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UNVEILING THE MECHANISMS OF CONN'S SYNDROME AND SECONDARY HYPERTENSION

[1]Sadullayeva U.S., [2]Juraev M.B.
[1]Tashkent medical academy, treatment faculty-2, group №226
[2]Tashkent medical academy, biochemistry department, teacher-assistant
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Abstract*. Conn's syndrome, also known as primary hyperaldosteronism, represents a common cause of secondary hypertension. This literature review aims to dissect the intricate mechanisms underlying Conn's syndrome and its association with secondary hypertension. Through a comprehensive exploration of recent research findings, this review elucidates the pathophysiological processes, diagnostic strategies, and therapeutic interventions pertinent to this condition. By synthesizing existing knowledge, this review provides valuable insights into the management of Conn's syndrome and secondary hypertension.*

Keywords*: renin, aldosterone, Conn's syndrome, angiotensinogen, angiotensin converting enzyme, antidiuretic hormone, aquaporin, nephron.*

Nowadays number of endocrine diseases are increasing continuously both due to genetic and enviromental factors. Here we discuss about Conn's syndrome, which is characterized by excessive aldosterone production from the adrenal glands, contributes significantly to secondary hypertension. Despite its clinical importance, the precise mechanisms driving aldosterone overproduction and its subsequent impact on blood pressure regulation remain subjects of ongoing investigation. This literature review endeavors to consolidate current understanding regarding the pathogenesis of Conn's syndrome and its implications for secondary hypertension management.

When it comes to pathophysiology of the disease, aldosterone, a mineralocorticoid hormone, plays a pivotal role in regulating electrolyte balance and blood pressure. In Conn's syndrome, dysregulation of aldosterone synthesis leads to sodium retention, potassium excretion, and ultimately, hypertension. Recent studies have implicated various molecular pathways in the pathogenesis of Conn's syndrome, including dysregulation of aldosterone synthase expression, somatic mutations in aldosterone-producing adenomas, and aberrant activation of the renin-angiotensin-aldosterone system (RAAS). These insights into the molecular underpinnings of Conn's syndrome have facilitated the development of targeted therapeutic approaches, such as mineralocorticoid receptor antagonists and surgical resection of aldosterone-producing adenomas. When it comes to exact mechanism of hypertension development, there are several possible pathways:

Firstly, increased sympathetic activity, decreased blood pressure or decreased sodium delivery to distal tubules stimulate renin secretion from kidney. Renin has enzymatic activity which convertes angiotensinogen (produced from liver) into angiotensin I.

After that, angiotensin I will be converted into angiotensin II with the help of angiotensin converting enzyme which is located in lung tissue.

Angiotensin II is the central part in the develoment of hypertension. It affects to blood pressure changes through several ways:

a) In the walls of blood vessel, there are receptors for the substance, when it is stimulated, it leads to vasoconstriction and in turn, elevated blood pressure.

b) In proximal convaluted tubules, there are specific transporters that reabsorbs sodium and hydrogen ions from the tubule, this increases blood volume, in turn, blood pressure.

c) This substance increases secretion of antidiuretic hormone from posterior pituitary, which goes to collecting tubules of nephron and binds to V2 receptors located in basolateral membrane. When the receptor is activated, there will be increased aquaporin channels in the apical membrane which promotes water reabsorption, in turn, increases blood volume and blood pressure.

d) Lastly, angiotensin II stimulates glomerulosa layer of adrenal cortex to secrete steroid hormone called aldosterone. The mechanism of aldosterone's influence on blood pressure regulation is intricate and multifaceted, primarily involving its actions on the kidneys and vascular system. Aldosterone, a mineralocorticoid hormone synthesized and secreted by the adrenal cortex, plays a crucial role in maintaining electrolyte balance and blood pressure homeostasis. Here's an overview of how aldosterone impacts blood pressure through its various mechanisms:

Initially, Renal Sodium and Water Retention: Aldosterone exerts its primary effects on the kidneys, specifically on the distal convoluted tubules and the collecting ducts. In these renal tubular segments, aldosterone promotes the reabsorption of sodium ions (Na^+) from the tubular lumen into the bloodstream in exchange for potassium ions (K^+), thereby increasing sodium retention. This enhanced sodium reabsorption leads to an increase in extracellular fluid volume, contributing to plasma volume expansion and consequent elevation of blood pressure.

Secondly, Potassium Excretion: Concomitant with sodium reabsorption, aldosterone stimulates the secretion of potassium ions (K^+) into the tubular lumen, facilitating potassium excretion. This mechanism helps maintain potassium homeostasis in the body. However, excessive aldosterone action can lead to potassium depletion, potentially resulting in hypokalemia, which may further exacerbate hypertension and increase cardiovascular risk.

Thirdly, Regulation of Blood Volume and Cardiac Output: By increasing sodium reabsorption and extracellular fluid volume expansion, aldosterone indirectly influences cardiac output. The increased blood volume leads to greater venous return to the heart, thereby enhancing cardiac preload and stroke volume. Consequently, cardiac output increases, contributing to elevated systemic blood pressure.

Lastly, Modulation of Vascular Tone: In addition to its effects on renal function and blood volume, aldosterone may also influence vascular tone through interactions with the endothelium and vascular smooth muscle cells. Aldosterone has been shown to promote endothelial dysfunction, inflammation, and oxidative stress, which can impair vasodilation and promote vasoconstriction. These vascular effects may further contribute to hypertension and cardiovascular pathology associated with aldosterone excess.

When we talk about diagnostics of the disease, the diagnosis of Conn's syndrome, also known as primary hyperaldosteronism, involves a systematic approach to confirm aldosterone excess and localize its source. Given the importance of accurate diagnosis in guiding appropriate management strategies, various diagnostic modalities are utilized to distinguish Conn's syndrome from other causes of secondary hypertension. Here's an overview of the diagnostic methods commonly employed:

Let’s start with clinical evaluation: Clinical assessment forms the initial step in diagnosing Conn's syndrome, with a focus on identifying signs and symptoms suggestive of aldosterone excess. Common clinical manifestations may include hypertension refractory to conventional antihypertensive therapy, hypokalemia, muscle weakness, polyuria, polydipsia, and metabolic alkalosis. However, it's important to note that Conn's syndrome may present with varying degrees of symptomatology or be entirely asymptomatic.

Then, of course, laboratory tests: Laboratory investigations play a crucial role in confirming the presence of aldosterone excess and differentiating between various etiologies of secondary hypertension. Key laboratory tests include:

Plasma Aldosterone Concentration (PAC): Measurement of PAC serves as a primary screening test for Conn's syndrome. Elevated PAC levels, particularly in the setting of suppressed plasma renin activity (PRA), suggest primary hyperaldosteronism.Plasma Renin Activity (PRA): Assessment of PRA helps determine the activity of the renin-angiotensin-aldosterone system (RAAS). In Conn's syndrome, PRA levels are typically suppressed due to negative feedback resulting from aldosterone-induced sodium retention.

Aldosterone-to-Renin Ratio (ARR): Calculation of the ARR by dividing PAC by PRA provides a valuable diagnostic tool for identifying patients at high risk of Conn's syndrome. An elevated ARR (>20–30 ng/dL per ng/mL/h) is suggestive of primary hyperaldosteronism.

Serum Potassium Levels: Evaluation of serum potassium levels can reveal hypokalemia, a common feature of Conn's syndrome resulting from aldosterone-induced potassium excretion.

To Confirm the disease, finally: Following initial screening with laboratory tests, confirmatory tests are often performed to establish the diagnosis of Conn's syndrome definitively. Common confirmatory tests include:

Additional tests may be helpful, such as Oral Sodium Loading Test: Administration of oral sodium chloride (NaCl) with subsequent measurement of urinary aldosterone and sodium levels can help differentiate between physiological and inappropriate aldosterone secretion. In Conn's syndrome, urinary aldosterone remains elevated despite sodium loading.

Here is the other one, Saline Infusion Test: Intravenous infusion of saline solution followed by measurement of aldosterone levels helps assess the suppression of aldosterone secretion in response to volume expansion. In Conn's syndrome, aldosterone fails to suppress adequately, indicative of autonomous aldosterone production.

Imaging Studies could be helpful: Localization of aldosterone-producing lesions is essential for determining the underlying etiology of Conn's syndrome and guiding appropriate management. Imaging modalities commonly employed include:

Computed Tomography (CT) Scan: High-resolution CT imaging of the adrenal glands enables visualization of adrenal masses, such as aldosterone-producing adenomas (APAs) or bilateral adrenal hyperplasia (BAH), which are characteristic of Conn's syndrome.

Magnetic Resonance Imaging (MRI): MRI may be utilized as an alternative to CT for adrenal imaging, particularly in patients with contraindications to ionizing radiation or iodinated contrast agents.

Adrenal Vein Sampling (AVS): Considered the gold standard for lateralizing aldosterone hypersecretion, AVS involves catheterization of adrenal veins to obtain simultaneous samples for aldosterone measurement from both adrenal glands. A selectivity index is calculated to determine the unilateral or bilateral nature of aldosterone production.

Therapeutic Interventions: The management of Conn's syndrome encompasses both pharmacological and surgical interventions aimed at mitigating aldosterone excess and reducing blood pressure. Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, serve as first-line pharmacotherapy for patients with Conn's syndrome, effectively blocking the effects of aldosterone on target organs.

Spironolactone has specific adverse effects,one of which is antiandrogenic effect, in case this condition develos the drug can be changed to the secons alternative one: eplerenone . This drug doesnot have antiandrogenic effect. For individuals with unilateral aldosterone-producing adenomas, surgical adrenalectomy offers a curative treatment option, yielding substantial improvements in blood pressure control and cardiovascular outcomes. However, optimal treatment selection necessitates careful consideration of patient-specific factors, including comorbidities, medication tolerability, and surgical candidacy.

In summary, Conn's syndrome represents a significant contributor to secondary hypertension, necessitating a thorough understanding of its pathophysiology and tailored management approaches. Through elucidating the molecular mechanisms driving aldosterone excess and exploring advancements in diagnostic and therapeutic modalities, this literature review aims to inform clinicians and researchers alike about the complexities of Conn's syndrome and facilitate the optimization of patient care. Further research endeavors are warranted to uncover novel therapeutic targets and refine diagnostic algorithms, ultimately improving outcomes for individuals afflicted by this condition.

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