CASE REPORT

Port J Nephrol Hypert 2023; 37(2): 102-105

Raising Awareness Towards Underdiagnosed Renal Hypouricemia: A Case Report

Pedro Lisboa-Gonçalves[1,2], Filipa Ferreira[1,2,3], Isabel Tavares[1,2,3], João Paulo Oliveira[3,4,5]

[1] Serviço de Nefrologia, Centro Hospitalar e Universitário de São João, Porto, Portugal
[2] Departamento de Medicina, Faculdade de Medicina, Universidade do Porto, Porto, Portugal
[3] Grupo de Investigação e Desenvolvimento em Nefrologia e Doenças Infeciosas, I3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal
[4] Serviço de Genética Médica, Centro Hospitalar e Universitário de São João, Porto, Portugal
[5] Unidade de Genética, Departamento de Patologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

Contributorship Statement:
All authors contributed to the conception and design, data acquisition, analysis and interpretation of data, article drafting, and critical revision.

ABSTRACT

Renal hypouricemia (RHUC) is an autosomal recessive disease caused by the dysfunction of uric acid (UA) transporters in the proximal tubule causing increased fractional excretion of uric acid (FEUA). It is associated with mutations of *SLC22A12* that codifies for URAT1, involved in RHUC type 1, or *SLC2A9* which codifies for GLUT9 and is involved in RHUC type 2. We present the case of a man diagnosed with RHUC type 2 following hospitalization for acute kidney injury (AKI).

A 43-year-old was hospitalized due to AKI after a 20 km walk at an outdoor temperature of 30°C. On the objective examination, he was dehydrated. Blood tests presented severe azotemia (creatininemia 16.43 mg/dL, uremia 254 mg/dL), UA 3.6 mg/dL, fosfatemia 6 mg/dL, Na 138 mEq/L, K 4.2 mEq/L, Cl 102 mEq/l, arterial gasometry with pH 7.35, pCO2 36 mmHg, HCO3 20 mmol/L, lactates 1.4 mmol/L. Urine test with proteinuria and unremarkable sediment. His kidneys had foci of microlithiasis. He started vigorous fluid therapy and sustained improvement in renal function was seen, with no need for renal function replacement therapy. The subsequent evaluation showed hypouricemia <1.5 mg/dL and FEUA of 32.5% (normal range 5.5%-8.5%). The molecular study identified the variant c.1221del p.(His407Glnfs*8) in the *SLC2A9* gene in homozygosis, which established the diagnosis of RHUC type 2.

This case highlights the importance of recognizing hereditary RHUC to prevent its manifestations, including exercise-induced AKI, nephrolithiasis, nephrocalcinosis, and more rarely, progression to stage 5 CKD. Its diagnosis should be considered in individuals with serum UA <2 mg/dL and elevated FEUA. Additionally, it should be confirmed by the identification of mutations in homozygous or compound heterozygous in *SLC22A12* or *SCL2A9*.

Treatment includes xanthine oxidoreductase inhibitors and adequacy of physical activity. The use of uricosuric antihypertensive drugs whose mechanism of action involves blocking the URAT1 transporter should be avoided.

Keywords: Mutation; Renal Tubular Transport, Inborn Errors; Uric Acid; Urinary Calculi

INTRODUCTION

Renal hypouricemia (RHUC) is a rare hereditary disease, transmitted on an autosomal recessive pattern and is defined by the presence of low serum uric acid (UA) levels due to increased renal excretion. This is a direct consequence of loss-of-function or inactivating mutations in one of the two main urate renal transporters located in proximal tubule cells. It is classified as type 1 or type 2 depending on the mutated transporter, urate transporter 1 (URAT1)[1] or glucose transporter 9 (GLUT9), respectively[2] More renal uric acid transporters have been identified, both on the apical and basolateral sides of the proximal tubular cell membranes.[3,4]

Other than URAT1 and GLUT9, only ATP-binding cassette transporter G2 codified by the *ABCG2* gene[5] and sodium-dependent phosphate transporters type 1 and 4 encoded respectively by the *SLC17A1* and *SLC17A3* genes, have been related to human diseases but they present with hyperuricemia and gout and not hypouricemia.[4,6] Nevertheless, there are reports of cases clinically diagnosed as RHUC without genetic resolution, suggesting that other transporters may be implicated diseases related with defects on renal UA handling.[7]

Incidence of RHUC has been estimated to be inferior to 1%, mostly from studies on the Asian population[8,9] but populations from other geographic areas are also affected.[10,11]

Received: 2022/12/01 • Accepted: 2023/03/25 • Published Online: 2023/05/05 • Published: 2023/06/30 • http://doi.org/10.32932/pjnh.2023.05.237

Despite the efforts of estimating its prevalence, this condition is probably underdiagnosed, due to its clinical heterogeneity and lack of awareness from healthcare providers.

Although frequently asymptomatic[12] RHUC may manifest with nephrolithiasis and nephrocalcinosis due to increased fractional excretion of uric acid (FEUA), and severe cases of exercise-induced acute kidney injury (EI-AKI).[13,14]

Data on long-term outcomes are lacking but due to the well-established relation between acute kidney injury (AKI) and chronic kidney disease (CKD), it seems likely that severe, repeated episodes of EI-AKI may lead to CKD and eventually end-stage kidney disease. We report the case of a man diagnosed with RHUC type 2 after hospitalization due to EI-AKI.

CASE REPORT

A 43-year-old man presented to the emergency department complaining of intense asthenia, right flank pain, nausea, and vomiting associated with a perception of decreased urinary output. The symptoms started some days after a 20 km walk during a hot day (outdoor temperature 30°C).

He had been diagnosed with type 2 diabetes mellitus, hypertension, and dyslipidemia 4 years before with no target organ damage diagnosed to that date. He was medicated with metformin 1 g bid, lisinopril/hydrochlorothiazide 20/12.5 mg id, fenofibrate 276 mg id and sinvastatin 40 mg id. He had no family history of kidney disease. His parents were born in close towns but there was no consanguinity.

At hospital admission, he was described as being pale but vital signs were normal, with blood pressure 130/60 mmHg, heart rate 70 bpm, auricular temperature 36.5°C, and respiratory rate 14 cpm. Cardiac and pulmonary auscultation was unremarkable and there was no pedal edema. The abdomen had no alterations at sight, there was no tenderness at palpation, and Murphy's renal sign was negative on both sides. Blood tests (Table 1) showed normal blood counts but severe azotemia, with serum creatinine (sCr) of 16.43 mg/dL, urea 254 mg/dL, glucose 118 mg/dL, UA 3.6 mg/dL, phosphorus 6.0 mg/dL, absence of analytic signs of rhabdomyolysis, mild hyponatremia 132 mEq/L and compensated metabolic acidosis with $HCO3^-$ of 17 mEq/L. Urinalysis had proteinuria 1+ but urinary sediment had no leukocyturia nor erythrocyturia. Glycosuria was not present. Proteinuria was of 700 mg on a 24-hour collection. Kidney ultrasound revealed normal-sized kidneys with preserved sinus-parenchymal differentiation and cortex thickness with no hydronephrosis, albeit some diffuse microcalculi. Doppler study showed no alterations in renal vasculature. The patient was admitted to the internal medicine ward and vigorous fluid therapy with normal saline was initiated alongside the withdrawal of ambulatory medication. The kidney function recovered rapidly, without requiring renal replacement therapy. The patient was discharged after 15 days with a sCr of 1.66 mg/dL and complete resolution of the acid-base disorder, and the diagnosis of AKI in the context of dehydration was assumed. Three years after the initial episode he was referred for evaluation at the outpatient clinic for genetic kidney diseases. At that time, his blood tests disclosed a sCr of 1.05 mg/dL, urea of 48 mg/dL, UA below 1.5 mg/dL, and phosphorus of 3.4 mg/dL. Urinalysis presented glycosuria, assumed to be related to dapagliflozin, hyperuricosuria with FEUA above 32.5% (normal range: 5.5%-8.5%), and unremarkable urinary sediment. There was no history of stone emission nor evidence of a systemic disease affecting the tubular compartment. Therefore, the patient was proposed for genetic testing using Sanger sequencing for the genes of interest (*SLC22A12* and *SLC2A9*). The molecular study identified the pathogenic variant c.1221del p.(His407Glnfs*8) at the *SLC2A9* gene in homozygosity compatible with the diagnosis of RHUC type 2. To the best of our knowledge this mutation has not been described previously, and was not reported on Genome Aggregation Database ("gnomAD"). Afterwards, patient's sister and mother, asymptomatic, were tested and both carried the same mutation, on heterozygosity. The father refused to be tested.The patient was advised to avoid intense and/or prolonged physical exercise, especially in hot environments, to ensure daily water ingestion over 3 L to prevent dehydration, and to avoid anti-hypertensive drugs with uricosuric effects, like losartan.

Table 1

Patient blood tests on hospital admission, discharge, and last follow-up

	Hospital admission	Discharge	Last follow-up
Hb, g/dL	12.7	16.4	16.8
Albumin, g/L	37	44,3	45
Glucose, mg/dL	177	110	116
Urea, mg/dL	254	48	41
Creatinine, mg/dL	16.43	1.05	1.11
Creatine Kinase, mg/dL	50	–	–
Sodium, mEq/L	132	140	140
Potassium, mEq/L	4.3	4.7	4.9
Chloride, mEq/L	96	103	105
Uric acid, mg/dL	4.0	–	<1.5
Total calcium, mEq/L	4.0	5.1	5.0
Phosphorus, mg/dL	6.0	3.4	3.5
Creatine-kinase, ng/mL	0.09	–	0.8
Myoglobin, ng/mL	73	–	29.1

At the last follow-up, his blood pressure was well controlled with perindopril and amlodipine and he was also taking dapagliflozin, metformin, and linagliptin for glycemic control, as long as, fenofibrate and atorvastatin for dyslipidemia. There were no further records of EI-AKI episodes and his last sCr was 1.11 mg/dL.

DISCUSSION

We present a case of a patient diagnosed with RHUC type 2 due to the homozygous variant c.1221del p.(His407Glnfs*8) at *SLC2A9* gene, detected 3 years after the development of a severe episode of EI-AKI. Despite being the most specific clinical manifestation, the diagnosis was not pursued at the presentation revealing the lack of awareness by the clinicians and consequently lack of the necessary therapeutic actions.

Serum UA levels rely on the balance between production and excretion. In normal conditions, two-thirds of urate are excreted in urine and the remaining one-third is eliminated by the intestine. Healthy individuals have FEUA between 5% and 10%.[15] A shift in increasing UA production and/or decreasing excretion will lead to hyperuricemia and the opposite to hypouricemia. Both conditions have been associated with kidney disease.[16]

Based on current knowledge, either URAT1 or GLUT9 transporters dysfunction is involved in RHUC pathophysiology. URAT1 is located on the apical side of the proximal tubule cell membrane and is codified by the *SLC22A12* gene[17] and is a molecular target for some uricosuric drugs, such as losartan, irbesartan, and dotinurab. On the other hand, GLUT9 is located on the basolateral side of the proximal tubule cell membrane, and is codified by the *SLC2A9* gene[18] and is responsible for the uptake of urate to systemic circulation. Genome wide association studies has previously identified several loci implicated on serum uric acid concentration on a population level, particularly *SLC2A9* and *ABG2*.[19] Furthermore, inactivating or loss-of-function mutations on *SLC2A9* have been reported to cause significant hypouricemia.[20]

The most frequent clinical manifestation in RHUC is nephrolithiasis, easily justified by the highly saturated urine with UA. EI-AKI pathophysiology is still a matter of controversy. Some theories have been advocated. On one side, intratubular obstruction by UA could explain AKI during strenuous exercise, which is a well-known trigger of higher UA production which in association with volume depletion can promote its crystallization in renal tubules.[21] Although this can be the culprit in some cases, most cases of EI-AKI related to RHUC show no deposition of UA crystals on renal biopsy specimens.[22] On the other side, an enhanced renal vasoconstriction response in the presence of oxygen reactive species, not counteracted by UA, a potent antioxidant, has also been proposed.[23] However, this hypothesis is counteracted by the absence of EI-AKI reports on patients with xanthinuria, who have also low UA levels due to absent production. A recently published experimental study reported a profound ATP loss in RHUC patients when compared with healthy and xanthinuric patients, proposing that the loss of hypoxanthine, a precursor of UA and a product of ATP/AMP metabolism may cause ATP loss in the renal tubules with tissue damage.[24] The development of a suitable mouse model may help to further clarify the mechanism underlying EI-AKI, with an investigational study using a double knockout for URAT1-Uricase mice model showing a temporary increase in UA serum levels and its urinary excretion during anoxic exercise leading to crystal formation and precipitation. Furthermore, urine pH was decreased after exercise, contributing to kidney dysfunction.[25] Finally, it has also been shown that EI-AKI in patients with RHUC, can be prevented by the administration of xanthine oxidoreductase inhibitors (XOI).[25,26]

To increase awareness of this disease and consequently improve diagnosis, a clinical practice guideline has been published concerning diagnosis criteria.[27] They suggest that RHUC should be suspected based on a continuous serum UA level below 2 mg/dL and increased FEUA while excluding the various alternative clinical scenarios, such as Fanconi syndrome, Wilson's disease, or syndrome of inappropriate secretion of antidiuretic hormone. As our case demonstrates and is also addressed in the guideline, during AKI episodes, serum UA level may be superior to the proposed threshold and should not lead to exclusion of RHUC. Genetic analysis of *SLC2A9* and *SLC22A12* demonstrating homozygous or compound heterozygous pathogenic mutations provides the definitive diagnosis of RHUC.

There is no specific treatment for this disease. Abundant water intake and avoidance of extenuating exercise are important to prevent the two main manifestations, nephrolithiasis and EI-AKI. The use of XOI protects patients from EI-AKI by decreasing UA production and its use is mandatory.[25]

Like the rest of the population, many of these patients will have common diseases such as diabetes or hypertension. A diagnosis of RHUC in this patient directly affects the drugs used to control these diseases. Both losartan and irbesartan are uricosuric drugs by inhibiting the URAT1 transporter, and should not be used in this pathology, especially in RHUC type 2, where the URAT1 transporter is intact and probably determining some degree of UA reabsorption. Similarly, sodium-glucose transporter type 2 inhibitors, recommended on many guidelines as a first-line agent for diabetes treatment, should be prescribed with caution in these patients. These drugs lead to uricosuria in association with increased sodium excretion and glycosuria, leading to inhibition of urate proximal reabsorption[28] and therefore promoting the formation of UA stones and increasing the likelihood of EI-AKI. In fact, enhancement of uric acid excretion by glycosuria seems to be dependent on URAT1 expression[29] and therefore patients with *SLC2A9* mutations may have a higher risk than patients with *SLC22A12,* if medicated with these drugs. This increased risk could be counteracted by increased water intake.

Regarding lesinurab, a recently developed drug used in the treatment of hyperuricemia acts by blocking URAT1, leading to increased excretion of UA, thus mimicking the RHUC type 1 phenotype. Data from phase 3 studies raised concern due to increased cardiovascular mortality and nephrotoxicity findings.[30]

In conclusion, we present a case of RHUC type 2 due to novel homozygous variant c.1221del p.(His407Glnfs*8) at the *SLC2A9* gene diagnosed after an episode of EI-AKI, a typical presentation of this condition. Our case emphasizes the lack of awareness of this disease and its implications. Definite diagnosis with genetic test should be pursued since it leads to therapeutic and lifestyle changes. Although there is no specific treatment available, XOI such as allopurinol should be strongly considered.

■ Acknowledgment

The authors wish to thank geneticists and lab staff from Serviço de Genética Médica, Centro Hospitalar e Universitário de São João, Porto, and from Unidade de Genética, Departamento de Patologia, Faculdade de Medicina, Universidade do Porto for their contribution to the diagnosis of this case.

References

1. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature. 2002;417:447–52.
2. Kawamura Y, Matsuo H, Chiba T, Nagamori S, Nakayama A, Inoue H, et al. Pathogenic GLUT9 mutations causing renal hypouricemia type 2 (RHUC2). Nucleosides Nucleotides Nucleic Acids. 2011;30:1105–11. doi: 10.1080/15257770.2011.623685.

3. Otani N, Ouchi M, Hayashi K, Jutabha P, Anzai N. Roles of organic anion transporters (OATs) in renal proximal tubules and their localization. Anat Sci Int. 2017;92:200–6. doi: 10.1007/s12565-016-0369-3.
4. Jutabha P, Anzai N, Kitamura K, Taniguchi A, Kaneko S, Yan K, et al. Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. J Biol Chem. 2010;285:35123–32. doi: 10.1074/jbc.M110.121301.
5. Zhou D, Liu Y, Zhang X, Gu X, Wang H, Luo X, et al. Functional polymorphisms of the ABCG2 gene are associated with gout disease in the Chinese Han male population. Int J Mol Sci. 2014;15:9149–59. doi: 10.3390/ijms15059149.
6. Sun HL, Wu YW, Bian HG, Yang H, Wang H, Meng XM, et al. Function of uric acid transporters and their inhibitors in hyperuricaemia. Front Pharmacol. 2021;12:667753. doi: 10.3389/fphar.2021.667753.
7. Nakayama A, Matsuo H, Ohtahara A, Ogino K, Hakoda M, Hamada T, et al. Clinical practice guideline for renal hypouricemia (1st edition). Hum Cell. 2019;32:83–7. doi: 10.1007/s13577-019-00239-3.
8. Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. Am J Hum Genet. 2008;83:744–51.
9. Wakasugi M, Kazama JJ, Narita I, Konta T, Fujimoto S, Iseki K, et al. Association between hypouricemia and reduced kidney function: a cross-sectional population-based study in Japan. Am J Nephrol. 2015;41:138–46. doi: 10.1159/000381106.
10. Stiburkova B, Bohatá J, Pavelcová K, Tasic V, Plaseska-Karanfilska D, Cho SK, et al. Renal Hypouricemia 1: Rare Disorder as Common Disease in Eastern Slovakia Roma Population. Biomedicines. 2021;9:1607. doi: 10.3390/biomedicines9111607.
11. Claverie-Martin F, Trujillo-Suarez J, Gonzalez-Acosta H, Aparicio C, Justa Roldan ML, Stiburkova B, et al. URAT1 and GLUT9 mutations in Spanish patients with renal hypouricemia. Clin Chim Acta. 2018;481:83–9. doi: 10.1016/j.cca.2018.02.030.
12. Wang C, Wang J, Liu S, Liang X, Song Y, Feng L, et al. Idiopathic renal hypouricemia: A case report and literature review. Mol Med Rep. 2019;20:5118–24. doi: 10.3892/mmr.2019.10726.
13. Zhou Z, Ma L, Zhou J, Song Z, Zhang J, Wang K, et al. Renal hypouricemia caused by novel compound heterozygous mutations in the SLC22A12 gene: a case report with literature review. BMC Med Genet. 2018;19:142. doi: 10.1186/s12881-018-0595-8.
14. 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;15:164–73.
15. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016;213:8–14. doi: 10.1016/j.ijcard.2015.08.109.
16. Park JH, Jo YI, Lee JH. Renal effects of uric acid: hyperuricemia and hypouricemia. Korean J Intern Med. 2020;35:1291–304. doi: 10.3904/kjim.2020.410.
17. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature. 2002;417:447–52.
18. Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. Am J Hum Genet. 2008;83:744–51.
19. Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. 2013;45:145–54. doi: 10.1038/ng.2500.
20. 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;21:64–72.
21. Yeun JY, Hasbargen JA. Renal hypouricemia: prevention of exercise-induced acute renal failure and a review of the literature. Am J Kidney Dis. 1995;25:937–46.
22. Shen H, Feng C, Jin X, Mao J, Fu H, Gu W, et al. Recurrent exercise-induced acute kidney injury by idiopathic renal hypouricemia with a novel mutation in the SLC2A9 gene and literature review. BMC Pediatr. 2014;14:73. doi: 10.1186/1471-2431-14-73.
23. Murakami T, Kawakami H, Fukuda M, Furukawa S. Patients with renal hypouricemia are prone to develop acute renal failure--why? Clin Nephrol. 1995;43:207–8.
24. Miyamoto D, Sato N, Nagata K, Sakai Y, Sugihara H, Ohashi Y, et al. Analysis of Purine Metabolism to Elucidate the Pathogenesis of Acute Kidney Injury in Renal Hypouricemia. Biomedicines. 2022;10:1584. doi: 10.3390/biomedicines10071584.
25. Hosoya T, Uchida S, Shibata S, Tomioka NH, Matsumoto K, Hosoyamada M. Xanthine Oxidoreductase Inhibitors Suppress the Onset of Exercise-Induced AKI in High HPRT Activity Urat1-Uox Double Knockout Mice. J Am Soc Nephrol. 2022;33:326–41. doi: 10.1681/ASN.2021050616.
26. Hosoyamada M. Hypothetical Mechanism of Exercise-Induced Acute Kidney Injury Associated with Renal Hypouricemia. Biomedicines. 2021;9:1847. doi: 10.3390/biomedicines9121847.
27. Nakayama A, Matsuo H, Ohtahara A, Ogino K, Hakoda M, Hamada T, et al. Clinical practice guideline for renal hypouricemia (1st edition). Hum Cell. 2019;32:83-7. doi: 10.1007/s13577-019-00239-3.
28. Suijk DLS, van Baar MJB, van Bommel EJM, Iqbal Z, Krebber MM, Vallon V, et al. SGLT2 Inhibition and Uric Acid Excretion in Patients with Type 2 Diabetes and Normal Kidney Function. Clin J Am Soc Nephrol. 2022;17:663-71. doi: 10.2215/CJN.11480821.
29. Novikov A, Fu Y, Huang W, Freeman B, Patel R, van Ginkel C, et al. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. Am J Physiol Renal Physiol. 2019;316:F173–85. doi: 10.1152/ajprenal.00462.2018.
30. Sanchez-Niño MD, Zheng-Lin B, Valiño-Rivas L, Sanz AB, Ramos AM, Luño J, et al. Lesinurad: what the nephrologist should know. Clin Kidney J. 2017;10:679–87. doi: 10.1093/ckj/sfx036.

■ Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Corresponding Author:
Pedro Lisboa-Gonçalves
Centro Hospitalar e Universitário de São João
Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
E-mail: Pedro.silgon@gmail.com