Liddle Syndrome

Liddle syndrome is a rare, autosomal dominant disease caused by mutations in genes that encode epithelial sodium channels (ENaC) in the collecting duct. This causes excess sodium and water reabsorption. Clinical features include decreased renin, decreased aldosterone, hypertension, and hypokalemia. A metabolic alkalosis may also be observed. Liddle syndrome is sometimes called a pseudohyperaldosteronism because it looks like hyperaldosteronism in its clinical features but aldosterone levels are actually low. Treatment consists of ENaC inhibitors like amiloride or triamterene.

PLAY PICMONIC

Pathophysiology

Autosomal Dominant

Dominos

Liddle syndrome is inherited in an autosomal dominant manner, meaning one defective/mutated copy of the gene is required for the disease to manifest, and that the gene is not located on a sex chromosome.

Collecting Duct

Collection Duck

Liddle syndrome is due to a dysfunction of the sodium channels in the renal collecting duct. The collecting duct is the final segment of the nephron, which is involved in electrolyte homeostasis. Major cell types of the collecting duct include alpha cells (for acid secretion), beta cells (for bicarbonate secretion), and principal cells (for water and sodium absorption and potassium secretion). Epithelial sodium channels (ENaC) are located on principal cells.

Gain of Function Mutation in Epithelial Sodium Channel (ENaC)

Up-arrow Mutant with Salty ENaC-Snacks

A gain of function (GOF) mutation in the genes encoding for beta and gamma subunits of the epithelial sodium channel is responsible for Liddle syndrome. This results in constitutive activation and decreased degradation of the sodium channels, causing excessive sodium reabsorption. The genes are SCNN1B and SCNN1G located on chromosome 16.

Excess Na+ and H₂O Reabsorption

Salt-Shaker with Water and Sponge

An inability to turnover ENaCs results in excessive sodium and water reabsorption in the collecting duct. The decreasing electropositivity in the tubular lumen causes passive diffusion of potassium (K+) and (H+) ions into the urine, which leads to a hypokalemic state with metabolic alkalosis.

Clinical Features

Decreased Renin

Down-arrow Wrenches

The increased reabsorption of sodium inhibits juxtaglomerular release of renin and thus decreases activation of the renin-angiotensin-aldosterine system (RAAS). Renin and aldosterone levels will be decreased, although the effects of RAAS will be evident e.g. hypervolemia, hypertension, and hypokalemia.

Decreased Aldosterone

Down-arrow Aldo-stereo

The increased reabsorption of sodium inhibits juxtaglomerular release of renin and thus decreases activation of the renin-angiotensin-aldosterine system (RAAS). Renin and aldosterone levels will be decreased, although the effects of RAAS will be evident e.g. hypervolemia, hypertension, and hypokalemia.

Hypertension with Hypokalemia

Hiker-BP with Hippo-banana

Hypertension occurs because of excessive sodium and water reabsorption while hypokalemia results from passive potassium ion diffusion into the renal tubule to balance the electrochemical gradient.

Metabolic Alkalosis

Metal-ball Elk-loser

In addition to potassium ions, hydrogen ions (H+) also diffuse into the renal tubule to balance the electrochemical gradient. This results in a serum metabolic alkalosis. Metabolic alkalosis is an elevated blood pH due to renal injury or disease (versus a respiratory cause).

Pseudohyperaldosteronism

Sumo-hiker-Aldo-stereo

Liddle syndrome mimics hyperaldosteronism in many ways, however it can be differentiated in that Liddle Syndrome, unlike hyperaldosteronism, has low plasma aldosterone. It is therefore sometimes referred to as causing pseudohyperaldosteronism. Pseudohyperaldosteronism is a condition that mimics hyperaldosteronism. Clinically, pseudohyperaldosteronism presents with hypertension, hypokalemia, and metabolic alkalosis.

Treatment

Amiloride and Triamterene

Amelia-rider and Triathlete

Patients with Liddle syndrome require lifelong therapy with potassium-sparing diuretics that are not aldosterone antagonists (e.g. spironolactone) because aldosterone levels are already reduced. Specifically ENaC antagonists such as amiloride and triamterene are required.