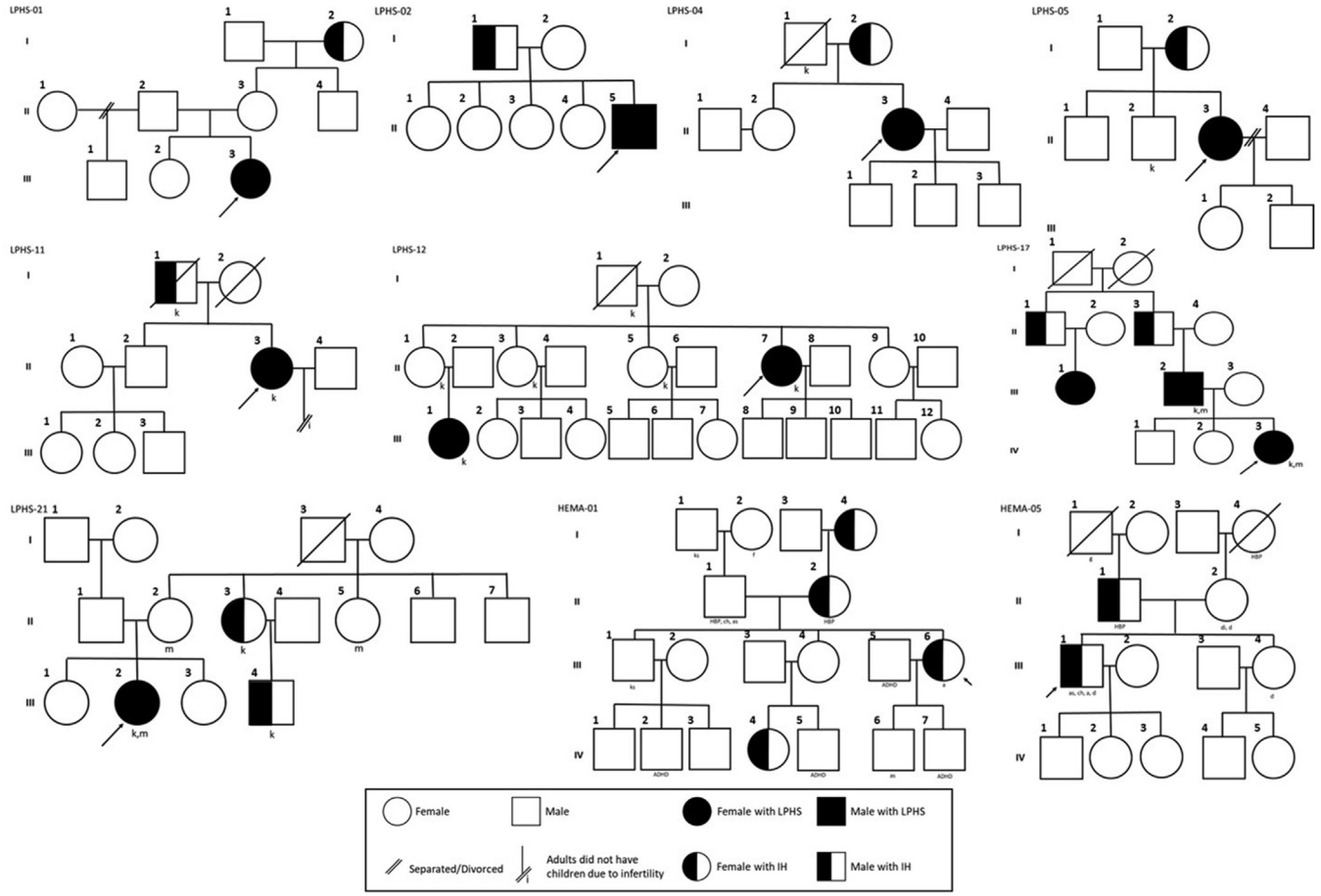

Figure 1. Pedigree analysis of selected patients with a positive family history. Roman numbers represent the generations of the family. The proband is indicated by an arrow. a, anxiety; ADHD, attention deficit hyperactivity disorder; as, asthma; ch, high cholesterol; d, depression; di, diabetes; f, fibroids; g, gout; HBP, high blood pressure; k, kidney stones; m, migraine; r, other renal disease (not IH or LPHS).

We found that patients with LPHS fell into 2 distinct categories. One group had premorbid history of renal stone disease (58%) and the second group had spontaneous onset with no precipitating triggers. Although a third phenotype of patients with LPHS with exercise being the trigger has been reported, we did not see any cases in our cohort. We attempted to have an in-depth look at these 2 groups, but we could not ascertain any differences in the comorbidities or their family history.

As reported in previous cohorts, a high proportion of our patients were predominantly female (87.5%) and the majority of our patients with LPHS were <30 years (54%). The patients with IH were identified during routine health check-ups, whereas patients with LPHS needed repetitive visits with numerous health care providers and emergency room visits for a mean of 6 years before being diagnosed. Of our patients, 58% had a premorbid history of renal stones. The presence of nonobstructive kidney stones on imaging at presentation has been reported by other groups. Leaker *et al.*[3] reported 10 of 25 patients had a prior history of renal stones. Similarly, Greenwell *et al.*[4] reported 10 of 32 patients with urinary tract stones.

Of the patients with LPHS in our cohort, 37.5% reported frequent urinary tract infections with intensification of pain during episodes. Our findings were similar to Goroszeniuk *et al.*[5] (25%) whereas Sheil *et al.*[6] reported 16% with recurrent urinary tract infections. Of our patients with LPHS, 5 of 24 reported asthma preceding the diagnosis of LPHS. Our findings are similar to the series by Bass *et al.* where 4 of 21 patients also reported asthma.[7] Of our cohort, 6 of 24 (25%) had a concurrent diagnosis of endometriosis and there have been previous reports that have reported endometriosis.[8] In our cohort, 50% of patients with LPHS and 20% of those with IH gave a history of migraine. This association has been previously reported with Bass *et al.*[8]

We noticed that 30% of patients with LPHS had a prior history of physical/sexual assault, a factor known to predispose them to chronic pain syndromes. This association, to our knowledge, has not been identified earlier. Chronic pain is often

accompanied by anxiety/depression, sleep, fatigue, and cognitive decline that impact patients' quality of life. Zubair *et al*.[9] reported anxiety and depression in 12 of 21 patients. In our cohort, 14 of 24 (60%) had a history of anxiety and depression with 11 of 14 patients being diagnosed before the diagnosis of LPHS. We observed that 12.5% of patients had chronic fatigue syndrome, and 37.5% of patients had irritable bowel syndrome. We relied on questionnaires for data collection which we acknowledge can result in reporting bias and is a limitation of the study. The sample size of 24 patients, although it limits generalizability of findings, is definitely a sufficient number for evaluation of a rare disease. Although the participants were all followed up with in a single clinic, we do get referrals from across Canada.

We are the first group to conduct a detailed evaluation of physical traits, associated comorbidities, and family genomic links. Phenotyping is the first step in gaining a deeper understanding of disease characteristics. However, there are still gaps in our understanding of this rare and debilitating disease. The next logical step will be to interrogate the genes that encode the filtration barrier. By linking phenotypes to genotypes, we hope to establish a more comprehensive clinical picture and help aid decision making.

DISCLOSURE

All the authors declared no competing interest.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. LPHS cohort characteristics based on subtype.

REFERENCES

1. Mariani AJ, Mariani MC, Macchioni C, Stams UK, Hariharan A, Moriera A. The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. *J Urol*. 1989;141:350–355. https://doi.org/10.1016/s0022-5347(17)40763-4
2. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol*. 2012;188(6 suppl):2473–2481. https://doi.org/10.1016/j.juro.2012.09.078
3. Leaker BR, Gordge MP, Patel A, Neild GH. Haemostatic changes in the loin pain and haematuria syndrome: secondary to renal vasospasm? *Q J Med*. 1990;76:969–979.
4. Greenwell TJ, Peters JL, Neild GH, Shah PJ. The outcome of renal denervation for managing loin pain haematuria syndrome. *BJU Int*. 2004;93:818–821. https://doi.org/10.1111/j.1464-410X.2003.04724.x
5. Goroszeniuk T, Khan R, Kothari S. Lumbar sympathetic chain neuromodulation with implanted electrodes for long-term pain relief in loin pain haematuria syndrome. *Neuromodulation*. 2009;12:284–291. https://doi.org/10.1111/j.1525-1403.2009.00237.x
6. Sheil AG, Ibels LS, Pollock C, Graham JC, Short J. Treatment of loin pain/haematuria syndrome by renal autotransplantation. *Lancet*. 1987;2:907–908. https://doi.org/10.1016/s0140-6736(87)91388-2
7. Bass CM, Parrott H, Jack T, Baranowski A, Neild GH. Severe unexplained loin pain (loin pain haematuria syndrome): management and long-term outcome. *Q J M*. 2007;100:369–381. https://doi.org/10.1093/qjmed/hcm034
8. Sollinger HW, Al-Qaoud T, Bath N, Redfield RR. The "UW-LPHS test": a new test to predict the outcome of renal autotransplant for loin pain hematuria syndrome. *Exp Clin Transplant*. 2018;16:651–655. https://doi.org/10.6002/ect.2018.0236
9. Zubair AS, Cheungpasitporn W, Erickson SB, Prieto M. Clinical and safety outcomes of laparoscopic nephrectomy with renal autotransplantation for the loin pain-hematuria syndrome: a 14-year longitudinal cohort study. *J Evid Based Med*. 2016;9:84–90. https://doi.org/10.1111/jebm.12199