Renal tubular acidosis type II associated with vitamin D deficiency presenting as chronic weakness

Yaseen Ali, Amila Parekh, Mirza Baig, Taseen Ali and Tazeen Rafiq

Ther Adv Endocrinol Metab

2014, Vol. 5(4) 86–89

DOI: 10.1177/

2042018814547359

© The Author(s), 2014.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Chronic vitamin D deficiency, though common in the elderly, is often under diagnosed and when progressing to renal tubular acidosis type II (RTA 2) can cause several simultaneous electrolyte imbalances that may present with weakness and pain as chief symptoms. We present such a case that after months of evaluation and symptomatic treatment did not lead to an effective establishment of the etiology causing chronic weakness and body pain in an elderly female patient. Eventually, after a careful review of the patient's history, repeat physical examinations, laboratory data evaluation, and diagnostic testing led to the establishment of the diagnosis of proximal RTA 2 associated with vitamin D deficiency, which caused the patient to develop several remarkable secondary electrolyte imbalances such as hypokalemia, hypocalcemia, hypophosphatemia, acidemia, hyperparathyroidism, with weakness and body pain.

Keywords: RTA type 2, Hypokalemia, Acidosis, Vitamin D deficiency, chronic weakness

Introduction

Weakness leading to falls is one of the most common reasons for outpatient clinic visits and inpatient hospitalizations among elderly patients, severely compromising their quality of life [Moreland *et al.* 2004]. Weakness accompanied by chronic generalized pain can be attributed to several etiologies and can lead clinicians to expend excessive time and healthcare resources in diagnosis and treatment [Bohl *et al.* 2012]. Even with all our advanced diagnostic capabilities, a single etiology is difficult to determine in some cases, and treatment can include the utilization of multiple therapeutic modalities [Bohl *et al.* 2012]. In essence, a careful history, physical examination, laboratory evaluation, and diagnostic testing should be employed to reach a diagnosis. Through this meticulous approach most diagnoses can be established and the patient treated appropriately, limiting further disability and improving quality of life.

We present an elderly African-American female patient with chronic weakness and body pain that after months of evaluation and symptomatic treatment did not lead to an etiological diagnosis. Eventually, after a careful review of the patient's

history, and laboratory data, diagnostic testing led to the diagnosis of renal tubular acidosis type II (RTA 2) associated with vitamin D deficiency that resulted in several remarkable secondary electrolyte imbalances.

Case report

A 64-year-old African-American woman with a past medical history of hypertension, diabetes mellitus type II, chronic kidney disease, hyperlipidemia, and osteoarthritis came to the clinic with symptoms of generalized weakness, muscle aches, lethargy, disturbed sleep, and a feeling of fatigue throughout the day that had started about a year ago and progressively worsened. She had been seen by multiple physicians, including a chiropractor, for her symptoms, and had tried everything possible, from acupuncture to drinking excess coffee, without success.

At this particular clinic visit, her history was carefully reviewed and she seemed to be on appropriate medications for all her comorbidities. Her medications included metformin 500 mg twice a day, simvastatin 40 mg every night, ibuprofen 200 mg every 4–6 h, multivitamins, and potassium

Correspondence to:

Yaseen Ali, MD

Ohio University, 120 Chubb Hall, Athens, OH 45701, USA

ya199312@ohio.edu

Amila Parekh, MD

Mirza Baig, MD

Ohio University, Athens, OH, USA

Taseen Ali, MD

Tazeen Rafiq, MD

Loretto Hospital, Chicago, IL, USA

Table 1. Basic metabolic profile.

Basic chemistry	Reference values
Sodium = 136 mEq/L	135–145 mEq/L
Potassium = 2.8 mEq/L	3.5–5.0 mEq/L
Chloride = 118 mEq/L	95–105 mEq/L
Bicarbonate = 18 mEq/L	22–28 mEq/L
Blood urea nitrogen = 6.1 mmol/L	2.9–8.2 mmol/L
Creatinine = 160 µmol/L	53–106 µmol/L
Serum glucose = 7.9 mmol/L	3.9–6.1 mmol/L
Calcium = 2.0 mmol/L	2.0–2.5 mmol/L
Magnesium = 0.78 mmol/L	0.65–1.05 mmol/L
Phosphorus = 0.84 mmol/L	0.7–1.5 mmol/L
Albumin = 49 g/L	35–55 g/L
Total protein = 68 g/L	60–78 g/L

chloride 20 mEq twice a day. Her laboratory values revealed consistently low serum potassium levels for which she had been started on oral replacement 6 months previously (Table 1). She also had consistently elevated serum chloride and subnormal serum bicarbonate levels that had been overlooked (Table 1). This pattern was consistent with hypokalemic hyperchloremic metabolic acidosis that was being treated with potassium replacement for months by her primary-care physician without adequately increasing her serum potassium levels. Her primary-care physician had attributed her weakness to hypokalemia from nutritional deficiency.

Albeit with a history of chronic kidney disease attributed previously by her primary-care physician to nephropathy of diabetes mellitus, multiple myeloma was considered in this visit as a primary diagnosis. However, in light of moderate microalbuminuria in the urine, normal serum protein, albumin, and calcium levels, specific tests such as serum protein electrophoresis and urine protein electrophoresis were deferred. The patient was previously screened with the serum antinuclear antibodies test that ruled out common autoimmune conditions such as Sjogren's syndrome with the absence of clinical symptoms also reported by her primary-care physician. Her medication profile seemed appropriate at this visit.

After most etiologies of non-anion gap metabolic acidosis (Table 2) were excluded, she was investigated for renal tubular acidosis with a basic

Table 2. Common etiologies of non-anion gap metabolic acidosis.

1. Diarrhea (gastrointestinal losses)
2. Fistula (diverticulosis)
3. Renal tubular acidosis type I
- 4. Renal tubular acidosis type II**
5. Ingestion of substances (acetazolamide, heavy metals, ifosfamide, etc.)
6. Rapid normal saline infusion
7. Early renal failure
8. Respiratory posthypocapnia

Table 3. Urinary studies.

Urine chemistry	Reference values
Sodium = 98 mEq/L	40–220 mEq/L
Potassium = 28 mEq/L	25–100 mEq/L
Chloride = 103 mEq/L	80–250 mEq/L
Fractional excretion of bicarbonate = 18%	< 15%
Urinary pH = 5.1	4.5–8.5
Urine protein (dipstick) = 5.55 mmol/L	1.665–16.65 mmol/L
Specific gravity = 1.015	1.005–1.030

metabolic profile, urine electrolytes for urine anion gap ($\text{UAG} = \text{UNa} + \text{UK} - \text{UCl}$), urinary PH, and fractional excretion of bicarbonate in urine (Thomas and Hamawi, 2013).

The laboratory investigation revealed basic metabolic profile values similar to those obtained at the initial visit (Table 1), a positive urine anion gap (Tables 3 and 4), a low urine pH, and an elevated fractional excretion of bicarbonate (Tables 3 and 4). A diagnosis of RTA 2 was thus established [Thomas and Hamawi, 2013].

Further evaluation of the patient's basic metabolic profile (Table 1) also disclosed abnormally low serum calcium and phosphorus that led to the measurement of vitamin D (25-OH D), alkaline phosphatase, and parathyroid hormone levels. Laboratory studies revealed a subtherapeutic vitamin D (25-OH D) level, and mildly elevated parathyroid hormone and alkaline phosphatase levels (Table 5). We therefore concluded that the patient had chronically low vitamin D levels associated with RTA 2, and the subsequent electrolyte disturbance of hypokalemic hyperchloremic metabolic acidosis, leading to the symptoms with which she presented. The patient was started on

Table 4. Diagnostic criteria for renal tubular acidosis.

Type I Distal	UAG +	U pH > 5.5	FeHCO ₃ < 5%	Hypokalemia
Type II Proximal	UAG + / –	U pH < 5.5	FeHCO₃ > 15%	Hypokalemia
Type IV Hypoaldosteronism	UAG +	U pH < 5.5	FeHCO ₃ < 5%	Hyperkalemia

FeHCO₃, fractional excretion of bicarbonate [5–15%, assumes serum bicarbonate > 20 mEq/L]; U pH = urine pH (4.5–8.5); UAG, urine anion gap (–10 to +10 mEq/L).

Table 5. Endocrine laboratory values.

Specialized chemistry	Reference values
Parathyroid hormone = 83 ng/L	10–65 ng/L
Alkaline phosphatase = 114 U/L	36–92 U/L
Vitamin D (25-OH D) = 47 nmol/L	62–200 nmol/L
Calcium = 2.0 mmol/L	2.0–2.5 mmol/L
Phosphorus = 0.3 mmol/L	0.7–1.5 mmol/L

replacement therapy with oral vitamin D, calcium, and potassium supplements, and in successive visits reported improvement in her symptoms. We briefly discuss this rare yet interesting phenomenon below.

Discussion

Severe vitamin D deficiency can present as rickets in children and osteomalacia in adults but the association of vitamin D deficiency with RTA 2 is rare in literature but not implausible [Taylor and Elbadawy, 2006]. Failure to recognize the association between vitamin D deficiency and RTA 2 can lead to missed diagnoses, increased health-care costs, and increased morbidity and mortality due to falls especially in the elderly population secondary to weakness owing to the electrolyte imbalances of calcium, phosphorus, and potassium [Bohl *et al.* 2012; Haque *et al.* 2012].

There are several etiologies for calcium deficiency, one of which is deficiency of vitamin D. Vitamin D increases calcium and phosphorus absorption in the intestines. In the absence of this action, calcium levels decrease in the human body, which leads to the secretion of parathyroid hormone from the parathyroid glands. The parathyroid hormone reacts by an increase in bone resorption as well as a decrease in calcium excretion in exchange for increased phosphate excretion by the kidneys.

Our patient was diagnosed with RTA 2 owing to vitamin D deficiency (Table 6). Vitamin D

Table 6. Common etiologies of renal tubular acidosis type II.

1. Multiple myeloma
2. Primary hyperparathyroidism
3. Wilson's disease
4. Genetic fructose intolerance
5. Cystinuria
6. Medications such as expired tetracycline (Fanconi syndrome), aminoglycoside, acetazolamide, ifosfamide, other antibiotics
7. Vitamin D deficiency
8. Sjögren's syndrome

deficiency is commonly seen in elderly patients and those who lack sufficient sun exposure for the normal synthesis of vitamin D. Briefly, the skin absorbs ultraviolet light from the sun and synthesizes 7-dehydrocholesterol in the skin, which is metabolized to 25-hydroxyvitamin D in the liver by the action of the enzyme 25 hydroxylase. It is finally converted to its active form calcitriol (1, 25-dihydroxyvitamin D) in the proximal tubules of the kidneys through the action of the enzyme 1- α -hydroxylase.

Vitamin D deficiency results in low serum calcium and phosphorus, elevated alkaline phosphatase, and parathyroid hormone levels that in effect reduce the bicarbonate recovery at the proximal renal tubules [Ahmed and Sims, 2001] (Figure 1). Impaired reclamation of the bicarbonate ion in the proximal tubule leads to bicarbonate loss in the urine, but serum bicarbonate levels typically do not fall below 15 mEq/L because of the ability of the collecting ducts to reclaim some of the bicarbonate missed by the proximal tubules [Thomas and Hamawi, 2013] (Figure 1).

Patients with RTA 2 generally have hypokalemia and increased urinary potassium wasting due to an increased rate of urine flow to the distal nephron caused by the distal delivery of bicarbonate ions (Figure 1). There is also activation of the renin-angiotensin-aldosterone system from the mild hypovolemia induced by bicarbonate loss in urine, leading to

Figure 1. Vitamin D Deficiency leading to Hypokalemia Causing Weakness.

increased collecting duct sodium reabsorption and potassium excretion [Thomas and Hamawi, 2013] (Figure 1). Administration of alkali in these patients increases bicarbonate wasting in urine and can worsen hypokalemia unless potassium is replaced simultaneously [Thomas and Hamawi, 2013].

Lessons learned

Vitamin D deficiency can cause hypocalcemia and hypophosphatemia, and when progressing to type II, renal tubular acidosis can, in addition, be associated with hypokalemia, all of which contribute to muscle weakness. Vitamin D levels should therefore be routinely measured in elderly patients with generalized weakness and muscle pains.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

- Ahmed, A. and Sims, R. (2001) Proximal renal tubular acidosis associated with osteomalacia. *Medscape South Med J* 94: 536–539.
- Bohl, A., Phelan, E., Fishman, P. and Harris, J. (2012) How are the costs of care for medical falls distributed? The costs of medical falls by component of cost, timing, and injury severity. *Gerontologist* 52: 664–675.
- Haque, S., Ariceta, G. and Battle, D. (2012) Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. *Nephrol Dial Transplant* 27: 4273–4287.
- Moreland, J., Richardson, J., Goldsmith, C. and Clase, C. (2004) Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 52: 1121–1129.
- Taylor, H. and Elbadawy, E. (2006) Renal tubular acidosis type 2 with Fanconi's syndrome, osteomalacia, osteoporosis, and secondary hyperaldosteronism in an adult consequent to vitamin D and calcium deficiency: effect of vitamin D and calcium citrate therapy. *Endocr Pract* 12: 559–567.
- Thomas, C. and Hamawi, K. (2013) Metabolic acidosis etiology. *Medscape*. <http://emedicine.medscape.com/article/242975-overview#aw2aab6b2b2aa>

Visit SAGE journals online
<http://tae.sagepub.com>

SAGE journals