

# A 67 YEAR-OLD MAN WITH FATIGUE

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## Case Report

A 67 year-old male with a past medical history of hypertension and insulin-dependent type II diabetes complicated by neuropathy, retinopathy, and chronic kidney disease presented to the hospital with a complaint of fatigue. The patient noted generalized weakness that had begun the morning of admission after two days of malaise and subjective fever. This weakness prevented him from being able to rise from a sitting position, resulting in a fall off the couch. He denied injury from this fall along with shortness of breath or chest pain, however, he did admit to two episodes of vomiting the day prior to admission.

The patient was taking the following medications: furosemide, aspirin, isosorbide mononitrate, lipitor, levothyroxine, candesartan, metoprolol, clopidogrel, doxazosin, calcitriol and Insulin 70/30. Medical history included, hyperlipidemia, hypothyroidism, benign prostatic hypertrophy, stable angina, and peripheral vascular disease along with the conditions listed above. Past surgical history included 2 stents in the LAD coronary artery, vitrectomy, and transurethral resection of the prostate (TURP). Additionally, the patient noted that he lived alone after having retired from teaching and denied any drugs, smoking or alcohol.

On physical exam, the patient was febrile at 102.2°F, heart rate was 99, respiratory rate was 17, and blood pressure was elevated at 183/56 mmHg. Generally, the patient was dehydrated and appeared to be somnolent but responsive to questions. Neurological exam was remarkable for generalized bilateral upper and lower extremity weakness and asterixis with no focal neurological deficits. His cranial nerves were intact. Skin exam was significant for a warm, erythematous, blanching, non-pruritic rash on the left anterior tibial surface, as well as an eschar on the 2nd toe of the left foot. The rest of physical exam was within normal limits.

An arterial blood gas was performed due to his overall lethargic state and demonstrated a pH of 7.34, PCO<sub>2</sub> 34, PO<sub>2</sub> 66 and oxygen saturation of 91% on room air. His electrolytes were Na 134, K 5.3, Cl 106, HCO<sub>3</sub> 19, significant for a non-anion gap metabolic acidosis with a compensatory respiratory alkalosis. Glucose was elevated at 412mg/dl. Additional laboratory values revealed a BUN of 79 and creatinine of 3.1 (previous baseline of 2.3). Urine studies showed protein >300 mg/dl, urine pH of 5.5, urine glucose 500, and rare hyaline casts. Urine electrolytes results included Na 49, K 30.2, Cl 54, and Cr of 98.7. Lactate was within normal limits.

The patient was treated acutely for dehydration and hyperglycemia with intravenous fluids and insulin. He was started on broad spectrum antibiotics for suspected cellulitis and osteomyelitis of the 2nd left toe. The combined results of the urine anion gap of + 25.2, the serum anion gap of 9, and

hyperkalemia led us to a preliminary diagnosis of renal tubular acidosis type IV. Finally, the renin level returned low at 1.4 ng/mL/hr (normal 1.9-3.7) indicating a low renin – low aldosterone as an underlying cause of the metabolic acidosis.

## Discussion

Type 4 Renal Tubular Acidosis is characterized by a low renin - low aldosterone state and non anion-gap metabolic acidosis. Low aldosterone levels impair the normal functioning of the Na-K-2Cl cotransporter in the distal nephron. This deficiency results in decreased reabsorption of Na<sup>+</sup> in the distal nephron and decreased excretion of K<sup>+</sup> and H<sup>+</sup>. Thus, RTA IV is characterized by salt wasting, hyperkalemia and acidosis.

RTA IV is caused by a decrease in ammonia recycling in medullary segments of the nephron and the subsequent increased gradient for alpha-intercalated cells of the collecting duct to pump protons against. In order to understand how ammonia recycling is affected in this condition we will examine the nephron from proximal to distal and discuss how hyperkalemia and acidosis derange normal physiology.

There are two mechanisms which are believed to be involved with the dysfunction of ammonia recycling. In the proximal convoluted tubule the presence of hyperkalemia creates an extracellular acidosis and intracellular alkalosis. In the loop of henle, there is competition between NH<sub>4</sub><sup>+</sup> and K<sup>+</sup> for transport in the thick ascending loop by the Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup> transporter.

In the proximal convoluted tubule, hyperkalemia leads to diffusion of K<sup>+</sup> across all cell membranes. In order to maintain electrical neutrality, H<sup>+</sup> diffuses out of the cell into the extracellular space. This leads to an extracellular acidosis and an intracellular alkalosis. The intracellular alkalosis inhibits the de-amination of glutamine and the subsequent exchange of NH<sub>4</sub><sup>+</sup> with Na<sup>+</sup> in the renal proximal collective tubule (PCT). The deficit of ammonium produced in the PCT makes less ammonia available in the ammonia recycling system of the renal medulla.<sup>1</sup>

In the loop of henle, hyperkalemia is believed to contribute to the acidosis by limiting the amount of ammonia/ammonium reabsorbed. Renal medullary ammonia recycling is reduced through hyperkalemia affecting the Na-K-2Cl cotransporter in the thick ascending limb. This cotransporter can take one ion of K<sup>+</sup> or NH<sub>4</sub><sup>+</sup> across the luminal membrane of the thick ascending limb along with a Na ion and two Cl<sup>-</sup> ions. NH<sub>4</sub><sup>+</sup> and K<sup>+</sup> directly compete for reabsorption. Under physiological conditions, NH<sub>4</sub><sup>+</sup> ions are transported intracellularly, lose their H<sup>+</sup>, and NH<sub>3</sub> diffuses freely into the medullary interstitium of the kidney while return to the tubule is prevented by a membrane that is impermeable to NH<sub>3</sub>. In the absence of pathology, the high ammonia concentration in the renal medulla allows diffusion of NH<sub>3</sub> down its concentration gradient into

the medullary collecting duct or the proximal tubule. Once in the medullary collecting duct,  $\text{NH}_3$  can accept a donated  $\text{H}^+$  ion, becomes ammonium, thereby facilitating the excretion of an acid load.

Under conditions of RTA IV, there is a lesser amount of ammonium available for renal medullary recycling, as less is generated in the proximal convoluted tubule, and this mechanism for excreting acid is further hampered by the high potassium in the tubule competing for and displacing ammonium from the loop cotransporter.<sup>2</sup>

Therefore, both mechanisms of RTA type 4 work together to inhibit the excretion of  $\text{NH}_3$  into the collecting duct of the kidney and subsequently inhibit the excretion of  $\text{NH}_4^+$  and an acid load.

Under normal conditions, both mechanisms of hampering renal medullary ammonia recycling can be repaired by aldosterone, which promotes the re-absorption of Na and the wasting of K. However, the hallmark of RTA IV is a low renin/low aldosterone state. In this situation, it is not possible for normal physiological mechanisms to break the hyperkalemic acidosis of RTA IV.

#### Treatment of RTA IV

Treatment of RTA type IV focuses on correction of hyperkalemia, optimizing renal function, and addressing the physiological root of the disorder.

Correction of hyperkalemia begins with withholding medications that can cause or exacerbate hyperkalemia. Potassium-sparing diuretics, ACE-Inhibitors and ARB medications are common causes. This is especially important because renal insufficiency in combination with ACEI/ARB medications can have synergistic hyperkalemic effects.<sup>3</sup>

Additionally, if the patient suffers from renal insufficiency he must be treated to optimize renal function. This includes omission of medications that aggravate interstitial nephritis such as NSAIDs, cyclosporine, or tacrolimus.<sup>4</sup> Also, adjusting for pre-renal insufficiency by treating volume status and maximizing renal perfusion is critical in the process of increasing potassium excretion. Improving renal function will increase potassium excretion. For long term management of RTA IV, in cases of renal insufficiency, dietary sources of potassium must be limited.

Adrenal insufficiency is suspected in a low renin-low aldosterone state. It is more common in cases of autoimmune disease and HIV infection.<sup>4</sup> If clinical suspicion is high for adrenal insufficiency, mineralocorticoids should be given. Fludrocortisone is an effective exogenous mineralocorticoid replacement.<sup>5</sup> However, mineralocorticoid replacement is contraindicated in hypertensive or edematous patients. Instead, in these patients, hyperkalemia can be managed with a loop or a thiazide diuretic.

#### References

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“Growth”

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