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Case Report Open Access

Persistent Hyperkalemia Associated with Hypotension Due to Relative Hyporeninemic Hypoaldosteronism: Recognition is Key

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Abstract

Introduction: Persistent hyperkalemia in adults can be caused hyporeninemic hypoaldosteronism (HH), which typically occur in diabetic patients with chronic kidney dysfunction and is associated with hypertension and a mild degree of hyperchloremic acidosis. Rarely, HH may occur and be featured by persistent hyperkalemia and renal salt wasting.

Case presentation: A 49-year-old female developed unexplained lightheadedness and hyperkalemia several months following unilateral nephrectomy for a renal cell carcinoma. She was treated by her local physician with dietary potassium restriction, salt tablets and regular dosage of sodium polystyrene sulfonate. Two years later, her symptoms progressed to episodes of near syncope and supraventricular tachycardia. On presentation to our clinic, her blood pressure (BP) was 95/49 mmHg and laboratory studies showed serum potassium of 6.7 mmol/L, creatinine 0.8 mg/dL, renin activity 1.4 ng/mL/hour, and aldosterone 6.2 ng/dL (reference range <21 ng/dL). Serial transtubular potassium concentration gradients (TTKGs) were obtained. Upon administration of a single 0.1 mg of oral fludrocortisone, her TTKG raised sharply to 6.91 from a baseline of 3.87. She was diagnosed with relative HH; fludrocortisone 0.1 mg daily was initiated. On return visits two week later, she denied any lightheadedness, her BP rose to 108-125/65-80 mmHg (6 measurements), serum potassium normalized to 5.1 mmol/L (4.4 mmol/L at three-month follow-up).

Conclusion: Although rare in adults, HH can develop and present with hypotension and persistent hyperkalemia. As illustrated in this case, recognizing such an occurrence is critical for correct management to avoid serous complications.

Keywords: Renin; Aldosterone; Hyperkalemia; Salt wasting; Renin-angiotensin-aldosterone system; Transtubular potassium concentration gradient (TTKG)

Learning Objectives:

1. Recognize the clinical presentations and characteristics of HH
2. Describe the role of the Renin Angiotensin Aldosterone System in the regulation of potassium, salt and water homeostasis
3. Understand the underlying pathophysiology of HH
4. Identify appropriate diagnostic tests for HH
5. Describe treatment plan for variant presentations of HH

Introduction

Persistent hyperkalemia in adult patients can be caused by hyporeninemic hypoaldosteronism (HH), which typically occur in patients with diabetes and kidney dysfunction and associated with hypervolemia (hypertension) and hyperchloremic acidosis (also known as type IV renal tubular acidosis).

We present an unusual case of relative hyporeninemic hypoaldosteronism (HH) in an adult, featured by marked chronic hyperkalemia and renal salt wasting resulting in hypotension and other associated complications. We also provide an outline of investigation and management of this condition. This case highlights the importance of recognizing all possible presentations of HH.

Case Presentation

A 49-year-old woman was referred for the evaluation and management of a 4-year history of hyperkalemia. She had multiple medical problems including obesity, gastric banding 20 years prior (no gastrointestinal disturbance after the procedure), fibromyalgia, bipolar disorder (never been on lithium), and unilateral, locally confined renal cell cancer requiring left nephrectomy and left adrenalectomy (no chemo or radiation therapy) 4.5 years ago. Prior to the cancer surgery, she was normotensive (multiple blood pressure readings ranged 120-140/70-90 mmHg) and had borderline high serum potassium concentrations on several measurements ranging between 4.6 and 5.6 mEq/L and was told to reduced dietary potassium.

Several months after the surgery, she began to experience generalized weakness and episodic lightheadedness. Evaluation at her local doctor's office revealed low blood pressure (90-95/50-56 mmHg) and hyperkalemia (K=6.8 mmol/L). She was called back to local emergency department (ED) where she received intravenous saline and oral Kayexalate and was discharged on maintenance dosages of salt tablets and Kayexalate. She was subsequently admitted to the local ED numerous times for similar episodes and always receiving the same treatment. About two years later, she developed episodes of palpitation associated with dizziness and near syncope. Evaluation revealed paroxysmal supraventricular tachycardia (PSVT). Her transthoracic echocardiogram showed normal cardiac chamber size and function. Apart from borderline hypotension and hyperkalemia, no specific abnormalities were identified. It was suspected that the PSVT had

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been related to the combination of hypotension and hyperkalemia. She tried, but was intolerant to, multiple medications for her PSVT and eventually was referred to Cardiology at Mayo Clinic Rochester where she underwent ablation of the PSVT. Before the procedure, she was treated with intravenous saline for hypotension and an intense course of Kayexalate to correct hyperkalemia. After the procedure she was referred to Nephrology for further evaluation and management.

Her medications included alprazolam, hydrocodone-acetaminophen, Lamictal, sodium chloride, Kayexalate, Vitamin A, D and E.

Physical examination showed BMI 30, respiratory rate 18/minute, blood pressure 95/49 mmHg, pulse 89/minute, clear lung fields, a non-tender abdomen, no dependent edema and no mucosal lesion or skin rash.

Laboratory results showed normal blood counts, sodium 142 mmol/L, potassium 6.7 mmol/L, chloride 106 mmol/L, bicarbonate 29 mmol/L, BUN 19 mg/dL, creatinine 0.8 mg/dL, and calcium 9.5 mg/dL TSH 2.2 mg/dL, AM cortisol 13 ug/dL, corticotropin 11 ug/dL, Renin activity 1.4 ng/ml/hour (reference range: ~0.2 to 4.0 ng/mL/hour), and aldosterone: 6.2 ng/dL (reference range: ≤ 21 ng/dL). Urine studies showed sodium 125 mmol/L, potassium 39 mmol/L, and osmolality 460 mosm/kg.

The patient was suspected of having relative renin and aldosterone deficiency versus resistance. Serial transtubular potassium concentration gradients (TTKGs) were obtained. As shown in Table 1, her baseline low TTKG was increased sharply in response to a single oral dose of fludrocortisones, consistent with relative aldosterone deficiency. She was started on fludrocortisone 0.1 mg daily supplement. On return visits, her blood pressure rose to 108-125/65-80 mmHg and serum potassium concentration normalized to 5.1 mmol/L at two-week follow-up and 4.4 mmol/L at three-month follow-up.

Diagnosis

This patient developed relative HH temporally related to unilateral nephrectomy and adrenalectomy for renal cancer. Such occurrence is quite unusual and, to our knowledge, has not been previously reported. Further, salt wasting variant of HH causing hypotension is rare in adults and is not known to occur following unilateral nephrectomy or adrenalectomy.

Serum potassium concentration is a final outcome of the balance between potassium intake, intracellular/extracellular shifting, and urinary excretion. Persistent hyperkalemia occurs mainly when there is a defect in urinary potassium excretion under three conditions: kidney failure, reduction in distal tubular sodium delivery or tubular fluid-flow, and hypoaldosteronism.

	Baseline	4 hr after fludrocortisone 0.1 mg	4 hr after fludrocortisones 0.2 mg
*TTKG	3.87	6.91	7.88
Plasma K (mEq/L)	6.4	5.6	5.2
Urine K (mEq/L)	39	92	69
Blood Pressure (mmHg)	90/40	102/60	109/61
U Na (mEq/L)	125	142	95
U Osm (mosm/kg)	460	692	500

*TTKG denotes transtubular potassium gradient

Table 1: Response to fludrocortisone.

In our patient, despite unilateral nephrectomy, her kidney clearance was largely preserved (eGFR 76 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation), the degree of her mild kidney dysfunction would not account for the persistent hyperkalemia. She was neither oliguric nor showing low urine sodium content, thus these factors would not have explained her persistent hyperkalemia. For several years, the etiology of her illness eluded her care physicians. HH, absolute or relative, was unsuspected, in retrospect likely because her presentation did not fit with the common and well-acquainted presentation of HH in adults in which diabetes, hypertension and kidney dysfunction are usually present and blood tests often exhibit some degree of hyperchloremic acidosis along with reductions in renin activity and aldosterone concentration [1,2]. It should also be noted that interstitial renal disease, autonomic dysfunction and certain medications including (but not limited to) nonsteroidal antiinflammatory drugs (NSIADs), calcineurin inhibitors, and heparin could all be potential sources of HH.

Aldosterone plays a major role in regulating sodium and potassium homeostasis. Its production is stimulated primarily by the renin-angiotensin-aldosterone system (RAAS) and to a degree by hyperkalemia (Figure 1). Aldosterone binds and activates the mineralocorticoid receptor (MR) in the principal cells of the collecting duct of the nephron, stimulating production and luminal-surface expression of epithelial sodium channels (ENaCs) resulting in enhanced sodium absorption. It also stimulates the production of Na^+/K^+-ATPase and activity of renal outer medullary K^+ channel (ROMK) channel (reviewed in [3]). The accelerated sodium absorption leads to the generation of lumen-negative potential that stimulates potassium and proton secretion. In vitro and animal (rat and dog) studies show that aldosterone also confers a direct, sodium-independent, stimulatory effect on proton secretion through upregulation of apical proton pumps on intercalated cells [4,5], such results, however, have not been demonstrated in human.

While virtually all patients with hypoaldosteronism develop some degree of hyperkalemia, hyperchloremic acidosis occur only in some, not in all, of them (unlike in rats and dogs). Perez GO et al. [6] studied a group of patients with bilateral adrenalectomy. They found that hyperchloremic acidosis develops exclusively in patients with moderate-to-severe kidney dysfunction (GFR: 15-39 ml/min/1.73m^2), not in those with better kidney clearances (GFR: 63-142 ml/min/1.73m^2). On further testing they found that, in the latter group of patients, despite the absence of an overt acidosis, their urine ammonium excretions were mildly reduced. Such reduction was amplified in those with kidney dysfunction. These observations suggest that aldosterone possibly, to some extent, contributes to or acts as a part of an integrative acid-base homeostatic system, the effects of aldosterone deficiency on kidney acid excretion, however, can be compensated when kidney clearance is sufficient. By extension, reduction in kidney clearance would attenuate such compensatory action and uncover the acid excretion defects of aldosterone deficiency. Additionally, reduction in kidney clearance itself can diminish the capacity of kidney reclamation/regeneration of bicarbonate (independent of aldosterone deficiency), leading to acidosis. In line with these deductions, a study in individuals with pre-existing metabolic acidosis (induced by NH_4Cl), aldosterone blockade (by spironolactone administration) heightens the magnitude of hyperchloremic acidosis [7]. Further, the integrative nature of renal acid regulation was also demonstrated in a study in which hyperkalemia, through altering epithelial cell ammonium genesis, contributed to the development of hyperchloremic acidosis in a patient

with kidney dysfunction, hypertension and hypoaldosteronism [8]. In keeping with these clinical observations, exogenous mineralocorticoid supplementation for patients with hypoaldosteronism can only correct acidemia partially [6,9]. Taken together, to date the precise role of aldosterone in the regulation of renal acid excretion in human has not been fully delineated (reviewed in [3]). Nevertheless, in our case, it is reasonable to assume that her preserved kidney clearance likely has protected her from manifesting effects of aldosterone on renal tubular acid excretion.

Our patient exhibited a low level of serum renin activity that was inappropriate in the setting of volume contraction. This occurrence correlated with the unilateral nephrectomy, which is consistent with the notion of kidneys being the major source of circulating renin. Of note, her high normal levels of serum potassium concentration prior to the nephrectomy suggested a less robust renin reserve at baseline. As demonstrated in her post surgery course, the loss of kidney mass further compromised the renin reserve; local tissue production of renin [10] (other than the kidney) which serves to amplify the effects of circulating RAAS appeared incapable of compensating for the loss of kidney source of renin and its circulating RAAS effects. Such presentation is novel in that, although known to occur in analogous rodent models [11,12], the human example has not been previously described.

As renin is the rate-limiting step in the RAAS cascade [13,14], it can be predicted that our patient had a concordant, suboptimal level of downstream renin effectors. Among these, angiotensin II is most powerful. Angiotensin II is known to participate in the physiological regulation of tubuloglomerular feedback (TGF) response and water homeostasis. Thus, suboptimal RAAS cascade/angiotensin II would have led to alterations in TGF response and water regulation.

TGF is a homeostatic negative feedback loop in that an inappropriate

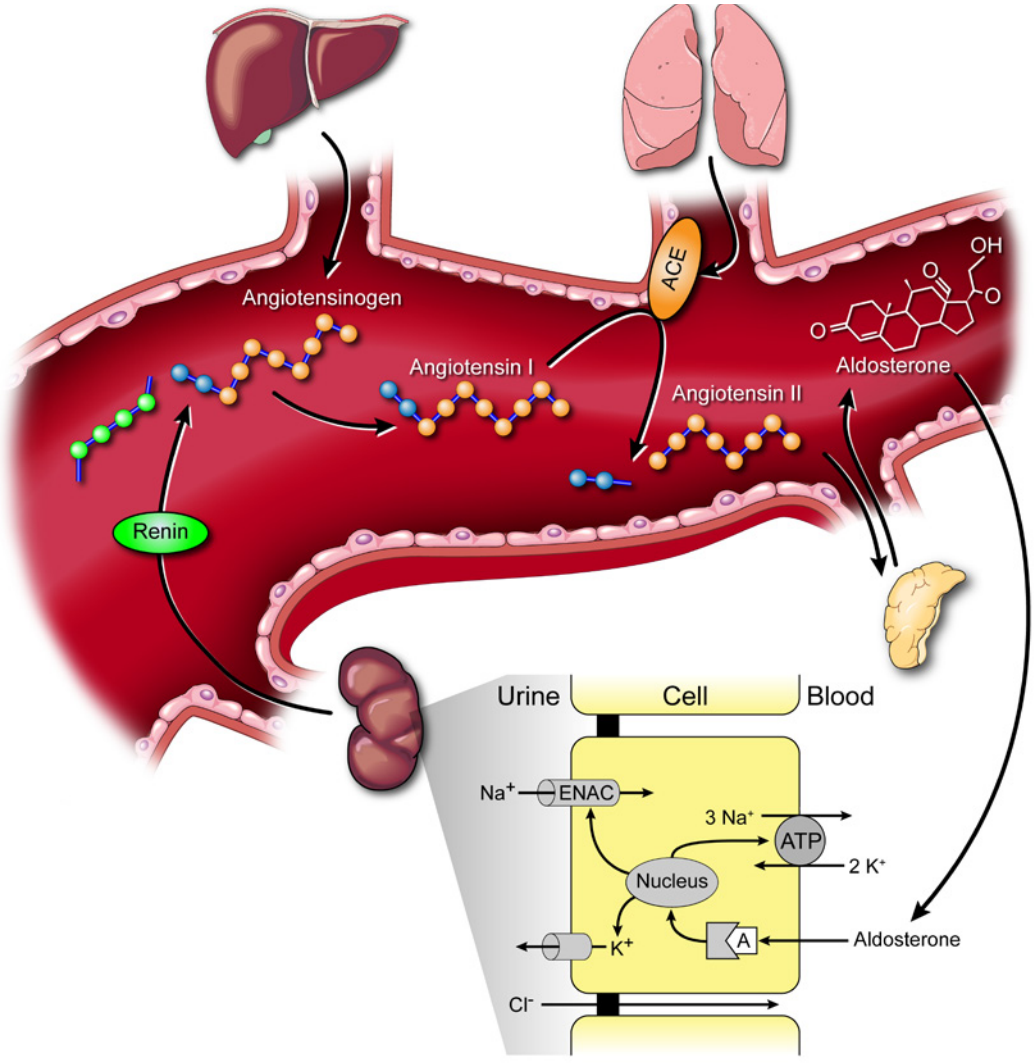

Figure 1: Schematic drawing of the circulating *renin-angiotensin-aldosterone system* **(RAAS).** RAAS is controlled at the level of renin. The reduced intra-luminal pressure in the afferent arteriole (renal hypoperfusion), reduced sodium concentration in the distal tubular fluid, and increased local sympathetic nerve activity stimulate renin release from Juxtaglomerular cells; in bloodstream, renin converts angiotensinogen to angiotensin I; angiotensin converting enzyme (ACE), rich in pulmonary vasculature, further converts angiotensin I to angiotensin II; angiotensin II stimulates adrenal gland at zona glomerulosa to secrete aldosterone; and lastly, aldosterone acts on kidney tubules to increase absorption of Na+ and excretion of K^+. Na^+ absorption leads to intravascular volume expansion.

elevation of salt concentration at the end of the ascending limb of Henle, sensed by the macula densa cells, results in afferent arteriolar vasoconstriction and reduction in GFR, thereby limiting distal tubular salt wasting, whereas a decreased tubular salt concentration triggers an opposite effect. TGF response is shown to be elicited through A1 adenosine receptor in juxtaglomerular afferent arterioles for which angiotensin II is a required cofactor [15,16]. Thus, angiotensin II enhances TGF responsiveness. Angiotensin-converting enzyme or angiotensin II receptor (AT1) deficiency in genetically engineered mice (AT1 gene deletion) diminishes TGF response, resulting in renal salt wasting [17,18]. In our case, hypotension and inappropriate renal salt wasting likely was likely reflective of insufficient TGF response related to the relative renin deficiency. Her preserved GFR despite hypotension may also have been reflective of insufficient TGF-mediated GFR reduction.

RAAS also exerts considerable impact on water regulation. Angiotensin II stimulates thirst response, resulting in increase in water ingestion [19]. At the kidney level, RAAS augments arginine vasopressin (AVP) mediated water conservation. Genetic deletion in each of the RAAS components in mice, including genes encoding renin, angiotensinogen [20,21] angiotensin I-converting enzyme (ACE) [22], AT_1 (both AT_{1a} and AT_{1b}) receptor [23] or AT_{1a} receptor alone [24], leads to polyuria and inappropriate renal water wasting. The underlying mechanisms for such RAAS-mediated water conservation has been studied intensely and evidence has pointed to the involvement of both AVP release from the central nervous system (CNS) and AVP-mediated signaling in kidney tubular cells. Mice with deletion of AT_{1a} angiotensin II receptor exhibit a diminished CNS AVP release in response to dehydration [24]. A recent study further revealed that there are multiple impairments of AVP V2 receptor-mediated signaling in the inner medulla principle cells, including defects in the amounts of aquaporin 2, adenylyl cyclases III and V/VI, and phosphorylated MAP kinases ERK 1/2 proteins. These defects ultimately mount to a phenotype of inappropriate tubular water wasting [25]. Interestingly, in our patient, despite being in a volume-contracted state, her serum sodium concentration was consistently in the high normal range, 139 to 144 mmol/L in all measurements in our institution and >140 mmol/L from her outside records. Such greater than expected sodium concentrations could potentially be tied to a degree of underlying water regulatory defect resulting from insufficient RAAS signaling.

Criteria for diagnosis of hypoaldosteronism include (1) normal adrenal glucocorticoid function, (2) low aldosterone excretion and (3) renal tubular responsiveness to exogenous mineralocorticoid. In patients with hyperkalemia, TTKG is also useful in discriminating overt aldosterone deficiency and relative hypoaldosteronism or aldosterone resistance. TTKG is an index of potassium concentration gradient between urine at the end of the cortical collecting tubule and plasma (Figure 2). It provides an estimation of the aldosterone activity. A TTKG below 5.0 in hyperkalemic patients is highly suggestive of hypoaldosteronism.

In our patient, her adrenal glucocorticoid function was adequate. Her baseline low TTKG (3.87) in the context of hyperkalemia (6.4mmol/L) indicated an insufficient potassium excretion, consistent with insufficient aldosterone in quantity or activity and/or intrinsic (genetic or acquired) molecular defects in relevant transporters in renal epithelial cells (Figure 1). Given her history of unilateral nephrectomy and adrenalectomy and a relatively low serum renin activity, relative deficiency in renin and aldosterone was suspected. Her relative HH became evident with the results of minoralcorticoid (fludrocortisone) challenge study (Table 1) and by the demonstration of a sustained responsiveness to fludrocortisone supplementation with resultant normalization of her serum potassium concentration and volume status.

$$TTKG = [Urine\ K] \div (urine\ osmolality / serum\ osmolality)] \div serum\ K$$

Figure 2: Transtubular Potassium Gradient (TTKG). This formula is valid when Uosm >300 mOsm/kg and UNa >25 mEq/L.

Treatment and Management

For hypo- or normotensive variant of HH, mineralocorticoid replacement and sodium bicarbonate are effective. In cases of aldosterone resistance or relative deficiency (as in our patient), supraphysiologic dosage of mineralocorticoid may be necessary. Adequate dosage is determined by the normalization of serum electrolytes and volume status. Patients with hypertensive variant of HH show an increased total body sodium and extracellular fluid volume. Mineralocorticoid or sodium containing preparations can further raise extracellular volume and can trigger volume-related deleterious complications i.e., worsening hypertension and symptomatic heart failure in patients with limited cardiac reserve. Therapeutic measures for these patients include regular administration of potassium-binding resins plus thiazide or loop diuretics. All patients with HH should be on a potassium-restricted diet and avoid medications that could raise serum potassium, including, but not limited to, antagonists to the elements in the RAAS cascade, prostaglandin synthetase inhibitors (NSAIDs), beta blockers and potassium-sparing diuretics [26,27].

Conclusion

This case represents a rare example of relative renin and aldosterone deficiency following unilateral adrenalectomy and nephrectomy, exhibited as inappropriate renal salt wasting, hypotension and hyperkalemia leading to morbid complications. Confirmatory diagnosis was established by mineralocorticoid challenge study and the restoration of potassium balance and volume status with mineralocorticoid supplementation. Taken together, in adult patients with salt wasting and persistent hyperkalemia, absolute or relative HH should be considered, and correct management is important to avoid serious complications.

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