Differential diagnosis of hyperkalemia: an update to a complex problem

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Abstract

Hyperkalemia is a relatively common and sometimes life threatening electrolyte disorder. Although its symptomatic treatment is relatively easy, since precise therapeutic algorithms are available, its differential diagnosis is more complicated. The present review aims to unfold the differential diagnosis of hyperkalemia using a pathophysiological, albeit clinically useful, approach. The basic elements of potassium homeostasis are provided, the causes of hyperkalemia are categorized and analysed and finally the required for the differential diagnosis laboratory tests are mentioned. Hippokratia 2012, 16, 4: 294-302

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Introduction

Hyperkalemia is a relatively common and sometimes life threatening electrolyte disorder¹². Although its symptomatic treatment is relatively easy, since precise therapeutic algorithms are available¹, its differential diagnosis is more complicated. The present review aims to unfold the differential diagnosis of hyperkalemia using a pathophysiological, albeit clinically useful, approach.

1. Pseudohyperkalemia

Diagnosis of hyperkalemia requires plasma potassium (K⁺) concentration more than 5mEq/L or serum K⁺ concentration greater than 5.5mEq/L. However, in rare cases, serum or plasma potassium elevation is factitious due to cell release within the sample tube. Causes of pseudohyperkalemia include errors during venipuncture that lead to hemolysis including sustained tourniquet application, use of thin needles, bad sample handling or systems of pneumatic tube transport⁴. Besides hemolysis, pseudohyperkalemia can be seen in polycythaemia as well as with WBC>100000/mm³ or platelet count >1000000/mm³, although there is a discrepancy concerning the role of white blood cell count⁵. Furthermore, familial pseudohyperkalemia is a rare disease in which potassium is released by red blood cells in the test tube because of a disorder in the permeability of the erythrocyte membrane⁶.

2. Potassium homeostasis

Potassium is the major intracellular cation with concentrations reaching 120-150 mEq/L. On the contrary, the extracellular fluid potassium concentration is much lower and kept within very narrow levels between 3.5-5.0 mEq/L. The above difference is attributed to Na⁺-K⁺-ATPase, a pump which is located in almost all cells and moves 3 sodium ions out of the cell and 2 potassium ions inside the cell. This K⁺ concentration gradient across the membrane is mainly responsible for the resting potential of the cellular plasma membrane. Maintaining this potential is of cardinal importance for the function of muscular and neuronal tissue⁸⁻¹⁰ (Figure 1).

Prevention of fatal hyperkalemia after a rich meal is attributed to postprandial secretion of insulin which moves K⁺ inside the cell. Insulin is secreted as a response to postprandial elevation of blood glucose (and blood K⁺) and increases Na⁺-K⁺-ATPase activity⁸,¹¹. Urine K⁺ excretion is also increased postprandially as discussed later. During physical exercise, catecholamines act in the same way in order to regulate K⁺ homeostasis⁸,¹²,¹³.

Typical Western diet provides 50-100mEq of K⁺ per day. 90% is secreted in the urine, 5-10% is excreted by the gut and 1-10% through the skin. Potassium absorption by the small intestine is not subjected to any regulation. Although potassium secretion by colonic epithelial cells is greatly increased in cases of hyperkalemia, up to three times in patients with end stage renal disease, this effect has a minor impact in K⁺ balance. Given the fact that aldosterone promotes intestinal K⁺ excretion, a study in dialysis patients was designed. 0.1 mg of fludrocortisone was daily administered for three months in these patients but no alterations in serum K⁺ concentrations were observed¹⁴. Currently, big K⁺ channels, also called maxi K⁺ channels, in the colonic crypts are considered to be involved in intestinal K⁺ excretion. These channels are upregulated in chronic hyperkalemia¹⁵.

Distal nephron is mainly involved in the regulation of K⁺ homeostasis. K⁺ is freely filtered in the glomerulus and is mainly reabsorbed in the proximal tubule and the thick ascending limb of Henle’s loop. Proximal reabsorption is...
Potassium, through its role in resting and action membrane potential, is of cardinal importance for the function of excitable tissues.

Figure 2: The principal cells and the potassium excretion in the cortical collecting duct.

passive, while in Henle’s loop, the Na-K-2Cl cotransporter (NKCC2) is required. Approximately 10% of the filtered load reaches the distal nephron. K+ excretion which takes place in the early distal nephron and the cortical collecting duct (CCD) is subject to strict regulation. The principal cells which are responsible for this process, mediate K+ excretion via Na-K-ATPase in their basal membrane. This pump creates a concentration gradient which promotes both K+ secretion from the principal cell to the tubule and Na+ reabsorption via certain channels (Figure 2). K+ concentration gradient between the principal cell and the tubular lumen, electric potential gradient between cell and lumen and luminal membrane permeability to potassium are the major forces regulating K+ excretion by the principal cells. These forces are mostly affected by Mineralocorticoids and distal sodium and water delivery16-19.

Aldosterone is secreted by the zona glomerulosa of the adrenal glands, is bound to its intracellular receptor in the principal cells and increases K+ excretion by 3 ways: 1. it increases the likelihood of epithelial sodium channels (ENaC) to be open to the luminal side while it inhibits their degradation by proteasomes. In this way, sodium reabsorption is increased, luminal electronegativity is increased and therefore, potassium secretion is enhanced, 2. it promotes Na-K-ATPase activity in the basal side and therefore increases intracellular potassium concentration and enhances K+ secretion to the lumen, and 3. it increases luminal membrane permeability to K+ 16-19.

Sodium and water supply to the distal nephron plays an important role in K+ excretion. Increased distal Na and water delivery enhances K+ excretion by creating a favorable electric potential and concentration gradient respectively.

Two types of channels for K+ excretion have been identified in the principal cells. Renal Outer Medullary Potassium channels (ROMK) and the big K+ channels, also called maxi K+ channels. The former are activated under typical physiological conditions while the latter in cases of increased sodium and water delivery which via mechanical pressure results in elevation of intracellular calcium in the principal cells16-19. Mechanical pressure mediated by increased sodium and water delivery also results in increased ENaC action and Na+ reabsorption20.

It has been demonstrated that a diet rich in K+ promotes kaliuresis and this effect is independent of Mineralocorticoids action. In this case, increased kaliuresis is attributed to movement of ROMK and maxi K+ channels to the luminal side of the principal cells’ membrane.
These changes are associated with the action of WNK (with-no-lysine kinases) kinases family. WNK1 kinase is expressed in many tissues but a smaller fraction is solely expressed in the kidney [kidney specific (KS)-WNK1]. Under normal circumstances, 85% of this kinase is found as KS-WNK1. K+ rich diets increase the KS-WNK1 to WNK1 ratio, and KS-WNK1, by counteracting WNK1 actions, inhibits ROMK endocytosis resulting in increased K+ excretion. Furthermore, KS-WNK1 promotes ENaC activity and sodium reabsorption thus creating an electrochemical gradient which favors K+ excretion

3. Differential diagnosis

A carefully obtained, detailed history is mandatory for the differential diagnosis of hyperkalemia. Diagnostic thought should be guided towards the three main causes of hyperkalemia: increased K+ intake, K+ release from cells and impaired renal K+ excretion.

3.1 Excessive potassium intake

Under circumstances of intact kidney function, renal K+ excretion is normal. Thus increased K+ uptake does not cause significant problems. Otherwise, when kidney function is impaired, consumption of foods rich in K+ can lead to life threatening hyperkalemia. This cause accounts for most cases of hyperkalemia in patients with end stage renal disease. Additional dietary sources of K+ include commercially available salt substitutes and K+ enriched foods which are reported to have a beneficial effect on blood pressure control and cardiovascular morbidity.

Individuals with normal K+ excretion require an extremely high amount (>160mEq) of orally administered potassium in order to develop dangerous hyperkalemia. Besides common sources of K+, coconut juice and noni contain high amounts of K+. Certain types of pica disorders like geophagia or cautopyrephagia can also lead to increased K+ intake. In case of neonates, serious hyperkalemia can be induced accidentally due to salt substitute ingestion or iatrogenically by intravenous administration of penicillin or blood transfusions. In stored blood, K+ is gradually released by the red blood cells and after 3 weeks, its concentration can reach 30mEq/L in total blood or 90mEq/L in packed RBCs. It is therefore preferable to use fresh or almost fresh blood (<5 days) whenever massive transfusions are required.

3.2 Potassium release from cells

3.2.1 Potassium release due to cells lysis

K+ shift from intracellular to extracellular space is a common cause of acute hyperkalemia. It can be secondary to tissue damage as in tumor lysis syndrome (associated or not with chemotherapy), acute intravascular hemolysis due to infection, transfusion reactions, severe hemolytic anemia, hemolysis within large hematomas, extended burns, rhabdomyolysis, ischemic colonic necrosis or hypothermia. In these cases, serum biochemistry can be helpful in identifying the cause e.g. elevated serum urate and phosphate in tumor lysis syndrome, increased serum creatine phosphokinase (CPK) in rhabdomyolysis or high levels of serum lactate dehydrogenase (LDH) in cases of hemolysis.

3.2.2. Potassium release with intact cell plasma membrane

However, increased K+ shift out of cells can be pro-
motored even if the cell membrane is intact. Use of drugs that inhibit \(\text{Na}^+\text{K}^+\text{-ATPase}\) is an example. Beta adrenergic receptor blockers promote \(\text{K}^+\) shift out of cells which is usually less than 0.5mEq/L. If \(\text{K}^+\) balance is disrupted, severe hyperkalemia may occur. In these cases, selective \(\beta_1\) adrenergic receptor blockers like atenolol should be preferred\(^{42-45}\). Usual dose of digitalis also results in \(\text{Na}^-\text{K}^-\text{ATPase}\) inhibition in a dose dependent way but severe hyperkalemia is developed, in cases of digitalis toxicity\(^{46,47}\). Succinylcholine, a paralytic drug, acts as a depolarizing agent. Cell membrane depolarization makes the inner cell less electronegative, a fact that enhances \(\text{K}^+\) shift out of the cell. In healthy individuals, \(\text{K}^+\) rise is less than 0.5mEq/L but it is much higher in patients with kidney failure, neuromuscular disease, extended burns or tetanus\(^{48,49}\).

Physical exercise may also cause \(\text{K}^+\) shift possibly due to a delay between rapid \(\text{K}^+\) shift out of muscle cells (during repolarization) and \(\text{K}^+\) reuptake by \(\text{Na}^-\text{K}^-\text{ATPase}\) (Figure 1). In rigorous exercise, \(\text{ATP}\) consumption enhances the opening of extra \(\text{ATP}\) dependent \(\text{K}^+\) channels and therefore promotes additional \(\text{K}^+\) shift out of cells\(^{50,51}\). Local tissue \(\text{K}^+\) induces a desirable vasodilatation but \(\text{K}^+\) concentration is also increased in systemic circulation up to 2 mEq/L and returns to normal levels after a few minutes\(^{49}\). Although intense exercise induced hyperkalemia is well tolerated, concomitant underlying conditions which affect \(\text{K}^+\) homeostasis like exhausting exercise induced rhabdomyolysis or use of beta blockers can contribute to the development of life threatening hyperkalemia\(^{51,52}\).

Metabolic acidosis can move \(\text{K}^+\) to the extracellular space so that cell membrane electric voltage is maintained after \(\text{H}^+\) cations enter the cell. For this to occur, acid load should be derived from a non organic acid. Experimentally, intravenous \(\text{HCl}\) administration results in a rise in serum \(\text{K}^+\) but this is not the case when lactic acid is administered. This is because chloride (\(\text{Cl}^-\)), the main extracellular anion, enters cells in a limited degree, a fact that results in less electronegativity in the internal of the cells due to \(\text{H}^+\) entry and therefore promotes \(\text{K}^+\) shift out of cells. \(\text{K}^+\) concentration rises by 0.2 to 1.7 mEq/L for every 0.1 fall in arterial pH. On the contrary, intrinsic monocarboxylic organic acids like lactic acid or \(\beta\)-hydroxy-butyrate follow \(\text{H}^+\) entry into cells thanks to the presence of the monocarboxylic acid transporter in the cell membrane. Stimulation of insulin production by mono- carboxylic acids which is accompanied by \(\text{Na}^+\text{K}^+\text{-ATPase}\) activation and \(\text{K}^+\) entry into cells could be another potential explanation. As exogenous non monocarboxylic acids like citric acid are unable to enter cells and reduce plasma bicarbonates, they cause acidosis. This leads to bicarbonate shift out of cells in exchange with \(\text{Cl}^-\) via the appropriate cotransporter. However, \(\text{Cl}^-\) moves out from cells via \(\text{Cl}^-\) channels, so cells become less electronegative and \(\text{K}^+\) excretion is enhanced\(^{44-47}\). Hyperkalemia observed in cases of acidosis by endogenous organic acids seems to develop from other causes. For example, hyperkalemia in lactic acidosis seems to be secondary to ischemic tissue necrosis and compromised kidney function. In diabetic ketoacidosis, insulin deficiency, hyperglycemia and decreased renal perfusion seem to be involved in the pathogenesis of hyperkalemia. Non organic acid induced hyperkalemia is caused in cases of administration of \(\text{HCl}\) precursor substances like arginine chloride salts used in the treatment of metabolic alkalosis\(^{49}\). In hemodialysis patients, administration of sevelamer hydrochloride for the management of hyperphosphatemia leads to mild acidos is by non-organic acid since for every bound molecule of phosphate, one molecule of \(\text{HCl}\) is released. This last case can be easily managed by raising dialysate bicarbonate concentration to 40 mEq/L\(^{19}\).

Hyperkalemia due to \(\text{K}^+\) shift from cells is encountered in patients with diabetic ketoacidosis or severe hyperglycemia without ketoacidosis. Despite the fact that, in these patients, total body \(\text{K}^+\) is reduced, insulin deficiency is the cause of hyperkalemia\(^{11,60,61}\). Additionally, hyperglycemia induced hyperosmolality promotes \(\text{K}^+\) shift out of cells. This is mostly because water movement out of cells causes a rise in intracellular \(\text{K}^+\) concentration which promotes \(\text{K}^+\) movement to the extracellular space via \(\text{K}^+\) channels. In addition, water shift via water channels also drifts \(\text{K}^+\) out of the cells. In general, for every 10 mosm/kg rise in plasma osmolality, \(\text{K}^+\) concentration increases by 0.3-0.8 mEq/L\(^{12}\). This is the reason why mannitol administration or other hypertonic solutions can cause hyperkalemia\(^{51}\). Life threatening hyperkalemia can also be documented in diabetic hemodialysis patients with poor blood glucose control\(^{46}\).

Finally, the syndrome of hyperkalemic periodic paralysis is an autosomal dominant disorder and is caused by a mutation in the gene encoding a specific alpha-subunit of a special population of sodium channels found in skeletal muscles. Under normal circumstances, during muscle contraction, sodium channels are closed when action potential reaches 50mV (Figure 1). In patients with hyperkalemic periodic paralysis these channels do not close adequately and create a less electronegative internal cell environment which promotes \(\text{K}^+\) exit from cells. A history of episodes of muscle weakness or paralysis with increased \(\text{K}^+\) concentration that last for 1-2 hours raise suspicion of this syndrome. The diagnosis is set by reproducing muscle weakness and hyperkalemia after a meal containing 0.5-1 mEq/kg of \(\text{K}^+\). Symptoms can also be exacerbated in response to a cold stimulus or exercise. Beta adrenergic agonists, like albuterol can be used in the management of acute episodes. Several measures are recommended for the prevention of acute episodes including refrain from physical exercise, meals rich in carbohydrates and poor in \(\text{K}^+\), thiazide diuretics and alatocorticoid administration (which cause mild potassium deficiency). Acetazolamide can be also helpful possibly by increasing renal \(\text{K}^+\) excretion\(^{63,64}\).

4. Impaired renal potassium excretion

Patient’s history helps to diagnose decreased \(\text{K}^+\) excretion but sometimes additional evaluation is required. The transtubular potassium gradient (TTKG) which is estimated by the formula \(\text{TTKG} = \frac{[\text{K}_u \times (U_{\text{osm}} / S_{\text{osm}})]}{[\text{K}_s]}\) expresses the magnitude of \(\text{K}^+\) concentration in the excreted urine (higher) compared with the concentration in the early CCD (lower) due to \(\text{K}^+\) excretion. To eliminate
the effect of water reabsorption across the collecting duct, urine K+ (K+) is divided by the urine to serum osmolality ratio (U\textsubscript{osm}/S\textsubscript{osm}). This approach is based on the assumption that besides water, no significant electrolyte or urea transport takes place in the medullary collecting duct. Furthermore, urine osmolality should be equal or higher than serum and urine Na⁺ should be more than 25mEq/L so that adequate sodium is delivered to the CDD. Normal TTKG values are 8-9 but it can be over 11 in cases of increased K⁺ intake. In patients with chronic hyperkalemia, TTKG values less than 5 are indicative of impaired renal K⁺ excretion\textsuperscript{66,70}. Alternatively, it has been proposed that in an urine spot from a hyperkalemic patient a ratio of urine K+ to urine creatinine less than 200mEq K⁺/gr creatinine indicates a renal defect in K⁺ excretion\textsuperscript{71}.

Potassium excretion by the kidneys is disturbed in three cases. Renal failure, effective plasma volume reduction and impaired aldosterone action. The latter can be either due to decreased production or CCD resistance to its action.

4.1 Hyperkalemia due to renal failure

Differential diagnosis of hyperkalemia requires serum creatinine and glomerular filtration rate (GFR) evaluation. In acute kidney injury, rapid decline of GFR leads to decreased Na⁺ and water delivery to the CCD and therefore reduced K⁺ excretion. This can explain the observation that hyperkalemia is associated with oligoanuric forms of acute kidney injury rather than non oliguric. In chronic kidney disease (CKD), the ability of each nephron to excrete K⁺ is increased under the influence of aldosterone and upregulated Na⁺-K⁺-ATPase activity\textsuperscript{72-75}. As kidney function worsens and urine output is reduced, decreased Na⁺ and water is delivered to the CCD and hyperkalemia ensues\textsuperscript{76}. If, after the administration of a K⁺ load, the renal K⁺ excretion (urine [K⁺] x urine volume) is divided by the GFR, the result will be the same in the absence or presence of CKD, a fact that implies that K⁺ retention is due to nephron loss and not to the impaired excretory ability of the residual nephrons\textsuperscript{77}. For this to occur, GFR must fall below 20ml/min. In cases of hyperkalemia in patients with mild or moderate kidney disease, other additional causes should be sought. Additionally, in patients with CKD, K⁺ entry into cells is reduced since intracellular K⁺ concentration is lower (in the presence of normokalemia or hyperkalemia) and also, cellular K⁺ uptake is decreased after K⁺ administration\textsuperscript{77,78}. Several mechanisms have been proposed to explain the latter observation, including reduced Na⁺-K⁺-ATPase activity in skeletal muscles, insulin resistance and metabolic acidosis\textsuperscript{79-81}.

4.2 Hyperkalemia due to reduced effective plasma volume

As discussed earlier, renal K⁺ excretion depends on Na⁺ and water delivery to the CCD. If it is decreased, K⁺ excretion is impaired even in the presence of normal or high aldosterone levels as observed in cases of reduced effective plasma volume. Measurement of aldosterone levels can be helpful in difficult diagnostic cases of hyperkalemia. Reduction in effective plasma volume can occur in hypovolemia but also in hypervolemia, for a variety of reasons including liver or heart failure, third space plasma losses, renal, skin or gastrointestinal fluid losses. Usually, the lost fluids are rich in K⁺ but the decreased plasma volume impairs renal K⁺ excretion. Additional factors are required for hyperkalemia to develop in such cases including frequent hypotension per se and subsequent sympathetic activation which via afferent vasoconstriction-reduce GFR, as well as renin-angiotensin-aldersterone system activation which results in angiotensin II induced proximal Na⁺ reabsorption\textsuperscript{82,85}.

4.3 Hyperkalemia due to decreased aldosterone action

Another cause of hyperkalemia due to defective K⁺ excretion is impaired aldosterone action which can be either due to decreased synthesis or due to resistance to aldosterone action secondary to CCD dysfunction. Evaluation of plasma renin and aldosterone levels is required for a correct diagnosis. Renin levels are measured by two methods. If plasma renin activity is estimated, plasma is incubated at 37°C so that plasma angiotensinogen is converted by renin to angiotensin I. The latter is measured by radioimmunoassay (RIA) and plasma renin activity is equivalent to the amount of angiotensin I produced after 90 minutes of incubation. Normal values are 1-4 ng/ml/h\textsuperscript{86,88}. Plasma active renin can also be measured and normal values are between 8 and 35mU/L. However, it should not be preferred to plasma renin activity because plasma active renin levels change inversely to the concentration of the substrate. Estrogens for example, decrease plasma active renin since they increase angiotensinogen\textsuperscript{89}. Renin levels are increased during sodium restriction and reduced in salt consumption. It is higher in the morning, increases during pregnancy and the luteinizing phase of the menstruation circle, in CKD and in postural position. Diuretics, angiotensin II type I receptor blockers and dihydropyridine calcium channel blockers increase renin levels. Non steroid anti inflammatory drugs (NSAIDs) via prostaglandin inhibition, beta adrenergic activity inhibitors including beta blockers, clonidine and methyldopa suppress renin levels\textsuperscript{90,92}. Normal plasma aldosterone levels in the morning are 5-30mg/d\textsuperscript{90}. Aldosterone levels are elevated in the morning, during pregnancy (up to 10 times higher in the third trimester), in salt restriction and postural position\textsuperscript{92,94,95}.

Besides hyperkalemia, various degree of Na⁺ loss and metabolic acidosis (type IV renal tubular acidosis) are seen in hypoaldosteronism, since aldosterone promotes salt and water retention and H⁺ secretion, both indirectly via Na⁺ reabsorption induced reduction of the lumen electronegativity and directly by H⁺-ATPase stimulation\textsuperscript{86,97}. Acidosis is partly secondary to hyperkalemia per se, given that correction of hyperkalemia also corrects metabolic acidosis\textsuperscript{86}. It is possible that high tubular K⁺ concentration inhibits ammonium connection to the K⁺ segment of the Na-K-2Cl cotransporter in the thick ascending limb of Henle’s loop and therefore disturbs ammonium recycling and accumulation in the renal medullary interstitium and secretion in the medullary collecting duct\textsuperscript{86}.

4.3.1 Hyperkalemia due to decreased stimuli for aldosterone production

Impaired aldosterone synthesis can be secondary to an in-
adequate stimulus for its production from the adrenal glands. Hyporeninemic hypoaldosteronism is such an example, most commonly encountered in elderly diabetics (50%) with mild to moderate kidney disease. It accounts for the 50-75% of cases of hyperkalemia of initially unknown cause. This syndrome is characterized by low plasma renin (85%), a fact that explains low aldosterone levels. The pathogenesis of this condition remains unclear and besides inadequate renin production, impaired adrenal response seems to be present because 15% of patients have normal plasma renin levels and angiotensin II infusion in these patients does not always result in aldosterone release. For renin underproduction, decreased prostaglandin synthesis, hyperkalemia and subsequent natriuretic peptide production which directly suppresses renin and aldosterone secretion, and the incomplete conversion of prorenin to renin due to a defect in juxtaglomerular cells have been suggested as potential causes. In hyporeninemic hypoaldosteronism, hyperkalemia is usually mild, unless another cause of hyperkalemia, such as concomitant use of angiotensin converting enzyme inhibitors, is also present. Hypoaldosteronism due to impaired adrenal stimulation can also be induced by drugs. Aliskiren, a renin activity inhibitor used as an anti-hypertensive drug, has been associated with hyperkalemia. Angiotensin converting enzyme inhibitors (ACEi) also suppress aldosterone production by blocking the conversion of angiotensin I to angiotensin II. Similarly but in a receptor level, angiotensin II type I receptor blockers (ARBs) can cause hyperkalemia. These anti-hypertensive drugs are generally well tolerated; however, extra caution is required in case of CKD for the likelihood of development of severe hyperkalemia. NSAIDs inhibit the production of prostaglandins which are necessary for renin release. Therefore, these agents can cause hyperkalemia by inhibition of the renin-angiotensin-aldosterone axis. Finally, cyclosporine can also cause a mild, in most cases, hyperkalemia by suppressing renin activity.

4.3.2 Hyperkalemia due to primary defect in aldosterone production

Besides the cases of impaired adrenal stimulation, decreased aldosterone levels and hyperkalemia can also be observed in adrenal diseases. Primary adrenal insufficiency or Addison’s disease is secondary to adrenal damage by infections (meningococcal septicaemia, tuberculosis, HIV), autoimmune diseases or coagulation disorders with intrarenal hemorrhage and is characterized by both cortisol and aldosterone deficiency. On the contrary, in secondary adrenal insufficiency cortisol production is mainly impaired due to decreased ACTH synthesis by the pituitary while aldosterone release, after the physiological stimuli that are hypovolemia, angiotensin II and hyperkalemia, remains intact.

Furthermore, suppressed adrenal production of aldosterone can be secondary to inherited causes. Although hypokalemia is mostly seen in congenital adrenal hyperplasia, in congenital 21-hydroxylase deficiency, hyperkalemia is present. In general, congenital adrenal hyperplasia is characterized by cortisol deficiency which leads to elimination of the negative feedback of ACTH production. Overproduction of ACTH results in adrenal hyperplasia and increased metabolite production prior to enzyme deficiency. In 21-hydroxylase deficiency, these metabolites are converted to androgens. In one to two thirds of cases, hypoaldosteronism is also present. Therapeutic measures include cortisol substitution which decreases, via ACTH suppression, androgens and aldosterone overproduction. Another rare cause of hypoaldosteronism is isolated hypoaldosteronism which is an autosomal recessive disorder. Finally, heparin acts directly in the adrenal glands and suppresses aldosterone production but does not cause significant hyperkalemia if administered alone.

4.3.3 Hyperkalemia due to resistance of distal nephron to aldosterone action

Drugs that counteract with aldosterone actions can cause hyperkalemia especially if CKD is also present but serum aldosterone levels are not suppressed. Potassium sparing diuretics spironolactone and eplerenone antagonize aldosterone to the level of its intracellular receptor. Occupation of aldosterone receptor by these agents results in insufficient K+ excretion via Na+-K+-ATPase, ENaC and ROMK inhibition in the principal cells. Potassium sparing diuretics amiloride and triamterene and the antibiotics trimethoprim and pentamidine have similar effects due to ENaC inhibition. If sodium reabsorption is impaired in the principal cells, the relative electronegativity of the CCD lumen is reduced and K+ excretion is disrupted. Cyclosporine, besides reducing renin activity, also acts directly in the principal cells and decreases K+ excretion by Na+-K+-ATPase and possibly K+ channels inhibition.

Pseudohypoaldosteronism is characterized by kidney resistance to aldosterone action which results in hypovolemia, Na+ loss, hyperkalemia and elevated renin and aldosterone levels. Acquired pseudohypoaldosteronism results from a tubular defect secondary to obstructive nephropathy, chronic pyelonephritis, acute interstitial nephritis and amyloidosis. There are two types (I and II) of inherited pseudohypoaldosteronism. In the autosomal recessive form of type I, all the target organs of aldosterone are involved and the defect is located in the ENaC channels in the principal cells. In type I autosomal dominant form, symptoms improve with age and the disorder is located in the mineralocorticoid receptor. Therapeutic management includes an initially sodium rich diet and, in refractory cases, high doses of fludrocortisone (1-2mg/d). Type II pseudohypoaldosteronism (also called Gordon’s syndrome) is characterized by hyperkalemia, metabolic acidosis, hypertension and low or normal plasma renin activity and aldosterone concentration. Salt (NaCl) consumption worsens symptoms; however, Na+ without Cl- administration is beneficial. Hypertension and hyperkalemia respond well to thiazide diuretics. Gordon’s syndrome is attributed to a defect in WNK1 and WNK4 kinases. Under normal circumstances, WNK4 reduces the expression of the thiazide sensitive Na/Cl cotransporter. It also enhances ROMK channels degradation in the principal cells. Mutated WNK4 loses the former ability of normal WNK4 but not the latter and the result is increased distal NaCl reabsorp-
tion and impaired K⁺ excretion in the CCD. Additionally, mutated WNK4 promotes paracellular Cl⁻ absorption which results in decreased luminal electronegativity and disturbs K⁺ and H⁺ excretion. Mutations that increase the activity of WNK1 kinase which normally inhibits WNK4, also lead to Gordon’s syndrome.

Finally, the hyperkalemic form of Type I renal tubular acidosis (hyperkalemic type I RTA) is a rare disorder characterized by a defect in H⁺ excretion which leads to metabolic acidosis and an inappropriately high urine pH more than 5.3. Hypokalaemia is common in this disorder due to the fact that defective H⁺ excretion requires that Na⁺ reabsorption takes place in exchange with K⁺. However, hyperkalaemia may occur in the setting of decreased distal Na⁺ reabsorption which reduces the electronegativity of the tubular lumen and impairs K⁺ and H⁺ excretion. This mostly happens in patients with obstructive nephropathy or sickle cell nephropathy, although these disorders can also be complicated by hyporeninemic hypoaldosteronism.

A simplified, based on the etiology, the pathophysiology and the laboratory findings of hyperkalaemia diagnostic approach is depicted in Figure 3. Certainly, albeit helpful, such algorithms cannot substitute a carefully obtained, detailed patient’s history since in real life hyperkalaemia is usually multifactorial.

References


