Bartter Syndrome

Bartter syndrome is a group of autosomal recessive disorders that affect the NKCC cotransporter in the thick ascending limb of the loop of Henle. A defective sodium-potassium-2 chloride cotransporter results in decreased sodium reabsorption, decreased calcium reabsorption, and increased aldosterone. Clinical features may include hypovolemia, polyuria and polydipsia, and metabolic alkalosis. Bartter syndrome mimics the presentation of a patient on loop diuretics, and can lead to nephrolithiasis. Spironolactone is the treatment of choice for these patients.

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Pathophysiology

Autosomal Recessive

Recessive-chocolate

Bartter syndrome is a group of genetic disorders that are inherited in an autosomal recessive manner.

Thick Ascending Limb of Loop of Henle

Thick Ascending Limb

Bartter syndrome primarily affects the thick ascending limb of the loop of Henle, a part of the renal nephron. This segment is impermeable to water, and in a normal functioning nephron plays an important role in countercurrent multiplication by reabsorbing Na^{+}, Cl^{-}, K^{+}, and inducing the reabsorption of Ca^{2+} and Mg^{2+}.

Defective NKCC Cotransporter

Tied-up Salt-shaker, Banana, and Chlorine-dispenser in (2) Tutu

Bartter syndrome is the result of a defective Na/K/2Cl cotransporter, or NKCC2, in the thick ascending loop of Henle (TAL). This cotransporter mediates the secondary active transport of one sodium, one potassium, and two chloride ions from the lumen into the tubular cells (across the apical membrane). Less commonly, Bartter Syndrome may arise from a loss of function mutation in renal outer medullary potassium channels, or ROMK channels. ROMK channels are ATP-dependent channels involved in renal potassium homeostasis. These channels play two critical roles in the TAL - potassium recycling (essential for sodium reabsorption) and generating a positive transepithelial gradient, which drives paracellular reabsorption of divalent cations (magnesium and calcium).

Decreased Na^{+} Reabsorption

Down-Arrow Salt-Shaker & Sponge

Due to the defective NKCC2 cotransporter, sodium ions are lost in the urine. The increased delivery of sodium to the distal convoluted tubule (DCT) results in excessive reabsorption here, which causes excessive potassium excretion into the urine to maintain electroneutrality.

Decreased Ca^{2+} Reabsorption

Down-Arrow Calcium-Cow and Sponge

Due to the defective NKCC2 cotransporter, calcium is also lost in the urine, resulting in hypercalciuria. This differentiates Bartter syndrome from Gitelman syndrome, which is associated with hypocalciuria.

Increased Aldosterone

Up-Arrow Aldo-Stereo

Failure to reabsorb sodium causes both salt lass (natriuresis) and water loss. This leads to volume depletion and hypotension. Hypotension is sensed by intrarenal baroreceptors (juxtaglomerular cells), and high sodium chloride concentration in the filtrate of the DCT is sensed by macula densa cells. Both of these stimuli activate the Renin-Angiotensin-Aldosterone System (RAAS), and an increase in aldosterone levels. Aldosterone exacerbates hypokalemia by promoting potassium and hydrogen ion excretion in exchange for sodium reabsorption.

Clinical Features

Hypovolemia

Hippo-volume-cup

Hypovolemia refers to a decreased fluid (water) volume. In Bartter syndrome, this occurs due to failure of sodium reabsorption and excess sodium excretion in the urine causing both salt lass (natriuresis) and water loss.

Polyuria and Polydipsia

Polly-urinating and Polly-drinking

Polyuria is defined as excess urine production measured over the course of 24 hours. Polydipsia is a condition of excessive thirst. In patients with Bartter syndrome, natriuresis causes polyuria while activation of RAAS causes polydipsia from stimulation of the thirst center in the hypothalamus.

Metabolic Alkalosis

Metal-Ball Elk-Loser

The loss of volume via urine causes a hypovolemic (contraction) metabolic alkalosis. Significant volume loss results in activation of RAAS, which increases aldosterone. Aldosterone promotes potassium and hydrogen ion excretion into the urine. The loss of hydrogen ions causes an increased ratio of bicarbonate in the blood from a renal etiology i.e. metabolic alkalosis.

Mimics Loop Diuretics

Mime and Loop-Hen Die-Rocket

This disorder mimics the effects of taking a loop diuretic such as furosemide. Loop diuretics are a class of diuretics that inhibit the Na-K-2Cl symporter.

Nephrolithiasis

Kidney Throwing Stones

Urolithiasis (nephrolithiasis, ureterolithiasis, cystolithiasis) are commonly made of calcium oxalate or calcium phosphate. In Bartter syndrome, increased calcium excretion in the urine (hypercalciuria) over time results in nephrocalcinosis (calcium deposition in renal tubules) and nephrolithiasis.

Treatment

Spironolactone (Aldactone)

Spiral-of-milk

Treatment of Bartter syndrome is lifelong potassium-sparing diuretics, particularly those that inhibit RAAS, such as spironolactone. Spironolactone is a mineralocorticoid receptor antagonist, which can help counteract the increased aldosterone levels in patients with Bartter syndrome.

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