CASE REPORT

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Hypouricemia-associated Xanthine Stones: A Case Report and Diagnostic Approach to Pediatric Genetic Stone Disease

Hipoürisemi ile Seyreden Ksantin Taşı Olgusu ve Çocukluk Çağı Genetik Taş Hastalıklarına Tanısal Yaklaşım

Seçil Kezer[1,2]

[1]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pediatric Nephrology, İstanbul, Turkey
[2]İstanbul University, Institute of Child Health, PhD Program in Kidney Transplantation Research, İstanbul, Turkey

Abstract

Xanthinuria is a rare cause of recurrent nephrolithiasis in childhood, resulting from inherited defects in purine metabolism and typically associated with hypouricemia. Early recognition of xanthine stones is critical, as conventional imaging modalities may fail to detect radiolucent calculi, and delayed diagnosis can lead to recurrent urinary obstruction and chronic kidney injury. Here, we report a pediatric patient with recurrent urinary tract stones and pronounced hypouricemia, in whom a genetic diagnosis of xanthinuria was confirmed. Differential diagnosis was established through evaluation of various biochemical phenotypes, including hyperuricemia, hypouricemia, and hyperuricosuria. In addition to the clinical presentation, this report reviews the genetic and metabolic etiologies of pediatric nephrolithiasis and emphasizes the importance of a structured diagnostic approach. This case underscores the critical role of stone analysis, targeted metabolic assessment, and genetic testing in the management of recurrent pediatric urolithiasis.

Keywords: Nephrolithiasis, purine, uric acid, xanthine

Öz

Ksantinüri, çocukluk çağında tekrarlayan taş hastalığının nadir bir nedenidir. Pürin metabolizmasındaki genetik bozukluklara bağlı olarak gelişir ve hipoürisemi ile ilişkilidir. Ksantin taşında erken tanı oldukça önemlidir; çünkü konvansiyonel radyolojik yöntemler radyolusent taşları gözden kaçırabilir ve geç tanı tekrarlayan obstrüksiyonlara ve kronik böbrek hasarına yol açabilir. Bu yazıda, tekrarlayan üriner sistem taşları olan ve belirgin hipoürisemiye sahip bir çocuk hasta, genetik olarak kanıtlanmış ksantin dehidrogenaz gen hastalığı tanısı ile sunulmaktadır. Hiperürisemi, hipoürisemi ve hiperürikozüri gibi çeşitli klinik tablolar üzerinden ayırıcı tanı yapılmıştır. Klinik tabloya ek olarak, çocukluk çağında taş hastalığının genetik ve metabolik etiyolojileri gözden geçirilerek tanısal yaklaşım vurgulanmaktadır. Bu olgu, tekrarlayan pediyatrik ürolitiazisde taş analizinin, hedefe yönelik metabolik değerlendirmenin ve genetik testlerin önemini ortaya koymaktadır.

Anahtar kelimeler: Ksantin, pürin, taş, ürik asit

Address for Correspondence: Seçil Kezer, MD, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pediatric Nephrology; İstanbul University, Institute of Child Health, PhD Program in Kidney Transplantation Research, İstanbul, Turkey
E-mail: s_alpago@yahoo.com **ORCID:** orcid.org/0000-0002-5828-331X
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Introduction

Urolithiasis represents a significant health burden, affecting approximately 1-5% of the pediatric population. When urinary stones are identified in childhood, a systematic diagnostic approach is essential to uncover the underlying etiology, typically involving a thorough clinical history, a physical examination, and specialized laboratory and imaging evaluations. Genetic investigations are strongly considered in cases characterized by recurrent stone formation, a positive family history, bilateral involvement, or an onset before the age of 5. Moreover, specific laboratory abnormalities, such as hypercalciuria, cystinuria, or hypouricemia, alongside clinical manifestations including nephrocalcinosis, growth failure, and rickets, frequently suggest a genetic basis for the disease. In addition to these systemic assessments, stone composition analysis remains a cornerstone for identifying the precise metabolic etiology of the disease (1-3). The most common causes of pediatric urolithiasis are summarized in Table 1 (adapted from reference 1).

While calcium oxalate remains the most common stone composition in the pediatric population, rare stones resulting from purine and pyrimidine metabolic disorders—including uric acid, 2-8 dihydroxyadenin, xanthine, and orotic acid stones—should not be overlooked (3-9). This case highlights a rare, recurrent stone entity and underscores the importance of a targeted diagnostic approach to underlying disorders of purine and uric acid metabolism.

Case Report

An 11-year-old boy was referred to our pediatric nephrology clinic due to persistent abdominal pain. His medical history was notable for a five-year history of recurrent urolithiasis, requiring two sessions of extracorporeal shock wave lithotripsy and one endoscopic ureterorenoscopy. Despite continuous urinary alkalinization therapy with potassium citrate for five years, the stone disease remained refractory. The patient was born to a consanguineous (first-degree relatives) marriage, and the family history was positive for recurrent nephrolithiasis.

Physical examination revealed a well-appearing child with growth parameters within age-appropriate percentiles. Renal ultrasonography identified a 4 mm stone in the right mid-pole and a 6 mm stone in the left lower pole. Extensive laboratory investigations—including renal function studies, blood gas analysis, electrolytes, 25-OH vitamin D, parathyroid hormone, and alkaline phosphatase—yielded results within reference ranges. However, serum uric acid was markedly low at 0.5 mg/dL. Routine urinalysis showed a pH of 6.0 with no other pathological findings. Further metabolic evaluation through 24-hour urine collection confirmed that the excretion of calcium, oxalate, cystine, citrate, and uric acid was within physiological limits for his age.

Prompted by the combination of profound hypouricemia and recurrent urolithiasis, genetic testing was performed. Molecular analysis identified a homozygous c.140dup p.(Cys48Leufs*12) variant in exon 3 of the *xanthine dehydrogenase* (XDH) gene, confirming the diagnosis of hereditary xanthinuria.

Therapeutic management was adjusted to include a strict purine-restricted diet and aggressive oral hydration, while urinary alkalinization was titrated to maintain a target pH of 7.0. At the one-year follow-up, the patient's condition remained stable, with no increase in stone burden or evidence of new stone formation.

Discussion

In the diagnostic landscape of pediatric urolithiasis, rare etiologies such as uric acid and xanthine stones warrant careful consideration when specific clinical and biochemical markers are present. The metabolic equilibrium between uric acid production and excretion is a delicate balance, and disruptions in this pathway frequently manifest as either hyperuricosuria or hypouricemia, both of which are strong drivers of stone formation. In children, hyperuricosuria is relatively common due to physiologically higher age-dependent excretion rates; however, it can also be a harbinger of pathological states such as tumor lysis syndrome, myeloproliferative disorders, or excessive intake of purine-rich foods and fructose-containing beverages. While chronic hyperuricemia in adults is primarily associated with gout resulting from decreased renal urate excretion (8), pediatric cases more often reflect underlying genetic etiologies, including SLC2A9 polymorphisms and rare enzymatic disorders such as PRPS1 superactivity and hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) (9).

A critical turning point in the evaluation of our patient was the detection of profound hypouricemia, defined as a serum uric acid level below 2.0 mg/dL. In the context of recurrent stone disease, hypouricemia serves as a hallmark for two distinct pathophysiological categories: Decreased production or increased renal wasting. The primary causes

Table 1. Genetic causes of urinary stone disease [adapted from Edvardsson et al. (1)]

Type of stone	Disease/metabolic disorder	Gen(s)	Mode of inheritance	Pathogenesis mechanism
Calcium oxalate	Primary hyperoxaluria Types 1-3	*AGXT, GRHPR, HOGA1*	AR	Increased oxalate production
Calcium phosphate	Distal renal tubular acidosis (dRTA)	*ATP6V1B1, ATP6V0A4, SLC4A1*	AD/AR	Alkaline urine, hypocitraturia
Calcium oxalate/ phosphate	Dent disease Types 1-2	*CLCN5, OCRL*	X	Proximal tubule dysfunction
Calcium phosphate	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	*CLDN16, CLDN19*	AR	Claudine defect → Ca/Mg loss
Calcium phosphate/ oxalate	Familial idiopathic hypercalciuria	*CASR, CLDN14, SLC34A1, SLC34A3 SLC8A1, SLC12A1*	Polygenic	Increased calcium excretion
Cystine	Cystinuria	*SLC3A1, SLC7A9*	AR	Reabsorption defect
Xanthine	Hereditary xanthinuria	*XDH, MOCOS*	AR	Xanthine oxidase deficiency
Uric acid	Lesch-Nyhan syndrome	*HPRT1*	X	Uric acid elevation (7)
Uric acid	PRPP synthetase superactivity	*PRPS1*	X	Elevation of purine synthesis (8)
Orotic acid	Orotic acidüria	*UMPS*	AR	Pyrimidine synthesis defect
2,8-dihydroxyadenine (DHA)	Adenine phosphoribosyltransferase (APRT) deficiency	*APRT*	AR	2,8 DHA crystal nephropathy
Calcium phosphate	Carbonic anhydrase II deficiency (CA II def.)	*CA2*	AR	Combined RTA + osteopetrosis
Calcium oxalate	Glyoxylate reductase/hydroxypyruvate reductase deficiency (PH2)	*GRHPR*	AR	Glycolate → oxalate stone
Calcium oxalate/ phosphate	NaPi-IIa/IIc transport defect	*SLC34A1, SLC34A3*	AR/AD	Hypophosphatemia, phosphate wasting hypercalciuria
Calcium phosphate	WDR72 mut.	*WDR72*	AR	dRTA phenotype
Calcium phosphate/ oxalate	KCNJ16 mut (dRTA variant)	*KCNJ16*	AR	New diagnosis of dRTA form
Calcium phosphate/ oxalate	TRPV5/TRPV6 mut.	*TRPV5, TRPV6*	AD	Calcium reabsorption defect
Calcium oxalate/ phosphate	Williams syndrome	*ELN*	AD	Nephrocalcinosis, hypercalciuria

of impaired uric acid production, which include various metabolic blockages, are summarized in Table 2. Within this spectrum, hereditary xanthinuria (Types I and II) results from mutations in the *XDH* or *MOCOS* genes, leading to a failure in the conversion of hypoxanthine and xanthine to uric acid. This metabolic arrest leads to markedly reduced serum uric acid levels accompanied by systemic accumulation of xanthine. Given its poor solubility in the renal environment, xanthine readily precipitates, resulting in stone formation, hematuria, or obstructive nephropathy, often manifesting before the age of ten (2,4). Notably, these stones are radiolucent, which complicates their detection on conventional radiography and necessitates a high index of suspicion.

The differential diagnosis of hypouricemia must also account for molybdenum cofactor deficiency and renal urate wasting syndromes. While molybdenum cofactor deficiency affects multiple enzymes and typically presents with devastating neurological sequelae in infancy, renal urate wasting is characterized by normal production but impaired tubular reabsorption. As detailed in Table 3, mutations in URAT1 (SLC22A12) and GLUT9 (SLC2A9) can lead to extremely low serum uric acid levels and remarkably high fractional excretion of urate, occasionally predisposing patients to exercise-induced acute kidney injury (10,11). Furthermore, adenine phosphoribosyltransferase deficiency represents another recessive purine disorder that mimics this clinical picture through the accumulation

of 2,8-dihydroxyadenine crystals (6). Distinguishing between these entities is vital; for instance, the allopurinol loading test remains a classical tool to differentiate Type I xanthinuria (isolated xanthine oxidase deficiency) from Type II (combined deficiency with aldehyde oxidase), a distinction that carries significant implications for the metabolism of drugs such as azathioprine or methotrexate.

Persistent hypouricemia in recurrent pediatric urolithiasis should prompt evaluation for hereditary xanthinuria even in the absence of abnormal urinary urate excretion. Although xanthine-related urolithiasis accounts for only 0.1% of pediatric stone cases, its management requires a multifaceted approach (12). The cornerstone of therapy is aggressive oral hydration and urinary alkalinization to maintain a target pH of 7.0, combined with strict dietary purine restriction. While the evidence for dietary intervention largely stems from case reports and observational data, reducing purine intake is essential to mitigate the overall stone-forming risk by lowering the daily excretion of xanthine and hypoxanthine (13). In our case, identifying the XDH mutation clarified the etiology and enabled a targeted therapeutic approach, resulting in stabilization of the patient's stone burden over one year. This highlights the indispensable role of genetic profiling and comprehensive metabolic workups in transforming the management of rare pediatric stone diseases from empirical treatments to precision medicine.

Table 2. Etiologies of hypouricemia resulting from ımpaired uric acid production

Disease	Mechanism	Serum uric acid	Urinary uric acid excretion
Xanthinuria Types I-II (XDH and MOCOS)	Deficiency of xanthine oxidase leading to impaired conversion of hypoxanthine and xanthine to uric acid	↓↓↓	↓
Purine nucleoside phosphorylase deficiency	Impaired purine degradation	↓	↓
Severe liver failure	Decreased hepatic uric acid synthesis	↓	↓
Malnutrition/low purine intake	Substrate deficiency for purine metabolism	↓	↓

Table 3. Differential diagnosis of hypouricemia associated with renal urate wasting

Condition	Mechanism	Serum uric acid	Urinary uric acid excretion	Gene(s)	Notes
Renal urate transporter defect	Impaired proximal tubular urate reabsorption	Decreased	Increased	*SLC22A12 (URAT1)*	High risk of exercise-induced acute kidney injury (EIAKI)
Idiopathic renal hypouricemia	Defect in renal urate reabsorption	Decreased	Increased	*SLC2A9 (GLUT9)*	Associated with EIAKI
Fanconi syndrome	Generalized proximal tubular dysfunction with multisubstrate loss	Decreased	Increased	*CLCN5, OCRL, SLC34A1, SLC34A3*	Aminoaciduria, phosphaturia, glycosuria
Dent disease	Proximal tubular dysfunction	Decreased	Increased	*CLCN5, OCRL*	X-linked disorder
Wilson disease	Copper-induced tubular injury	Decreased	Increased	*ATP7B*	Fanconi-like syndrome
Drug-induced hypouricemia	Increased renal urate excretion	Decreased	Increased	Not applicable	Losartan, probenecid, salicylates, rasburicase
Carbonic anhydrase inhibitors	Impaired tubular reabsorption	Decreased	Increased	Not applicable	Acetazolamide (reversible)
Systemic conditions (thyrotoxicosis, SIADH, sepsis)	Increased GFR with enhanced urate clearance	Decreased	Increased	Not applicable	Transient hypouricemia

SIADH: Syndrome of inappropriate antidiuretic hormone, GFR: Glomerular filtration rate

Conclusion

The contemporary diagnostic paradigm for pediatric urolithiasis prioritizes targeted metabolic investigations and focused genetic panels, followed by expanded sequencing when initial findings remain inconclusive. Elucidating the precise underlying etiology is paramount, as it directly informs therapeutic interventions, family counseling, and long-term renal preservation strategies. In the presence of unexplained hypouricemia, clinicians must maintain a high index of suspicion for rare metabolic disorders. Because xanthine stones are radiolucent and often remain undetected on standard radiography, stone analysis and molecular testing are essential for establishing a definitive diagnosis. This case underscores the critical importance of a comprehensive metabolic and genetic evaluation in children with recurrent stone disease to ensure early intervention and protect renal function.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents for publication of this case report.

Footnotes

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References

1. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28(10):1923-1942.
2. Ichida K, Hosoyamada M, Hisatome I, Enomoto A, Hikita M, Endou H, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. J Am Soc Nephrol. 2004;15(1):164-173.
3. Dinour D, Gray NK, Campbell S, Shu X, Sawyer L, Richardson W, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. J Am Soc Nephrol. 2010;21(1):64-72.
4. Arikyants N, Sarkissian A, Hesse A, Eggermann T, Leumann E, Steinmann B. Xanthinuria type I: a rare cause of urolithiasis. Pediatr Nephrol. 2007;22(2):310-314.
5. Akıncı N, Çakıl A, Öner A. Classical xanthinuria: a rare cause of pediatric urolithiasis. Turk J Urol. 2013;39(4):274-276.
6. Mandal AK, Mount DB. Uric acid nephrolithiasis. Annu Rev Physiol. 2015;77:323-345.
7. Edvardsson VO, Sahota A, Palsson R. Adenine phosphoribosyltransferase deficiency. 2012 Aug 30 [updated 2019 Sep 26]. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.
8. Woodward OM, Köttgen A, Coresh J, Boerwinkle E, Guggino WB, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. Proc Natl Acad Sci U S A. 2009;106(25):10338-10342.
9. Torres RJ, Puig JG. Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet J Rare Dis. 2007;2:48.
10. Price KL, Sautin YY, Long DA, Zhang L, Miyazaki H, Mu W, et al. Human vascular smooth muscle cells express a urate transporter. J Am Soc Nephrol. 2006;17(7):1791-1795.
11. Ichida K. [Uric acid metabolism, uric acid transporters and dysuricemia]. Yakugaku Zasshi. 2024;144(6):659-674. Japanese.
12. Sarkissian A, Babloyan A, Arikyants N, Hesse A, Blau N, Leumann E. Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. Pediatr Nephrol. 2001;16(9):728-732.
13. Valik D, Jones JD. Hereditary disorders of purine and pyrimidine metabolism: identification of their biochemical phenotypes in the clinical laboratory. Mayo Clin Proc. 1997;72(8):719-725. Erratum in: Mayo Clin Proc. 1998;73(2):200.