Case report

Distal renal tubular acidosis in a patient with Hashimoto's thyroiditis: a case report

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Abstract

Renal tubular acidosis (RTA) is a rare disorder that can be inherited or acquired, and results in an inability of the kidneys to maintain normal acid-base balance. We present a case of recurrent, severe hypokalaemia and rhabdomyolysis in a young woman who had an associated normal anion gap metabolic acidosis and was subsequently diagnosed with distal RTA associated with Hashimoto's thyroiditis. Distal RTA associated with Hashimoto's thyroiditis is rare and probably develops because of autoimmune-mediated mechanisms, causing an inability of the H^+-ATPase pump in alpha-intercalated cells of the cortical collecting duct to secrete H^+, with subsequent failure of urinary acidification. In this case, this hypothesis was supported by the exclusion of common genetic mutations associated with distal RTA. We illustrate that utilizing a systematic, physiology-based approach for challenging electrolyte and acid-base disorders enables identification of the root cause and underlying disease mechanisms.

Keywords: renal tubular acidosis; Hashimoto's thyroiditis; hypokalaemia; rhabdomyolysis

Introduction

Renal tubular acidosis (RTA) is a rare disorder that can be inherited or acquired, and results in an inability of the kidneys to maintain normal acid-base balance. The incidence and prevalence is largely unknown; however, a recent study reported a prevalence of 0.46 *per* 10,000 persons (1). Four types of RTA have been described, namely type 1 (distal), type 2 (proximal), type 3 (proximal and distal) and type 4 (hyperkalaemic type) (2). Conditions affecting the proximal tubule result in an inability to reabsorb filtered bicarbonate, while conditions affecting the connecting tubule and cortical collecting duct (CCD) result in an inability to excrete acid and hence generate new bicarbonate (3). This may result from an inability to secrete either ammonia (NH_3) or H^+, with subsequent failure to excrete sufficient acid in the form of ammonium (NH_4^+) (3).

We present a case of recurrent, severe hypokalaemia and rhabdomyolysis in a young woman who had an associated normal anion gap metabolic acidosis and was subsequently diagnosed with distal RTA associated with Hashimoto's thyroiditis, and discuss the diagnostic and therapeutic challenges that were confronted.

The patient gave written, informed consent to publish and was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC reference number: C22/10/033; Project identification number: 26729).

Case presentation

A 19-year-old woman with no previous medical history presented to her local hospital with severe generalized weakness which started 3-4 days earlier. There was no previous history of similar episodes. The weakness was not preceded by strenuous exercise or a large carbohydrate meal. She denied drinking alcohol, smoking, or using recrea-

tional drugs. She also denied the use of diuretics or laxatives. Other than revealing proximal muscle weakness, the clinical examination was unremarkable. Blood pressure was 117/65 mmHg. There were no clinical features suggestive of systemic lupus erythematosus or Sjogren's syndrome. Laboratory investigations revealed hypokalaemia, a normal anion gap metabolic acidosis and an elevated creatine kinase (Table 1). The urine biochemistry revealed an alkaline urine and a urine potassium-to-creatinine (K/Cr) ratio of 18.2, indicative of renal potassium wasting. The urine sodium concentration was not measured on this initial sample; therefore, the urine net charge could not be calculated. Glycosuria was absent. She was treated with intravenous potassium chloride and had a good response to therapy.

Three months later, the patient returned with the same clinical picture and laboratory profile (Table 1). In addition, the urine net charge (Na + K - Cl) was + 3.6 mmol/L, indicating the absence of uri-nary NH_4^+ excretion. A diagnosis of renal tubular acidosis (RTA) was made. Again, she had a good response to intravenous potassium supplementation. On further enquiry, she denied having a dry mouth, itchy eyes, arthralgia or dyspnoea, but reported unusual cravings for sour foods, particularly lemons. Physical examination revealed normal vital signs, she did not have a goitre, and cardiopulmonary evaluation was unremarkable. Her neurological evaluation revealed decreased muscle strength in upper and lower extremities, both proximally and distally. The tendon reflexes were decreased throughout; however, sensation was intact. Further investigation revealed elevated thyroid stimulating hormone and a low free thyroxine level, with positive anti-thyroglobulin and anti-thyroid peroxidase antibodies in keeping with Hashimoto's thyroiditis. Other tests for autoimmune disorders were negative including anti-nuclear antibodies, anti-double stranded DNA antibodies, anti-SS-A (Ro) and anti-SS-B (La) antibod-

TABLE 1. Blood and urine biochemistry at first and second presentations

Parameter, unit	Normal range	Initial presentation		Second presentation three months later	
		Blood	Urine	Blood	Urine
Na, mmol/L	136-145	141	–	137	101
K, mmol/L	3.5-5.1	1.6	63.6	1.6	17.6
Urea, mmol/L	2.1-7.1	4.3	–	3.8	–
CREA, µmol/L	49-90	67	3500	64	1200
K/Cr ratio	< 1.5 during hypokalaemia	–	18.2	–	14.7
Cl, mmol/L	98-107	116	164	117	115
Osmolality, mOsm/kg	275-295 (serum) 50-1200 (urine)	296	435	297	269
CK , IU/L	20-180	15,390	–	1185	–
pH	7.35-7.45 (serum)	7.20	8.0	7.29	7.5
HCO_3^- , mmol/L	23-29	16	–	17	–
Alb, g/L	35-52	44	–	40	–
Alb-corrected AG*, mmol/L	9-16	9.0	–	4.0	–
Urine net charge, mmol/L	–	–	–	–	+ 3.6
TSH, pmol/L	0.51-4.30	–	–	26.5	–
fT4, pmol/L	12.6-21.0	–	–	9.4	–

*Alb-corrected anion gap (AG) = AG + 0.25 x (44 – measured albumin [in g/L]). Na – sodium. K – potassium. CREA – creatinine. K/Cr ratio – potassium to creatinine (K/Cr) ratio. Cl – chloride. CK – creatine kinase. HCO_3^- – bicarbonate. Alb – albumin. TSH - thyroid-stimulating hormone. fT4 - free thyroxine.

ies. She was initiated on levothyroxine as well as potassium chloride supplementation and was subsequently referred to our centre for further diagnostic investigation.

Further investigations

We performed an intravenous sodium bicarbonate ($NaHCO_3$) loading test for two reasons: (1) to distinguish between proximal and distal RTA, and (2) in the case of distal RTA, to identify whether there was failure of alpha-intercalated cells to pump H^+ into the lumen of the distal nephron. Prior to performing the test, additional oral potassium chloride was administered to correct hypokalaemia. Following the administration of 10 mL of 10% calcium gluconate infusion, an infusion of 4.2% $NaHCO_3$ was started at a rate of 160 mL/h (2.7 mL/kg/h) to alkalinize the urine to a target pH
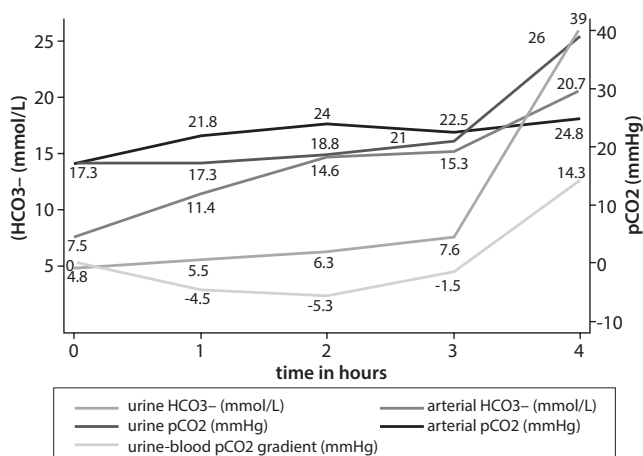

Figure 1. Hourly blood and urine sample results during the 4-hour sodium bicarbonate loading test. HCO_3^- – bicarbonate. pCO_2 - partial pressure of carbon dioxide.

Table 2. Blood and urine biochemistry at baseline and 4-hours following sodium bicarbonate loading test

Parameter, unit	Normal range	Baseline		4 hours	
		Blood	**Urine**	**Blood**	**Urine**
Na, mmol/L	136-145	135	155	138	117
K, mmol/L	3.5-5.1	5.9	105	3.5	100
Urea, mmol/L	2.1-7.1	4	107	4.2	237
CREA, µmol/L	49-90	66	4300	54	8700
Cl, mmol/L	98-107	112	274	103	179
Glc, mmol/L	5.6-6.9 (serum) 0 (urine)	–		6.2	0.4
Osmolality, mOsm/kg	275-295 (serum) 50-1200 (urine)	290	623	292	706
NH_4^+, mmol/L	–	–	0.7	–	0.8
Urine osmolal gap, mmol/L	–	–	- 4	–	35
Urine net charge, mmol/L	–	–	- 14	–	38
HCO_3^-, mmol/L	23-29	7.0	4.3	20.7	26.0
pH	7.35-7.45 (serum)	7.22	6.77	7.51	7.52
Urine pCO_2, mmHg		–	17.3		39.0
Arterial pCO_2, mmHg	35-45	17.3	–	24.7	
U-B pCO_2 gradient, mmHg	> 30	0		14.3	
Fractional excretion of HCO_3^-, %	< 5 > 15 (Proximal RTA)	–	0.94	–	0.78

U-B pCO_2 - urine-blood partial pressure of carbon dioxide. RTA - renal tubular acidosis. Na – sodium. K – potassium. CREA – creatinine. Cl – chloride. Glc – glucose. HCO_3^- – bicarbonate. NH_4^+ - ammonium.

of 7.5. Hourly blood and urine samples were collected. At 4 hours, the urine pH target was reached (Figure 1). The calculated fractional excretion of bicarbonate was only 0.78%, eliminating the diagnosis of proximal RTA and therefore supporting a diagnosis of distal RTA. The calculated urine-blood PCO_2 gradient was 14 mmHg (normal > 30 mmHg), suggesting that the mechanism of the distal RTA was failure of alpha-intercalated cells of the distal nephron to pump H^+ into the lumen (Table 2).

We also performed genetic testing for inherited mutations causing distal RTA because the patient mentioned that her father had similar complaints; however, no potentially pathogenic variants were identified.

Our patient was informed that no genetic mutations were identified. She had a good response to oral potassium chloride, oral sodium bicarbonate and levothyroxine replacement. She was also advised to continue consuming lemons.

Methods

Blood samples for laboratory testing were obtained using a serum separation tube (BD Vacutainer, Becton Dickinson, Wokingham, UK), while blood gas samples were collected via a butterfly needle into a pre-filled, spray-dried calcium-balanced heparin syringe, specifically the BD A-line syringe (also manufactured by BD Vacutainer, Becton Dickinson, Wokingham, UK). The Roche Cobas 6000 analyser (Roche Diagnostics, Mannheim, Germany) was used to measure concentrations of Na, K, Cl, urea and CREA. OsmoTECH Single-Sample Micro-Osmometer (Advanced Instruments, Massachusetts, USA) was used to measure urine osmolality. The plasma ammonia assay on the Roche Cobas 6000 analyser was used to determine urine NH_4^+ concentration. Arterial blood and urine samples were collected at baseline to measure pH (arterial), HCO_3^- and partial pressure of carbon dioxide (pCO_2) using the GEM Premier 5000 from Instrumentation Laboratory Company (Massachusetts, USA). Urine pH was measured at the bedside using a Beckman Coulter pHi 520 pH-meter. Serum creatine kinase, albumin, thyroid stimulating hormone, free thyroxine, anti-thyroglobulin, and anti-thyroid peroxidase were measured on the Roche

Cobas 6000 analyser (Roche Diagnostics, Mannheim, Germany). Manual enzyme immunoassays from Bio-Rad Laboratories Inc. (California, USA) were used to perform tests for anti-double stranded DNA, anti-SS-A, and anti-SS-B antibodies. A manual indirect fluorescent antibody assay from Bio-Rad Laboratories Inc. (California, USA) was used to test for anti-nuclear antibodies.

The genetic testing was carried out using the Invitae diagnostic testing. A saliva sample was obtained and analysed using the Invitae renal tubular disorders panel, which examines 39 genes, including ATPV0A4, ATP6V1B1, FOXI1, SLC4A1, and SLC4A4, for sequence analysis and deletion/duplication testing.

Discussion

We present a case of recurrent, severe hypokalaemia and rhabdomyolysis in a young woman who had an associated normal anion gap metabolic acidosis. The first step was to determine if the patient was in any imminent danger related to hypokalaemia. Due to the muscle weakness, we were concerned about respiratory muscle involvement; therefore prompt treatment with intravenous K^+ was initiated to avoid this. As our patient had recurrent hypokalaemia, intracellular shift of K^+ due to periodic paralysis was initially considered; however, we thought this unlikely because of the associated acid-base disturbance and the obvious renal K^+ wasting indicated by the high urinary K/Cr ratios. This also made gastrointestinal losses of K^+ unlikely.

Renal K^+ wasting due to hyperaldosteronism or diuretic abuse were unlikely since our patient was normotensive and had metabolic acidosis rather than metabolic alkalosis. We believe that the excessive K^+ excretion in the CCD was due to the more negatively charged lumen, related to the bicarbonaturia.

To establish a diagnosis of RTA, urine NH_4^+ excretion should be estimated. The normal renal response to an acidosis is to increase the excretion of NH_4^+, which can be as much as 200 mmol *per* day (3). There remains controversy on the best method for estimating urine NH_4^+ excretion. We prefer using the urine osmolal gap because the

urine net charge assumes, sometimes erroneously, that NH_4^+ is only excreted with chloride (3). A previous study reported a strong correlation between the urine osmolal gap and measured urine NH_4^+ concentration, while the urine net charge performed poorly (4). Urine NH_4^+ can also be measured directly on auto-analysers using the plasma ammonia assay after predilution of the urine specimen (5). In our patient, the urine osmolal gap indicated absent urine NH_4^+ excretion, supporting a diagnosis of RTA.

Diseases affecting the proximal tubule will result in an inability to reabsorb filtered bicarbonate (proximal or type 2 RTA), while diseases affecting the distal nephron may result in failure to excrete acid in the form of NH_4^+ salts (distal or type 1 RTA). Following $NaHCO_3$ loading, the fractional excretion of bicarbonate was only 0.78%, eliminating proximal RTA (6). Therefore, we concluded that distal RTA was present.

The $NaHCO_3$ loading test was also used to probe the mechanism causing the distal RTA. At a urine pH of 7.5, the urine-blood PCO_2 difference was 14 mmHg, indicating a failure of the H^+-ATPase pump to secrete sufficient H^+. A previous study reported that at a urine-blood PCO_2 difference cut-off value of 30 mmHg, the sensitivity and specificity was 100% for a defect involving the H^+-ATPase pump (7). The expression of other targets in alpha-intercalated cells has also been shown to be affected in distal RTA and include the anion exchanger-1 located in the apical membrane, pendrin in the basolateral membrane and intracellular carbonic anhydrase-II (8). Failure of these channels inhibit H^+-ATPase action by causing intracellular alkalosis.

Few case reports have reported on the exclusive association between distal RTA and Hashimoto's thyroiditis (9-13). Females were mostly affected, and at an average age of 30 years. It is speculated that autoantibodies directed toward the H^+-ATPase pump, among others, in the apical membranes of alpha-intercalated cells may be responsible (8). Most studies regarding autoantibody mechanisms of distal RTA have been conducted in patients with Sjogren's syndrome (7,8). Studies that performed immunohistochemical staining have reported absent H^+-ATPase pump expression (7,14,15). Since we did not identify any known genetic mutations resulting in inherited forms of distal RTA, an autoimmune-mediated mechanism was postulated.

Treatment mainly involves correcting hypokalaemia and metabolic acidosis, as well as thyroxine replacement. A recent case report reported dramatic improvement of hypokalaemia and metabolic acidosis within two weeks of potassium citrate and oral prednisone therapy, adding further support to an autoimmune mechanism (16). Our patient responded well to oral potassium chloride, oral sodium bicarbonate and levothyroxine replacement. In addition, our patient had a peculiar craving for lemons, particularly when she experienced leg cramps, which subsided following consumption. Since lemons contain potassium citrate, this may also be considered adjunctive therapy.

One of the study's limitations was the use of the plasma ammonia assay on the Roche Cobas 6000 analyser to measure urine NH_4^+ concentrations, which is not an officially validated method for urine analysis in the laboratory (5). The study could have benefited from additional testing, such as immunohistochemical staining of kidney tissue for the H^+-ATPase pump, as demonstrated by other studies (14,15).

In conclusion, distal RTA, which is linked to Hashimoto's thyroiditis, is rare. The prevailing theory suggests that an autoimmune-mediated mechanism may be the cause, resulting in the inability of the H^+-ATPase pump in alpha-intercalated cells of the CCD to secrete H^+ and subsequent failure in urinary acidification. In this case, this hypothesis has been supported by the exclusion of common genetic mutations associated with distal RTA.

Potential conflict of interest

None declared.

Data availability

All data generated and analysed in the presented study are included in this published article (and its supplementary files).

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