Renal Tubular Acidosis Type 4

PLAY PICMONIC

Characteristics

Aldosterone Resistance

Aldo-stereo with Resistance Bandana

Aldosterone resistance is due to insensitivity of target tissues, especially the kidney, to aldosterone. Aldosterone is a mineralocorticoid synthesized by the zona glomerulosa of the adrenal glands. It has several effects including increasing sodium reabsorption and potassium urinary excretion. Resistance to aldosterone can occur in many cases. Potassium-sparing diuretics (e.g., spironolactone, amiloride) prevent aldosterone from acting on the kidney. Some antibiotics especially trimethoprim are another etiology. Additionally, pseudohypoaldosteronism type 1 describes genetic mutations leading to loss-of-function of the mineralocorticoid receptor protein and loss-of-function mutations in the genes encoding the epithelial sodium channel.

Decreased Aldosterone Production

Down-arrow Aldo

Decreased production of aldosterone can be seen in multiple conditions. Primary adrenal insufficiency is one example and will have decreased cortisol as well. Hyporeninemic hypoaldosteronism is another example, occurring when renal injury and damage to the juxtaglomerular apparatus decreases renin production (e.g., in diabetic nephropathy or nephrotoxic medication use). Rare etiologies include genetic disorders such as Gordon syndrome or pseudohypoaldosteronism type 2. It is noteworthy that although aldosterone promotes sodium retention, hypoaldosteronism is not typically associated with prominent sodium wasting (except in young children) because of the compensatory action of other sodium-retaining factors (such as angiotensin II).

Causes Of Hypoaldosteronism

Addison's Disease (Primary Adrenal Insufficiency)

Add-sun

Addison's disease, also known as primary adrenal insufficiency is a state of decreased adrenal production of adrenocortical hormones, including mineralocorticoids (aldosterone). The most frequent cause is autoimmune adrenalitis. Other causes include infection such as tuberculosis and cytomegalovirus, or adrenal hemorrhage. Without aldosterone, type 4 RTA can result.

Hyporeninism

Down-arrow Wrenches

Another cause of hypoaldosteronism may be decreased renin activity. This is termed hyporeninemic hypoaldosteronism. Without renin, aldosterone won't be produced. It is most commonly caused by diabetic nephropathy or chronic interstitial nephritis. In diabetic nephropathy, the hypoaldosteronism is due to damage to the juxtaglomerular apparatus which is where renin is synthesized. It can also be caused by drugs that inhibit renin synthesis in the juxtaglomerular apparatus such as NSAIDs, ACE inhibitors, beta-blockers, heparin, and cyclosporine.

Causes Of Aldosterone Resistance

Trimethoprim-Sulfamethoxazole

Tampon SMX-snowmobile

Trimethoprim is a bacteriostatic antibiotic that inhibits bacterial dihydrofolate reductase. It's often compounded with a sulfonamide (such as sulfamethoxazole). Trimethoprim can cause hypoaldosteronism by directly inhibiting the epithelial sodium channels (ENaC) located in the collecting duct, preventing normal aldosterone function.

Potassium Sparing Diuretics

Bananas Shooting Dice-rockets

Potassium-sparing diuretics are a class of diuretic drugs that do not increase the secretion of potassium into the urine. They work by either competing with aldosterone for binding sites or directly blocking sodium channels, therefore generating resistance to aldosterone action. Other drugs causing aldosterone resistance are angiotensin receptor blockers (ARBs) and pentamidine.

Labs

Hyperkalemia

Hiker-banana

Hyperkalemia is a serum potassium level > 5 mEq/L. Aldosterone normally acts by increasing the number of open sodium channels in the luminal membrane of the principal cells in the cortical collecting tubule, leading to increased sodium reabsorption. This reabsorption of sodium from the tubular fluid makes the lumen electronegative, creating an electrical gradient that favors the secretion of cellular potassium into the lumen through potassium channels in the luminal membrane. Reduced actions of aldosterone in the context of hypoaldosteronism reduces this potassium excretion and lead to an increase in plasma potassium concentration.

Low Urine pH

Down-arrow pH scale with urine

The hyperkalemia caused by the hypoaldosteronism impairs ammonia (NH3) genesis in the proximal tubule and therefore reduces the availability of ammonia to buffer urinary hydrogen ions. As there is an inadequate amount of NH3 available for buffering protons, the urine pH can decrease (<5.5).

Diminished Ammonium (NH4) Urinary Excretion

Down-arrow Ammo in Urine

In hypoaldosteronism (type 4 RTA) there is decreased urinary ammonium (NH4+) excretion. There are various mechanisms explaining the decreased ammonium excretion. Hyperkalemia causes diminished ammonia production because potassium shifts into cells causing hydrogen to shift out of cells, resulting in intracellular alkalosis in the renal tubules. In response, ammonia production by the proximal renal tubular cells is decreased. This reduces the availability of ammonia (NH3) to buffer urinary hydrogen ions and decreases hydrogen ion excretion in urine. Hyperkalemia also decreases medullary cycling by inhibiting ammonium reabsorption in the thick ascending limb as they compete for the same transporter.

Treatment

Furosemide

Fur-rose

Furosemide is a loop diuretic that inhibits sodium and chloride resorption by competitively inhibiting the Na+/K+/2Cl- cotransporter in the ascending limb of the loop of Henle. It leads to potassium wasting. Therefore in some cases of hyperkalemic type 4 RTA, furosemide may be useful.

Fludrocortisone

Flower-court-sun

Since the pathophysiology is due to diminished aldosterone or aldosterone resistance, part of the treatment can include mineralocorticoid replacement. Fludrocortisone is a mineralocorticoid similar to aldosterone and can be used for replacement. If the cause of type 4 renal tubular acidosis is primary adrenal insufficiency, these patients may also require glucocorticoid replacement.