CASE REPORT

Persistent Hypokalemia: Case Report and Literature Review

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Abstract

Introduction. *Hypokalemia is a common clinical disorder. The most common causes of hypokalemia are decreased intake, intracellular shift and increased loss of potassium. In clinical practice, most frequently patients present with hypokalemia due to increased loss of potassium, especially renal loss.*

Case presentation*. A 62-year-old woman, known with hypothyroidism under treatment with Euthyrox, diagnosed with COVID-19 four months before, presented for nausea and vomiting, headache, generalised muscular hypotony and palpitations, with the onset three weeks before. On physical examination, the blood pressure was 140/90 mmHg, regular pulse frequency of 96/min, the patient had pale skin and mucosa and abolition of osteotendinous reflexes at the inferior members. The laboratory tests revealed severe hypokalemia and moderate normocytic normochromic anemia, mixed alkalosis. The patient had no history of treatment with diuretics or penicilines, or any other condition that could have explained the severe hypokalemia. The patient was admitted in the Internal Medicine Clinic and treatment with high doses of intravenous potassium chloride, potassium - sparing diuretic (Spironolactone) and supplements of potassium and magnesium was initiated, with partial correction of the serum potasssium level. The patient was extensively investigated, to establish the etiology of kypokalemia. Finally, the only identified cause was a nephropathy with losses of potassium.*

Conclusions. *Hypokalemia can be determined by multiple factors, such as digestive or renal losses, during a long term hospitalization. Proper treatment of substitution may lead to normal values of serum potassium and a better life quality.*

Keywords: *persistent severe hypokalemia, mixed alkalosis, COVID-19.*

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Introduction

Potassium is the main intracellular cation, only 2% of the total potassium in the body is extracellular [1]. The serum potassium levels are maintained by the uptake of K^+ into cells (governed by the activity of Na^+/K^+-ATPase), renal excretion (increased by aldosterone) and extrarenal losses (e.g. gastrointestinal, skin) [2]. Hypokalemia is defined as a serum potassium level of less than 3.5 mEq/L and

represents a common electrolyte disturbance mainly in hospitalized patients, having various causes [3]. It results from the intracellular shift or increased potassium excretion (renal or non-renal) and rarely from reduced potassium intake [3]. The most common causes of chronic hypokalemia are hyperaldosteronism and diuretic treatment (especially thiazides) [2]. However, in hospitalized patients, acute hypokalemia is mainly caused by the use of intravenous fluids without potassium, diuretic treatment (loop/ thiazide) and redistribution into cells (especially in diabetic ketoacidosis) [2].

Hypokalemia is usually asymptomatic but severe hypokalemia (<2.5 mEq/L) causes muscle weakness, which can lead to paralysis and respiratory failure [1]. Hypokalemia is associated with an increased frequency of atrial and ventricular ectopic beats [4].

The underlying cause oh hypokalemia must be established, for a correct management. In most cases, withdrawal of the hypokalemic medication (oral diuretics or purgatives) accompanied by the oral administration of potassium supplements are enough for the correction of the serum potassium.

Case presentation

A 62-year-old woman, known with hypothyroidism under treatment with Euthyrox, diagnosed with COVID-19 four months before, presented in February 2022 for nausea and vomiting, headache, generalised muscular hypotony, and palpitations, with the onset three weeks before.

The patient had a severe form of COVID-19 in October 2021, for which she was intubated and ventilated, complicated by massive pulmonary embolism treated by thrombolysis in November 2021. Also, the patient had a resuscitated cardiac-pulmonary arrest in November 2021, several infections treated with numerous classes of antibiotics for long periods of time (Clostridium difficile infection treated with glycopeptides –Vancomycin and imidazole derivatives - Metronidazole, urinary infection with Proteus mirabilis and Klebsiella pneumoniae in tracheal secretion, treated with third generation cephalosporins combined with beta-lactamase inhibitor - Ceftazidime/Avibactam, another urinary infection with Providentia Stuartii treated with aminoglycosides – Gentamicin and tetracyclines - Tigecycline), reinfection with SARS-CoV-2 in February 2022. She also had laparoscopic cholecystectomy for an acute cholecystitis in February 2022.

On physical examination, the blood pressure was 140/90 mmHg, regular pulse frequency of 96/min, pale skin and mucosa, abolition of osteotendinous reflexes at the inferior members. The laboratory tests revaled severe hypokalemia (K 2.03 mmol/L) and moderate normochromic normocytic anemia. At the time of admission, the patient presented mixed alkalosis, both metabolic and respiratory (pH 7.6, pCO_2 29 mmHg, HCO_3 28.5 mmol/L). Throughout the hospitalization, the alkalosis persisted as a partially compensated primary respiratory alkalosis (pH 7.46, pCO_2 25.1 mmHg, HCO_3 17.8 mmol/L). The chest computed tomography (CT) revealed interstitial septal thickening in all the pulmonary lobes, interstitial fibrosis, and also difuse peripheral cylindrical bronchiectasis, especially in the middle lobe and lingular segments.

In our hospital, the patient was admitted dirrectly in the Intensive Care Unit, for 3 weeks and received antibiotic treatment with tetracyclines (Tigeciclina), carbapenems (Meropenem), aminoglycosides (Amikacin), monobactams (Aztreonam), polymyxins (Colistin), antifungal treatment with Fluconazole, because of positive results for Pseudomonas aeruginosa, Klebsiella pneumoniae and Candida albicans from tracheal secretion, and also for Staphylococcus haemolyticus from plague culture (presacral bedsore).

The first step of investigation has aimed to establish the differential diagnosis (DD)

of hypokalemia and metabolic alkalosis. The DD of hypokalemia includes three main categories. First, decreased potassium intake is not relevant because no clinical signs of malnutrition and no other laboratory nutritional deficiencies were observed, and hypokalemia was persistent despite continuous potassium replacement. Hypokalemia also persisted despite the treatment of nausea and vomiting.

Secondly, potassium redistribution into cells can also cause hypokalemia, mainly due to hormones, drugs, and anabolic states (e.g. insulin, β-agonists, granulocyte-colonystimulating factor [G-CSF] analogues, vitamin B12 supplements); however, all of these causes were excluded by history and laboratory tests. Two other specific diseases, familial hypokalemic periodic paralysis and thyrotoxic periodic paralysis, are also not relevant because in the former hypokalemia should be corrected by supplements and in the latter, thyroid function tests should reveal hyperthyroidism.

The third category, which is relevant to this case, includes potassium renal loss. Because of her persistent hypokalemia, supplementary investigations were performed, meaning collecting total urine for 24 hours with determination of potassium (K 37.9 mmol/L), sodium (Na 148 mmol/L), creatinine (Cr 4.8 mg/dL) and proteins (0.27 g/L). Following the diagnostic algorithm, the results were suggestive for a renal cause of potassium deficiency. Because renal causes for potassium loss are numerous, the first step was to exclude the possibility of drug renal impairment, that causes increased distal delivery of non reabsorbed anions and this was possible because none of the medications the patient has received has such an effect (an example of such drugs being the penicillins, which the patient did not receive). Also, we excluded at an early stage the use of diuretics as a possible cause of renal excess excretion of potassium – diuretics increase the distal renal flow and distal delivery of sodium and they determine an increase in the renal loss of potassium. Because the value of the proteins lost through urine in 24h is only 0.27 g/L, the nephrotic syndrome was excluded.

The next step was an endocrinological evaluation, so the blood levels of the adrenocorticotropic hormone and aldosterone were measured, also the plasma renin concentration. All three values were normal, so hyperaldosteronism, Bartter or Gitleman syndrome were excluded. Besides, these syndromes usually have the onset in adolescence or early adulthood. The plasma cortisol level was also determined, with normal result, so a Cushing syndrome was excluded. There was no imaging suspicion for an adrenocortical adenoma or other secretant tumours.

During hospitalisation, the normal values of potassium were maintained only with high doses of intravenous potassium chloride, potassium-sparing diuretic (Spironolactone) and supplements of potassium and magnesium. Initially, the patient received a 100mg/24h dose of Spironolactone, further increased to 225 mg/24h. After approximately 2 months of intensive treatment, the serum potassium values stabillised around 4 mmol/L.

Discussion

Causes of hypokalemia

The main three mechanisms that can lead to hypokalemia are: decreased intake, intracellular shift and increased loss of potassium. Decreased intake can result either from dietary deficiency or by administration of intravenous fluids without potassium.

Intracellular shift is defined by the uptake of the potassium in the cell (mainly stimulated by insulin and beta-adrenergic stimulation) and can result from an anabolic status, hormonal changes, acid-base disorders or other conditions that stimulate the uptake of the potassium in the cell. The anabolic status appears in the following conditions: total parenteral nutrition or

enteral hyperalimentation that cause hypokalemia due to glycogenesis which is stimulating insulin release, correction of megaloblastic anaemia (e.g. B12 vitamin or folic acid deficiency) which results in red blood cell production and treatment with granulocyte-macrophage colony-stimulating factor which results in white blood cell production. Insulin administration, the stimulation of the sympathetic nervous system (through beta-adrenergic stimulation, beta-2 agonist administration such as salbutamol, acute myocardial infarction or thyrotoxicosis-hypokalemic thyrotoxic periodic paralysis) and the downstream stimulation of Na^+/K^+-ATPase by theophylline or caffeine are some of the causes of hypokalemia through hormonal mechanisms. Regarding the acid-base status, that promotes the uptake of the potassium in the cell, there is alkalosis (metabolic more often than respiratory) that stimulates the exchange of the potassium and H^+ between the intracellular and extracellular space to restore the pH balance [1]. Other causes that stimulate the uptake of the potassium in the cell are pseudohypokalemia (in patients with chronic myeloid leukemia with more than 10^5/uL leucocytes, if the blood sample remains at room temperature before being processed - the false hypokalemia appears due to absorption of the potassium into the abnormal leucocytes), hypothermia, familial hypokalemic periodic paralysis (rare autosomal dominant channelopathy characterized by muscle weakness or paralysis when there is a fall in potassium levels in the blood - usually occurs in childhood or adolescence) and barium toxicity (systemic inhibition of “leak” K+ channels) [1,7].

Increased loss of potassium can occur in both renal and non-renal conditions. The non-renal causes consist in gastrointestinal loss (in which the urinary K^+ is less than 20 mmol/day) and integumentary loss (sweat). Gastrointestinal losses of potassium usually are due to prolonged diarrhea (potassium is secreted by the colon and diarrheal fluid contains 10-30 mmol/L of potassium; profuse diarrhea can therefore induce marked hypokalemia) or vomiting (vomiting contains only around 5-10 mmol/L of potassium but prolonged vomiting causes hypokalemia by inducing sodium depletion, stimulating aldosterone, which increases renal potassium excretion), chronic laxative abuse, ileus, intestinal obstruction or infections [2]. Other causes involving gastrointestinal losses are villous adenoma of the colon (can rarely cause massive potassium secretion), ileostomy or ureterosigmoidostomy, fistulae and clay ingestion (binds potassium and greatly decreases absorption).

Excessive excretion of potassium in the urine (kaliuresis) may result from increased distal flow and distal Na^+ delivery (in which the urinary K^+ is greater than 20 mmol/day) or from increased secretion of potassium. Diuretics (thiazides more often than loops diuretics), osmotic diuresis and salt-wasting nephropathies increase the distal flow and the distal Na^+ delivery and therefore can result in hypokalemia. The main hormone involved in the urinary secretion of the potassium is a mineralocorticoid hormone (aldosterone), therefore a mineralocorticoid excess may lead to hypokalemia in the following conditions:

- primary hyperaldosteronism;
- primary or unilateral adrenal hyperplasia;
- idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia and adrenal carcinoma;
- familial hyperaldosteronism;
- secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia);
- Cushing's syndrome;
- Bartter's syndrome (characterized by metabolic alkalosis, hypokalemia, hypercalciuria, occasionally hypomagnesemia, normal blood pressure and an elevated plasma renin and aldosterone);

- Gitelman's syndrome (characterized by metabolic alkalosis, hypokalemia, hypocalciuria, hypomagnesemia, normal blood pressure and elevated plasma renin and aldosterone);
- nephrotic syndrome;
- heart failure;
- liver failure;
- Conn's syndrome;
- ACTH- producing tumors;
- administration of exogenous mineralocorticoid: corticosteroids, liqorice (potentiates renal actions of cortisol).

An apparent mineralocorticoid excess can appear in:

- a genetic deficiency of 11 B-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess);
- an inhibition of 11 ß-dehydrogenase-2 (glycyrrhetinic/ glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs);
- Liddle's syndrome (characterized by alkalosis, hypokalemia, high blood pressure and low renin and aldosterone production).

A high secretion of urinary potassium can also result from a distal delivery of non-reabsorbed anions, a phenomenon that can appear in:

- vomiting;
- nasogastric suction;
- renal tubular acidosis types 1 and 2;
- Fanconi syndrome;
- diabetic ketoacidosis;
- glue sniffing (toluene abuse);
- administration of penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin).

Finally, hypomagnesemia is very important. More than 50% of clinically significant hypokalemia cases associate concomitant magnesium deficiency and is clinically most frequently observed in individuals receiving loop or thiazide diuretic therapy [3]. Hypomagnesemia can itself lead to increased urinary potassium losses via an uncertain mechanism.

Clinical features of hypokalemia

Hypokalemia is usually asymptomatic but severe hypokalemia (<2.5 mEq/L) causes muscle weakness, which can lead to paralysis and respiratory failure [1]. Hypokalemia is associated with an increased frequency of atrial and ventricular ectopic beats [4]. Hypokalemia increases the risk of digoxin toxicity by increasing binding of digoxin to cardiac cells, potentiating its action and decreasing its clearance [2]. Other signs and symptoms include metabolic acidosis, rhabdomyolysis, leg cramps, fasciculations, tetany, ascending paralysis, ileus, polyuria with polydipsia (hypokalemia can reduce the renal capacity of concentration), renal failure, ECG changes (U wave, T wave flattening, ST-segment changes), heart failure [1,2,5,6].

Diagnostic algorithm in hypokalemia

The diagnosis of hypokalemia is made by measuring a low potassium level in the blood (<3.5 mEq/L). The underlying cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. If there is no obvious cause in the history (especially medication) further investigations are required (Fig. 1.) [4].

Management

Hypokalemia is treated by identifying and treating the underlying cause. In most cases withdrawal of the hypokalemic medication (oral diuretics or purgatives) accompanied by the oral administration of potassium supplements are enough for the correction of the serum potassium. Hypokalemia is resistant at any correction if there is hypomagnesemia, which should be measured and corrected. Intravenous potassium replacement is needed only in conditions such as cardiac arrhythmias, muscle weakness or severe diabetic ketoacidosis. For the intravenous

replacement, the potassium should be mixed in 0.9% saline, not in glucose solution, as this would make hypokalemia worse due to the increase of the insulin [2,4,6].

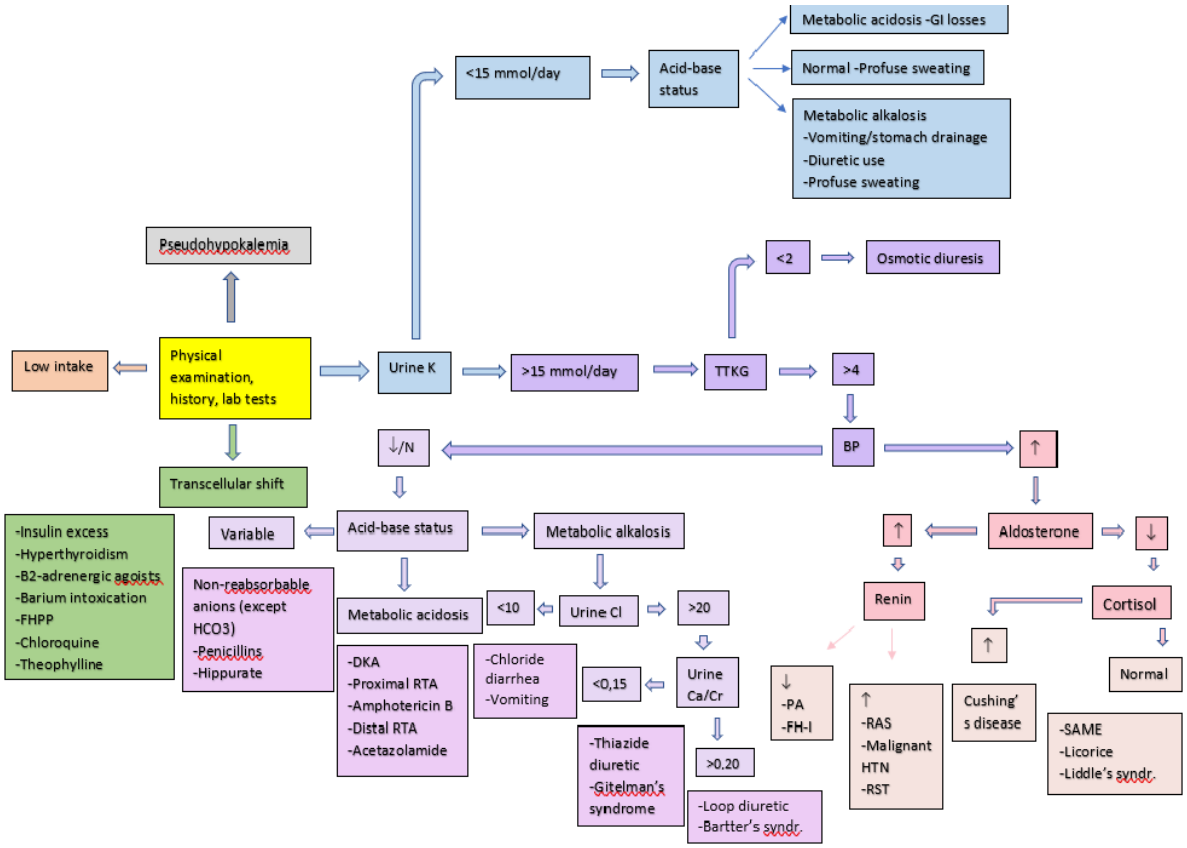

Fig. 1. BP- blood pressure, FH-I- familial hyperaldosteronism type I, DKA- diabetic ketoacidosis, FHPP- familial hypokalemic periodic paralysis, PA- primary aldosteronism, HTN- hypertension, RST- renin-secreting tumor, RAS- renal artery stenosis, SAME-syndrome of apparent mineralocorticoid excess, RTA- renal tubular acidosis, TTKG- transtubular potassium gradient.

Conclusions

Severe hypokalemia is a clinical condition with potentially life-threatening manifestations. We presented a 62-year-old woman, known with autoimmune thyroiditis with substitutive hormonal therapy, with recent history of SARS-CoV-2 severe infection with extensive residual fibrosis and bronchiectasis, with massive pulmonary embolism treated by thrombolysis, resuscitated cardiac-pulmonary arrest, prolonged septic status with multiple nosocomial infections and large spectrum antibiotherapy, post-cholecystectomy status, who developped during hospitalisation persistent hypokalemia, with a dominant renal component. Most probably, in this case more mechanisms were involved. Initially, the patient presented mixed alkalosis, the metabolic component probably in the context of vomitting and chloride loss, while the respiratory component in the context of the post-COVID-19 extensive fibrosis and bronchiectasis. Throughout the hospitalization, the alkalosis persisted as a partially compensated primary respiratory alkalosis and contributed to mantaining the hypokalemia. Also, the patient presented arterial hypotension, most probably because of sepsis (multiple persistent infections), which activates the sympathetic nervous system (intracellular shift of

potassium) and renin-angiotensin-aldosterone system (renal loss of potassium).

The patient needed high doses of intravenous potassium chloride, potassium-sparing diuretic (Spironolactone) and supplements of potassium, with a partial and late correction of serum potassium. This patient needs long-term monitorization and reassessment of other possible causes of hypokalemia, in case of persistance.

Author Contributions:

E.G. and C.D. conceived the original draft preparation. I.C., C.C., and A.P. were responsible for conception and design of the review. I.C., C.V and A.P. were responsible for the data acquisition. I.C, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. E.G., C.D., I.C, C.C., and A.P. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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