Port J Nephrol Hypert 2018; 32(1): 89-91 • Advance Access publication 5 April 2018

An adult patient with hypokalemia

Sandra Brum[1], Ana Rita Santos[1], Catarina Silveira[2], Fernando Nolasco[1], José Rueff[3], Joaquim Calado[3]

[1] Department of Nephrology, Centro Hospitalar de Lisboa Central.
[2] Genomed, Campus do Centro Hospitalar de Lisboa Norte.
[3] Centre for Toxicogenomics and Human Health (ToxOmics), Genetics, Oncology and Human Toxicology, Nova Medical School/ Faculdade de Ciências Médicas, Universidade Nova de Lisboa.

Received for publication: Mar 30, 2018
Accepted in revised form: Mar 30, 2018

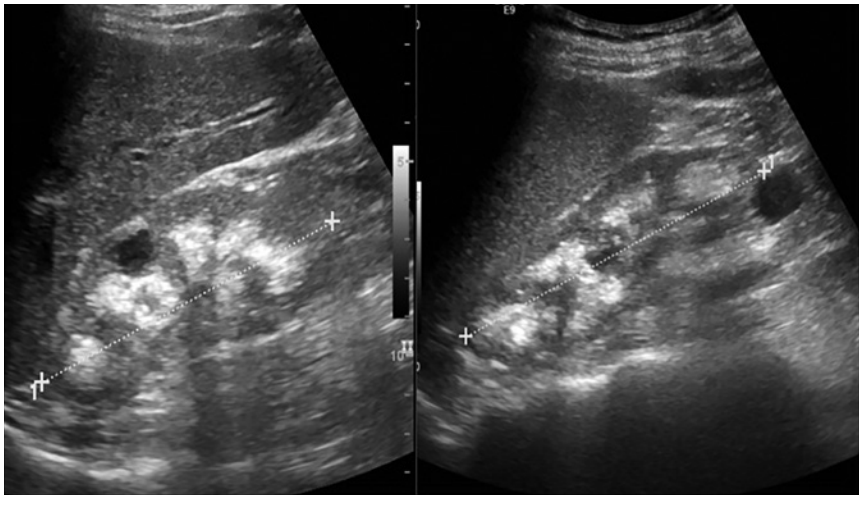
CASE PRESENTATION

SP, a southeast Asian male born in East Timor, was 53 years old by the time he came to our attention. On admittance (13Oct2007) he was complaining of extreme fatigue and lower limb paresis. He was normotensive, hemodynamically stable and not septic. Initial and subsequent lab work is displayed in table 1. Severe hypokalemia of 1.7 mEq/L, together with a hyperchloremic metabolic acidemia, was the most striking finding (EKG is, unfortunately, missing). He had a urine pH of 7; glycosuria was absent. Importantly, since the age of 29 he reported recurrent episodes of symptomatic nephrolithiasis and, on two different occasions, surgical procedures were performed to remove renal stones. A renal ultra-sound revealed bilateral nephrocalcinosis (Figure 1). Potassium supplementation was initiated intravenously. We refrained from initiating iv sodium bicarbonate, in light of the risk of worsening hypokalemia. Ciprofloxacin was prescribed due to leukocytosis and leucocyturia and the possibility of urinary tract infection.

There was no familial history of nephrolithiasis. Recognizable inherited syndromic forms (ocular abnormalities or deafness) of renal tubular acidosis were not apparent. Acquired causes, such as Sjögren syndrome, were also excluded. A diagnosis of primary (and

Figure 1

Renal ultra-sound findings. Papilla and medullary calcifications. Dimensions: left kidney 10.1 cm; right kidney: 10.2 cm.



sporadic) distal tubular renal acidosis (dRTA) was made. The urinary tract infection was thought to have precipitated the clinical presentation. The patient was prescribed potassium citrate 1080 mg orally bid and discharged from the hospital.

■ Hypokalemia – what are the relevant findings in this case?

In an adult patient, hypokalemia can have several causes. The finding of a concomitant hyperchloremic metabolic acidosis excludes extra-renal, such as vomiting, or renal potassium losses, such as surreptitious (loop) diuretic abuse or the inherited Gitelman syndrome. In these circumstances, metabolic alkalosis is the rule, but urinary chloride and potassium concentrations would have been extremely useful. The finding of a non-anion gap metabolic acidosis, in the absence of diarrhea and with a preserved glomerular filtration rate, makes the diagnosis of RTA highly probable in this hypokalemic setting.

■ Renal Tubular Acidosis – what are the relevant findings in this case?

A urinary pH of 7 in tandem with a hyperchloremic (non-anion gap) metabolic acidemia is the most important clue for the diagnosis of dRTA. In addition, nephrocalcinosis (NC) makes a longstanding dRTA highly probable. Proximal RTA rarely causes NC, but the hypophosphatemia could be reminiscent of a more generalized defect of the proximal tubule, Fanconi syndrome. Still, in our case, glycosuria is distinctly absent and the urinary pH is 7. In proximal RTA the distal tubule maintains the ability to properly acidify urine and once plasma HCO_3^- concentration falls below the renal threshold for HCO_3^- excretion -the reduction of it being the major pathophysiology event in proximal RTA- urine can be appropriately acidified.

Although the renal phenotype was correctly assigned to dRTA, its etiology remained unknown. Some acquired causes, such as Sjögren syndrome, can be easily ruled out. In addition, toxic exposure to amphotericin or vanadium are reported as plausible causes. Regarding the latter, the heavy metal vanadium is present at higher than usual concentrations in the soil of some parts of south east Asia, where, for that reason, dRTA is endemic. Our patient, although born in East Timor, lived there only until he was 15, making vanadate toxicity highly improbable. Finally, in an adult patient, a rather mild ("incomplete") inherited phenotype is still a possibility, particularly in autosomal dominant dRTA forms, even in the absence of a family history. However, molecular genetic testing, contrary to pediatric cases, is seldom successful in the adult population.

■ FOLLOW-UP

As an outpatient, he continued to have mild symptomatic nephrolithiasis. While he was on potassium citrate, we periodically checked bone mineralization by dual X-ray absorptiometry, with evidence of moderate mineral bone loss. When the patient was 55 years old, a renal stone was recovered from the urine and its composition was evaluated by infra-red mass spectrometry, revealing calcium phosphate as the major constituent. On follow-up, the patient maintained

Table 1

Relevant laboratory findings at admission and follow-up.

	13/10/2007	19/10/2007	02/2008	03/2011	05/2015	03/2018
Hb (g/dL)	14.3	13.8	14.2	14.7	14.7	14.7
Creat. (mg/dL)	0.92	0.64	1.3	1.1	1.2	1.17
K (mEq/L)	1.7	3.1	3.1	3.9	3.5	4.3
Cl (mEq/L)	111	115	108	111	108	113
Pi (mg/dL)	0.8	2.8	3.2	na	na	na
LDH (U/L)	451	na	653	432	188	151
Bilirubin (mg/dL)	2.9	na	na	1.8	1.9	2.4
pH (art)	7.26	7.35	na	7.38	7.33	na
HCO_3^-(mmol/L)	16	18	na	22.3	16.3	na
CO_2(mmHg)	na	31.5	na	37.3	31.5	na
pH (urine)	7	na	na	7	6.5	7

na, not available.

elevated LDH and total bilirubin levels. When he was 57 years old, a routine abdominal ultra-sound revealed cholelithiasis and cavernous transformation of the portal vein. Since cholelithiasis in pediatric populations often complicates chronic hemolysis, we then performed additional workup and characterized a Coombs negative chronic hemolysis, with persistent undetectable haptoglobin and displaying the typical findings of spherocytosis in the blood smear together with hemosiderosis in liver biopsy. Significantly, and throughout follow-up, anemia was never present.

■ What is the relevance of chronic hemolysis in a dRTA phenotype?

The Cl^-/HCO_3^- exchanger (AE1), encoded by *SLC4A1*, is differentially expressed in the erythrocyte and kidney. The full transcript (eAE1) has a major structural role in the red cell, while the shorter isoform (kAE1) is essential for renal acidification in the distal tubule. In the basolateral membrane of type A intercalated collecting duct cells, AE1 exchanges exiting HCO_3^- by Cl^-, and is therefore critical for distal acidification. Therefore *SLC4A1* mutations can account for hemolytic anemia or dRTA. Since mutations that give rise to spherocytosis/ovalocytosis are different from those responsible for dRTA, the occurrence of a dual hemolytic and dRTA phenotype is extremely rare[1]. Although homozygocity for the V488M allele (variant Coimbra)[2] has been described in the pediatric setting, reported cases involve mostly a compound heterozygous condition for the Δ400-408 allele, responsible for the autosomal dominant southeast Asian ovalocytosis, together with a restricted number of mutations usually responsible for recessive isolated dRTA. So our patient's phenotype and ethnicity made him an ideal candidate in whom such an unusual genotype should be investigated.

■ GENETIC TESTING, FINAL DIAGNOSIS AND CONCLUDING REMARKS

Our patient's *SLC4A1* gene was Sanger sequenced and 3 sequence variations, all in heterozygocity, were found: the c.1199_1225del27 (Δ400-408), the c.166A>G (p.Lys56Glu), known to be in linkage with the former (and therefore in *cis*), and the c.1936C>G (p.Arg646Gly) *novel* mutation. This latter allele is not found within the 1000 Genomes Project or the Exome Aggregation Consortium and is predicted to be pathogenic by *in silico* analysis. The former accounts for hemolysis and the latter for dominant dRTA. The awareness that *SLC4A1* may account for dRTA in the adult populations prompts us to screen for *SLC4A1* mutations in other unexplained and sporadic adult/late-onset cases of dRTA. And, at least, one additional patient was identified with the p.Gly609Arg in heterozycocity, in this instances, an already described disease causing allele.

Table 2

Fully penetrant mendelian phenotypes of RTA

Type of RTA	Gene	Phenotype	Inheritance
Proximal	***SLC4A4*** (NBCe1)	RTA + ocular abnormalities	AR
Proximal & distal	CAII	RTA + osteopetrosis	AR
Distal	***SLC4A1*** (AE1)	RTA ± ovalocytosis	AD & AR
	ATP6VIB1	RTA + hearing loss	AR
	ATP6V0A4	RTA	AR

Different genes can account for inherited forms of RTA, the most frequent are displayed in Table 2 (and reviewed in [3]). Autosomal dominant inherited phenotypes are usually responsible for late onset/adult cases, and, as exemplified in this report, they can sometimes occur in the absence of a positive family history. The advent of next generation sequencing technologies will soon enable a purely genomic approach for the study of tubulopathies, nephrolithiasis in particular[4]. However, and until these gene panels are widely available, a detailed phenotype evaluation can provide invaluable clues for a molecular diagnosis.

Disclosure of potential conflicts of interest: none declared

References

1. Fry AC, Su Y, Yiu V, Cuthbert AW, Trachtman H, Karet Frankl FE. Mutation conferring apical-targeting motif on AE1 exchanger causes autosomal dominant distal RTA. J Am Soc Nephrol. 2012;23(7):1238-49.
2. Ribeiro ML, Alloisio N, Almeida H, Gomes C, Texier P, Lemos C, Mimoso G, Morlé L, Bey-Cabet F, Rudigoz RC, Delaunay J, Tamagnini G. Severe hereditary spherocytosis and distal renal tubular acidosis associated with the total absence of band 3. Blood. 2000;96(4):1602-4.
3. Lifton R, Smolo S, Giebisch G, Seldin D. Genetic diseases of the kidney. First Edition. Academic Press, 2009.
4. Halbritter J, Baum M, Hynes AM, Rice SJ, Thwaites DT, Gucev ZS, Fisher B, Spaneas L, Porath JD, Braun DA, Wassner AJ, Nelson CP, Tasic V, Sayer JA, Hildebrandt F. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. J Am Soc Nephrol. 2015;26(3):543-51.

Correspondence to:
Joaquim Calado, MD, PhD
Department of Nephrology, Centro Hospitalar de Lisboa Central
E-mail: jcalado@nms.unl.pt