

Aldosterone Resistance; A Rare Differential Diagnosis for Persistent Hyperkalemia

Abstract

In the human body, Aldosterone is an important hormone for sodium conservation in the kidneys, salivary glands, sweat glands and colon. Aldosterone is synthesized exclusively in the zona glomerulosa of the adrenal gland. Significance of aldosterone production along with its appropriate action on the receptors is undeniable as far as hemostasis of intracellular and extracellular electrolytes is concerned. Destruction or dysfunction of the adrenal gland in conditions such as primary adrenal insufficiency, congenital adrenal hypoplasia, isolated mineralocorticoid deficiency, acquired secondary aldosterone deficiency (hyporeninemic hypoaldosteronism), acquired primary aldosterone deficiency and inherited enzymatic defects in aldosterone biosynthesis cause clinical symptoms and laboratory characteristics owing to aldosterone deficiency. Pseudohypoaldosteronism is an aldosterone resistance syndrome i.e. a condition due to insensitivity of target tissues to aldosterone resulting in hyponatremia, hyperkalemia and metabolic acidosis. For a proper diagnosis of Aldosterone resistance; serum Sodium levels, serum Potassium levels, ACTH levels, plasma Renin and Aldosterone activity along with serum Cortisol levels play key roles. High doses of Fludrocortisone therapy helps in overcoming aldosterone resistance and assist in maintaining electrolyte balance in the body.

Keywords: Hypoaldosteronism; Hyponatremia; Hyperkalemia; Aldosterone resistance; Pseudohypoaldosteronism

Case Report

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Abbreviations: Na-K ATPase Pump: Sodium Potassium ATPase pump; ACTH: Adrenocorticotrophic Hormone; WNK Kinase protein: With No (K) Lysine kinase Protein [lysine deficient protein kinase]

Introduction

Aldosterone is an important hormone for sodium conservation in the kidney, salivary glands, sweat glands and colon. In normal states within the kidney, aldosterone increases sodium reabsorption through opening epithelial sodium channels within the principle cells of the cortical collecting tubule causing the development of an electronegative potential in the lumen. This results in an electrical gradient that favors secretion of cellular potassium through the potassium channels. It also promotes active sodium transport and excretion of potassium via the Mineralocorticoid receptor (MR) and results in activation of the Na-K ATPase pump in the target tissues. In hypoaldosterone states, there is reduced sodium reabsorption in the cortical collecting tubules; therefore a lesser electrical gradient forms to facilitate secretion of cellular potassium, which results in hyperkalemia along with hyponatremia and acidosis [1]. Many patients with hyperkalemia have a readily identifiable cause, not limited to acute and chronic kidney disease but also include adrenal insufficiency, metabolic acidosis, insulin deficiency, rhabdomyolysis, burn injuries, intravascular hemolysis and medications, which leads to appropriate management. In others,

particularly those having a reduced glomerular filtration rate, differentiating between (relative) hypoaldosteronism (HA) and renal aldosterone resistance (RAR) can be problematic [1-3].

Case Presentation

A 63 years old male was first seen in the clinic with alleged diagnosis of adrenal insufficiency. He was started on fludrocortisone (0.1 mg q daily) and hydrocortisone (25 mg q AM and 12.5 mg q PM) by an outside physician but self-discontinued Hydrocortisone a few months prior to his visit. Patient was not on any antibiotics or diuretic treatment and was found to have low-normal blood pressure, normoglycemia, hyperkalemia, hyponatremia, and metabolic acidosis. Further testing revealed decreased early morning cortisol level of 11.7 mcg/dL (0.7 to 22.4 mcg/dL) and ACTH level of 20 pg/ml (0-46 pg/mL). ACTH stimulation test was done and baseline cortisol level was 10.89 mcg/dL, followed by 15.47 mcg/dL at 30 minutes and 19.72 mcg/dL at 60 minutes as well as aldosterone level was 111.7 ng/dL at 30 minutes and 249.2 ng/dL at 60 minutes (0-30 ng/dL) after stimulation test. Additional tests revealed negative 21-Hydroxylase antibodies and elevated plasma renin activity of 78 ng/ml/hr (0.2-3.3 ng/ml/hr). Patient was continued on fludrocortisone. He presented to clinic in following visit after missing his medication for 2 weeks and found to have low blood pressure (80/58 mmHg), hyperkalemia and metabolic acidosis. Resuming his fludrocortisone normalized his blood pressure.

Discussion

Clinical presentation of hypoaldosteronism can manifest either with aldosterone deficiency or due to aldosterone resistance. Aldosterone deficiency results in conditions like hyporeninemic hypoaldosteronism (due to diabetic kidney disease, non-steroidal anti-inflammatory drugs, calcineurin inhibitors), angiotensin inhibitors, heparin therapy, primary adrenal insufficiency, critical illness, congenital isolated hypoaldosteronism, and pseudohypoaldosteronism type-2 (Gordon's syndrome or familial hyperkalemic hypertension) that is due to abnormalities in WNK kinases in the distal nephrons which increase chloride

reabsorption leading to reduced renal potassium secretion and is characterized by hypertension, hyperkalemia, metabolic acidosis, normal renal function, and low or low-normal plasma renin activity and aldosterone concentrations [1,2,4]. Whereas, aldosterone resistance occurs due to inhibition of the epithelial sodium channel (potassium-sparing diuretics, trimethoprim, pentamidine) and pseudohypoaldosteronism type-1 that is characterized by marked elevations of plasma aldosterone levels [1,2,5-8]. Hypoaldosteronism can be due to an autosomal recessive inheritance pattern, an autosomal dominant pattern or via sporadic form. The autosomal dominant form tends to be associated with milder symptoms [1,2] (Table 1).

Table 1: Diagnostic findings for major causes of hypoaldosteronism [1].

Disorder	Plasma Renin Activity	Plasma Aldosterone
Hyporeninemic hypoaldosteronism	Low to normal	Low
Primary adrenal insufficiency	High	Low
Pseudohypoaldosteronism type 1	High	High
Pseudohypoaldosteronism type 2	Low to normal	Low to normal

This case represents a challenging differential diagnosis between primary adrenal insufficiency and aldosterone resistance syndrome. Although persistent hyperkalemia and hyponatremia are more commonly seen with adrenal insufficiency but normal basal cortisol and ACTH levels and negative ACTH stimulation test ruled out hypoadrenalism. In our case, aldosterone levels found significantly elevated in the face of hyperkalemia and raised suspicion of aldosterone resistance syndrome [6]. Fludrocortisone therapy has been approved by FDA for primary replacement in adrenocortical insufficiency (Addison's Disease), salt-losing forms of congenital adrenogenital syndrome and hyporeninemic hypoaldosteronism. It is also used off label for the treatment of severe orthostatic hypotension refractory to high salt diet and adequate fluid intake since it has vasoconstrictive effects through V1A vascular smooth muscle receptors. Patients with aldosterone resistance may also need fludrocortisone to maintain their blood pressure along with high salt diet, because high doses of fludrocortisone overcome aldosterone resistance, as it was seen in our case.

Conclusion

While hyperkalemia can be due to adrenal insufficiency, clinician should be aware of the possibility of aldosterone resistance if there is no evidence of hypocortisolemia and should not give glucocorticoids in addition to mineralocorticoids.

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