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PEARLS OF LABORATORY MEDICINE

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TITLE: Aldosterone and Renin

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Hello, my name is **Jieli Shirley Li**. I am an **assistant professor and lab director at Ohio State University Wexner Medical Center**. Welcome to this Pearl of Laboratory Medicine on "**Aldosterone and Renin**"

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Anatomically, the adrenal glands are divided into two distinct parts, the medulla, the inner layer and the cortex, the outer layer. The cortex is further divided into three zones. The outermost zona glomerulosa, which produces mineralocorticoids; the zona fasciculata, which is responsible for glucocorticoid production; and the inner zona reticularis, which synthesizes androgens. The cortex makes up about 80% to 90% of the adrenal gland. The medulla stores and secretes catecholamines.

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The hormones of the adrenal cortex are steroid derivatives, synthesized from cholesterol. Cholesterol travels across the mitochondrial membrane. In the zona glomerulosa, 3β-hydroxysteroid dehydrogenase, 21-hydroxylase and 11β-hydroxylase are the major enzymes which are involved in the aldosterone synthesis. In addition, aldosterone is synthesized by aldosterone synthase, an enzyme encoded by CYP11B2. Aldosterone synthase expresses almost entirely in the adrenal cortex and exclusively in the zona glomerulosa layer. Isolated

deficiencies of aldosterone biosynthesis could be caused by inactivating mutations in the CYP11B2 gene.

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The chief mineralocorticoid is aldosterone. It plays an important role in maintaining blood volume, pressure, pH, and electrolyte balance. It promotes the reabsorption of sodium, and meanwhile increases potassium and hydrogen ion excretion which increases blood pH. Therefore, in hyperaldosteronism, the overproduction of aldosterone leads to the retention of sodium and loss of potassium in the body, resulting in high hypertension, hypokalemia and alkalosis.

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At least 20 million people in the United States have hypertension. The role of the Renin-Angiotensin-Aldosterone System is to maintain blood pressure within normal limits by sensing and responding to changes in plasma volume, salt balance, and renal perfusion pressure. Aldosterone production and secretion are regulated by the Renin-Angiotensin-Aldosterone System. The production and release of renin is regulated by the juxtaglomerular apparatus in kidney. Renin acts on angiotensinogen, which is formed by the liver, breaking angiotensinogen to angiotensin I. Angiotensin I in turn is converted into angiotensin II by the angiotensin converting enzyme (ACE). The majority of ACE has been found on the pulmonary capillary endothelium, but also found in kidney epithelial cells. Low plasma volume and low serum sodium stimulate the secretion of renin, resulting in formation of angiotensin II, and subsequently aldosterone release via angiotensin II receptor, which, in turn, causes sodium retention along with an increase in plasma volume and blood pressure, and potassium loss. An increase in effective blood volume or acute elevation in blood pressure results in low renin, low angiotensin II, low aldosterone, and subsequent sodium loss.

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Hyperaldosteronism has primary and secondary types. Primary aldosteronism is a syndrome caused by aldosterone excess. Overproduction of aldosterone may be due to autonomous and inappropriate secretion of aldosterone by (1) adrenal adenoma (2) bilateral adrenal hyperplasia, which is the most common cause (3) glucocorticoid remediable hyperaldosteronism (4)

unilateral adrenal hyperplasia (5) adrenal carcinoma. Among these, aldosterone producing adrenal adenoma is synonymous with Conn Syndrome.
Secondary hyperaldosteronism is characterized by volume depletion, edema, and hypokalemic alkalosis. Usually secondary hyperaldosteronism refers to hypertension caused by hyperreninemic hyperaldosteronism as caused by renal arterial stenosis or other vascular underperfusion of the kidney and rarely reninoma.

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According to the Endocrine Society Guidelines, the diagnosis of primary aldosteronism includes:

- Hypertension resistant to three conventional anti-hypertensice drugs
- Controlled blood pressure on four or more anti-hypertensive drugs
- Hypertension in the presence of a known adenoma
- Hypertension and spontaneous or diuretic-inducedhypokalemia
- Hypertension and sleep apnea
- Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years old)

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Pseudoaldosteronism, sometimes also referred to pseudohyperaldosteronism. Its clinical presentations are similar with primary aldosteronism. However, pseudohyperaldosteronism differs by having low plasma aldosterone, because of the activation of the mineralocorticoid receptor without an increase in aldosterone. This occurs because of functional increases in cortisol or other steroid hormones with some mineralocorticoid activity. In Cushing's syndrome or high dose steroid therapy, the mineralocorticoid receptor can also be activated. The active agent in licorice, glycyrrhizin, inhibits the enzyme 11-beta-hydroxysteroid dehydrogenase type 2, which metabolizes cortisol to cortisone in the kidney. Genetic deficiency of 11-beta-steroid hydroxylase can lead to overproduction of 11-deoxycorticosterone and decreased aldosterone. Liddle syndrome is an autosomal dominant genetic disorder leading to increased activity of the amiloride-sensitive sodium channel, characterized by

hypertension with hypokalemic metabolic alkalosis, hyporeninemia and suppressed aldosterone secretion.

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Primary defects in adrenal secretion of aldosterone, results from progressive destruction or dysfunction of the adrenal glands by a systemic disorder, an inborn error of metabolism (endogenous causes) or an exogenous cause such as infection. Tests to confirm aldosterone deficiency in such patients are not usually necessary because hyperkalemia and hypotension support the diagnosis of primary adrenal insufficiency in patients with cortisol deficiency, elevated ACTH, and hyperpigmentation.

The causes of hypoaldosteronism usually includes:

- Congenital causes (eg. Congenital adrenal hyperplasia)
- Acquired causes, the most common cause is autoimmune adrenal destruction (eg. Addison's disease)
- Infectious adrenal destruction (eg. Amyloidosis, sarcoidosis)
- Traumatic, hemorrhagic or thymbotic adrenal destruction
- Bilateral adrenalectomy

Slide 10:

Measurement of aldosterone is technically challenging because the concentration of this hormone in blood is very low. Radioimmunoassay methods were developed for aldosterone measurement. Immunoassays, especially chemiluminescent methodology for measuring aldosterone in blood and urine are available. LC/MS-MS has also been applied to aldosterone measurements.

Methods for measuring renin include renin activity and direct renin. Measuring renin activity provides an indication of the biologically active fraction of renin in the specimen because it measures the primary function of the enzyme, which converts angiotensinogen to angiotensin I. Renin activity measurements are difficult to standardize. Then direct renin measurements are developed. Direct renin measurement is renin concentration measurement. The concentration of renin can be measured by immunoassay or LC/MS-MS. However, direct renin measurements are difficult to standardize too, due to the issues on calibration or pro-renin activation.

The aldosterone-to-renin ratio was proposed as a sensitive screening test because most cases of primary aldosteronism have normal aldosterone levels. However, due to the variation of aldosterone and renin measurement methods, specifying a universal aldosterone-to-renin ratio is impossible.

Slide 11: References

Slide 12: Disclosures

Slide 13: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Aldosterone and Renin**."

Question Bank

A 42-year-old Caucasian male complaining of muscle weakness, has no significant past medical history. His blood pressure is 180/105 mmHg on supine, and 190/110 mmHg on standing. Laboratory evaluation shows low level of plasma renin activity and potassium level at 3.0 mmol/L. Which of the following structures is most likely overactive in this case?

a) Zona glomerulosa of the adrenals
b) Zona fasciculate of the adrenals
c) Zona reticulate of the adrenals

d) Extra-adrenal paraganglion cells

Answer: **a**

Discussion: The zona glomerulosa synthesized mineralocorticoids, the zona fasciculata predominantly produces cortisol, and the zona reticularis predominantly produces androgens. Secretion of aldosterone from the zona glomerulosa is regulated by the renin-angiotensin system and potassium. Aldosterone's main effect is to stimulate sodium absorption and potassium and hydrogen ion excretion at the distal renal tubule. Thus, overproduction of aldosterone by tumors or hyperplastic zona glomerulosa cells can result in sodium retention, hypertension, hypokalemia and metabolic alkalosis.

Source: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics - 6th Edition

Difficulty: Easy

A 4-year-old girl presented to the ER because of high-grade fever, vomiting and altered mental status. Physical examination shows hypotension, tachycardia, neck stiffness and petechial rash over the trunk and lower extremities. Laboratory results:

Hemoglobin	12.0 g/L
Platelets	100,000/mm^3
Serum sodium	130 mmol/L
Serum potassium	5.6 mmol/L
Blood urea nitrogen (BUN)	30 mg/dL
Serum creatinine	1.8 mg/dL
Blood glucose	50 mg/dL

Which of the following is the most likely reason for the patient's symptom?

a) Cardiac tamponade
b) Pulmonary embolus
c) Adrenal hemorrhage
d) Rupture of coronary artery aneurysm

Answer: **c**

Discussion: the presence of shock in combination with hyponatremia, hyperkalemia and hypoglycemia strongly suggests adrenal crisis. The patient also has fever, vomiting, nuchal rigidity and petechial rash, which indicates meningococcal meningitis. The meningococcal septicemia can cause adrenal hemorrhage leading to acute adrenal crisis, which can occur at any age.

Source: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics - 6th Edition

Difficulty: Intermediate