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CASE REPORT

Life-threatening hypokalaemic paralysis associated with distal renal tubular acidosis

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ABSTRACT

A 56-year-old woman developed acute respiratory failure requiring mechanical ventilation due to acute hypokalaemic paralysis. There was no gastrointestinal potassium loss nor was she taking diuretics. Additional analyses revealed a normal anion gap metabolic acidosis with a positive urine anion gap. An acid-load test revealed a renal urine acidification defect, leading to the diagnosis of distal renal tubular acidosis. Normalisation of serum potassium level was established with oral bicarbonate suppletion and temporary potassium suppletion.

KEYWORDS

Acute paralysis, distal renal tubular acidosis, hypokalaemia, metabolic acidosis

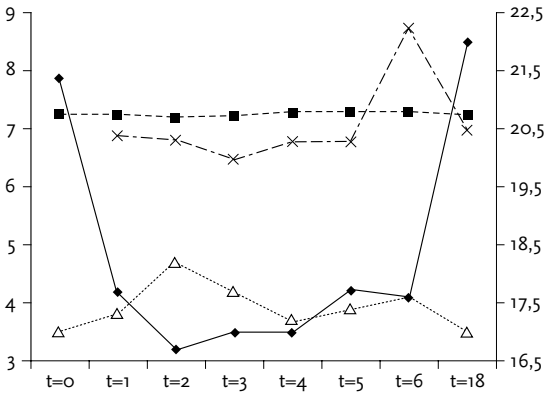
INTRODUCTION

Renal tubular acidosis (RTA) type I or distal RTA is a rare disorder consisting of a defect in renal regulation of acid-base balance and, consequently, in electrolyte excretion. The disease is generally asymptomatic and discovered upon the presence of a chronic, normal anion gap metabolic acidosis in combination with a persistently high urine pH. Although uncommon, patients with RTA type I may present with symptomatic hypokalaemia. We describe a rare case of a patient with this disorder, who presented with acute hypokalaemic paralysis complicated by acute respiratory failure requiring mechanical ventilation.

CASE REPORT

While on holiday, a 56-year-old woman was admitted to the intensive care unit of an Indonesian hospital for acute paralysis complicated by respiratory failure necessitating mechanical ventilation. Severe hypokalaemia (K 1.8 mmol/l) was noted, without symptoms indicating gastrointestinal potassium loss or use of diuretics. Chloroquine was used as malaria prophylaxis. She was referred to our outpatient department of nephrology for investigation of persistent hypokalaemia despite potassium substitution (potassium chloride 600 mg orally four times daily). Besides a transient episode of loss of strength and sensibility in her fingers and complaints of a dry sensation of the mouth but not eyes, her medical history was unremarkable. Physical examination revealed no abnormalities; blood pressure was 100/70 mmHg. Relevant laboratory investigation after cessation of potassium supplementation revealed persistent, mild metabolic acidosis (pH 7.30; base excess -5.4) with a normal serum anion gap (AG 6 mmol/l; N <11 mmol/l) and normal renal function (creatinine 92 µmol/l). Urine pH was high (pH 7.0), urine sodium amounted to 91 mmol/l and urinary calcium excretion to 1.6 mmol/l. A positive urine AG was calculated (38 mmol/l). Additional laboratory investigation revealed a raised erythrocyte sedimentation rate (61 mm/h; N 0 to 20 mm/h), transient hypergammaglobulinaemia (IgG 17.30 g/l; N 7.00 to 16.00 g/l; negative for monoclonal gammopathy) and positive antinuclear antibodies with specificity for anti-SSa and anti-SSb. Plasma aldosterone level (0.45 nmol/l; N 0.04 to 0.35 nmol/l) and plasma renin activity (5.0 ng/ml/h; N 0.3 to 3.5 ng/ml/h) were elevated. Because of the persistent hypokalaemic state with normal AG metabolic acidosis and a positive urine AG, we suspected a renal tubular defect as the primary cause. An acid-load test with NH_4Cl demonstrated a renal acidification defect, indicated by a urine pH persistently above 5.3 despite low plasma bicarbonate levels (*figure 1*). Findings were compatible with a diagnosis of distal RTA. The patient was treated with sodium bicarbonate 1.5 g orally three times daily and temporary potassium suppletion, resulting in normalisation of serum potassium level and of metabolic acidosis.

Figure 1. *Results of acid load test (0.1 g/kg NH_4Cl, orally)*



x-axis presents time in hours after acid load; ■ = serum pH (left y-axis); ◆ = serum bicarbonate levels (mmol/l , right y-axis); △ = serum potassium (mmol/l, left y-axis); × = urine pH (left y-axis).

DISCUSSION

Here we present a patient who suffered from life-threatening hypokalaemic paralysis due to RTA type I. The diagnosis was suspected upon the presence of a normal AG metabolic acidosis with a high urine pH and high urine AG, in the absence of gastrointestinal bicarbonate loss or urine tract infection with an urea-splitting organism.[1] No definitive differentiation between the various types of RTA could be made based solely upon these findings, since clinical data describing the values of the urine AG accompanying proximal RTA during acidosis are few and contradictory.[1,2] Therefore an acid-load test was performed, demonstrating a renal defect in urine acidification due to diminished proton excretion, which only occurs in case of distal RTA.[1]

The incomplete type of distal RTA is a subtype usually presenting with nephrolithiasis or nephrocalcinosis with (near) normal serum pH and bicarbonate levels. Contrary to RTA 1, which originates from a defect in proton excretion, proximal RTA (RTA type II) is caused by a proximal renal bicarbonate reabsorption defect. In the presence of a high plasma bicarbonate level, the distal tubular reabsorption capacity of bicarbonate is exceeded and a higher amount of bicarbonate is excreted. Thus, RTA type II can be verified by determining the presence of a high bicarbonate excretion fraction (>15%) after bicarbonate infusion in a patient with low plasma bicarbonate levels, in contrast to a maximum of 3% in normal subjects and patients with another type of RTA.[1] Features of the different types of RTA are summarised in *table 1*.

Distal RTA can arise as a primary condition, but is usually secondary to other diseases (*table 2*). Hypergammaglobulinaemia was detected initially in our patient, which in itself is a possible cause of distal RTA. The combination of dry mouth and anti-SSa and anti-SSb suggests Sjögren's syndrome. However, signs and/or symptoms necessitating immunosuppressive treatment were absent. Hypokalaemic paralysis may be the solely presenting symptom of Sjögren's syndrome[4-8] or another autoimmune disease (such as systemic lupus erythematosus),[9] sometimes preceding other symptoms by five years.[1]

Several mechanisms in the pathogenesis of the hypokalaemic state in RTA type I are proposed and summarised in *figure 2*. Some small studies and case reports have suggested both the absence of H-ATPase in the apical and cytoplasmic anion-exchanger 1 (AE 1, a bicarbonate/Cl-ATPase) in the basal membrane after immunohistochemical staining of tubular cells underlying RTA I in Sjögren's syndrome.[10,11] Furthermore, higher antibody titres against carbon anhydrase II (CA II) have

Table 1. *Features of the different types of renal tubular acidosis (RTA)*

	RTA I	Incomplete RTA I	RTA II	RTA IV /aldosterone resistance
Defect	Reduced distal H secretion	Reduced distal H secretion	Reduced proximal HCO_3 resorption	Hypoaldosteronism
Plasma pH	(Very) Low	Normal	Low	Low
Plasma HCO_3	Very low – low	Normal	Low	Low - normal
Urine pH	>5.3	>5.3	Variable	<5
Plasma potassium	(Very) Low*	Normal	Low	High
Confirmation test	Acid-load test	Acid-load test	Bicarbonate loading	Plasma
Symptoms & signs	Hypokalaemia (/hyperkalaemia) Osteopenia/osteomalacia Nephrolithiasis/ nephrocalcinosis	Nephrolithiasis/ nephrocalcinosis	Hypokalaemia Osteomalacia	Hyperkalaemia

Omitted is RTA III: a rare, genetic disorder due to carbon anhydrase II deficiency with combined features of type I and II; * = in some cases hyperkalaemia can be present; ** = during metabolic acidosis; * = not obligatory, diagnosis can be made upon laboratory findings alone. Adapted from Rose *et al.* and Soriano *et al.*[1,2]**

Table 2. *Aetiology of distal renal tubular acidosis*

Primary

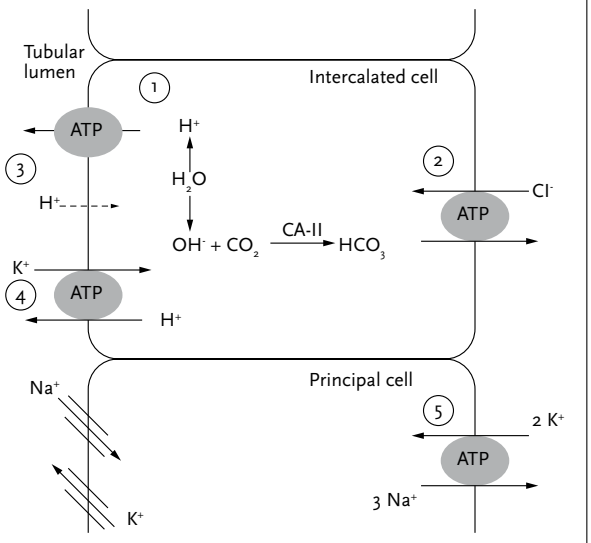
- Idiopathic
- Familial/genetic disorders (autosomal dominant or recessive, Marfan's syndrome, Ehler-Danlos syndrome, Wilson's syndrome)

Secondary

- Autoimmune disorders: Sjögren's syndrome, rheumatoid arthritis, fibrosing alveolitis, systemic lupus erythematosus*
- Hypercalciuria: idiopathic, hypervitaminosis D, familial hypercalciuria, primary hyperparathyroidism, medullary sponge kidney
- Dysproteinaemia: hypergammaglobulinaemia, cryoglobulinamia, amyloidosis
- Medication / toxins: e.g. iphosphamide, analgesics, toluene amphotericin B, lithium carbonate, amiloride, trimethoprim
- Liver disease: (primary biliary) cirrhosis, chronic active hepatitis
- Hyperthyroidism: hypercalcaemic
- Renal disease: transplant rejection*, medullary sponge kidney, obstructive nephropathy*
- In context of genetic diseases: e.g. Sickle cell anaemia*, hereditary ovalocytisus
- Marked volume depletion

***may be accompanied by hyperkalaemia.**[1,2]

Figure 2. *Possible pathophysiological mechanisms underlying RTA type I (schematic representation of cortical part of distal tubules)*



1. Absence or nonfunctional H-ATPase decreasing H excretion of the intercalated cells; 2. Anion Exchanger 1 (HCO3/Cl-ATPase) deficiency/ malfunctioning, preventing HCO3 resorption, and as a result less H formation and excretion; 3. Increased permeability allowing H back diffusion from the lumen (amphotericin B); 4. Inhibition/dysfunction of CA II diminishing H production for secretion; 5. Diminished Na resorption (reduced Na delivery [volume depletion] or Na/K-ATPase dysfunction).

Mechanisms 1 to 4 lead to hypokalaemia through enhanced K excretion in the principal cells in order to balance electronegativity; in case of mechanism 5 decreased amounts of both H and K are secreted, creating a hyperkalaemic, acidotic state; adapted from Rose *et al.*, Nicoletta *et al.*, and Koul *et al.*[1,3,4]

been noted in Sjögren's patients with RTA, suggesting a role in the pathophysiology of RTA I.[12] In absence of (properly functioning) H-ATPase, AE 1 or CA II, less protons are secreted in distal tubular cells, leading to metabolic acidosis. The electronegative gradient created by distal sodium resorption is therefore compensated by an increased potassium secretion, leading to renal (potassium) salt wasting. Notably, during metabolic acidosis, less sodium absorption takes place in the proximal tubuli as a result of a lower amount of glomerular filtrated bicarbonate. The enhanced delivery of sodium distally creates a hyperreninaemic hyperaldosteronism state, stimulating distal sodium reabsorption and thereby additional potassium wasting. Our patient also had an elevated plasma aldosterone level and plasma renin activity. Whether the use of chloroquine, known to be able to induce hypokalaemia possibly by stimulating potassium transport to the intracellular compartment,[13] aggravated the hypokalaemic state is unclear. Our patient, however, only used prophylactic doses of this medicine which makes chloroquine intoxication less likely.

Clinical signs and symptoms accompanying distal RTA, other than hypokalaemia and symptoms related to the primary disorder causing distal RTA, are the effects of metabolic acidosis. Acidosis promotes the release of calcium from bone tissue, causing osteoporosis and (rarely) osteomalacia.[1,14,15] The enhanced calcium release and, consequently, increased excretion, combined with a high urine pH and hypocitraturia (due to acidosis) promotes urinary precipitation of calcium phosphate, resulting in nephrolithiasis and nephrocalcinosis.[16,17]

Increased calcium excretion could not be detected in our patient. Nevertheless, the presence of high urine pH (and possible concomitant hypocitraturia) predisposes for nephrocalcinosis or nephrolithiasis development.

Treatment of distal RTA is based upon alkali supplementation correcting the metabolic acidosis, and not upon potassium suppletion. Preferably, potassium citrate (1-2 Eq/kg daily, orally) should be given which is better tolerated and, in contrast to sodium bicarbonate, produces no natriuresis.[1] Unfortunately, potassium citrate is not readily available in our region. Generally, no additional potassium supplementation is required, since correction of the serum pH and bicarbonate levels reduces renal potassium wasting by diminishing distal sodium delivery. However, a mild hypokalaemic state can persist since potassium wasting is not completely abolished. This effect can be corrected by simultaneous potassium supplementation using potassium citrate. Treatment of the underlying disease may partially reverse the acidification defect in distal RTA, as in cases of Sjögren's syndrome.[1]

In conclusion, distal RTA should be considered in case of unexplained hypokalaemia, particularly with concomitant

(normal AG) metabolic acidosis. The disorder can be primary or hereditary, but usually occurs secondarily to other conditions. Several pathophysiological mechanisms have been proposed to originate the defect in renal acidification and potassium balance. Therapy primarily consists of bicarbonate suppletion in order to prevent a hypokalaemic state and negative effects of chronic metabolic acidosis. In some cases, however, additional potassium supplementation may be required to correct mild, residual hypokalaemia.

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