

Bartter's syndrome with pulmonary tuberculosis: a shortly outlook

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ABSTRACT

Bartter's syndrome is a rare condition, described for the first time by Bartter and coauthors in 1962. It currently represents a group of interrelated inherited renal tubular disorders, characterized by hypokalemia, hypochloremia, metabolic alkalosis and hyperreninemia with normal blood pressure and no associated edema. We present the case of a 51-year-old woman with Bartter's syndrome who presented to our clinic complaining of polyuria, polydipsia, dehydration, night sweats, cough episodes, chills, fever, and weight loss, that had been present for about three weeks. Surprisingly, the laboratory tests revealed the presence of Mycobacterium Tuberculosis by positive microbiological smears and positive cultures. It is a therapeutic challenge to treat a patient with Bartter's syndrome complicated with end-stage renal failure, being on nephrotoxic antibiotics for tuberculosis. The case is distinct first of all because of the late diagnostic time at the age of 39, and the long course of the disease namely 12 years with proper therapy throughout all of this period. On the other hand, the long follow up of our case was characterized by multiple admissions the last one being very important as the patient had been diagnosed with pulmonary tuberculosis. The presentation of this case is a good opportunity to highlight the immunodepression caused/associated with renal tubulopathies, respectively Bartter's syndrome. We consider that additional studies are welcome and further more, essential in understanding the complex mechanisms that characterize this rare disorder.

Keywords: Bartter's syndrome, tuberculosis, immunosuppression, inherited renal tubular disorders, hypokalemia, metabolic alkalosis

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BACKGROUND

Acquired or inherited renal tubular disorders can be observed in a broad spectrum of disease processes. Bartter syndrome is a hereditary distal tubular disorder characterized by secondary hyperaldosteronism, hypokalemia, alkalosis and low-normal blood pressure (1). Looking back to 1962, Frederic Crosby Bartter's made the first description of Bartter's syndrome, by reporting the cases of two young black American males aged 5 and 25 years diagnosed with hypokalemia, metabolic alkalosis, hyperaldosteronism, juxtaglomerular hyperplasia on renal biopsy, and normal to low blood pressure, and decreased pressor responsiveness to angiotensin II infusion (2).

To our knowledge, we present a rare case of long follow up Bartter's syndrome complicated with chronic renal failure and pulmonary tuberculosis. The discussion of this case is a helpful chance to highlight the immunodepression caused/associated with renal tubulopathies, respectively by Bartter's syndrome. □

CASE REPORT

A 51-year-old woman presented to the emergency department with polyuria, polydipsia, wasting syndrome and cramps. Her past medical history revealed during a four years period, multiple admissions in different medical departments for connective tissue disease unresponsive to specific treatment. It is important to note that during these numerous admissions, the endocrinological consult ruled out autoimmune thyroiditis involvement and recommended specialised renal function investigations. On her first admission in our department in 1999, her physical examination revealed intense signs of dehydration (poor skin turgor, dry mucous membranes), with 36.8°C, cold extremities, positive Chvostek's sign, blood pressure of 70/55mmHg, tachycardia of 100 bpm, respiratory rate of 28/min, polyuria, and bradiphasia (abnormally slow manner of speech, often associated with mental illness). Laboratory evaluation showed leukocytosis (12.100/mm³), hyponatremia (123 mEq/L), severe hypokalemia (1.34 mEq/L), BUN (67 mg/dL), metabolic alkalosis pH=7.40, HCO₃⁻ = 30 mmol/L, hyperchlorinurie (urinary chlorine=57 Eq/L). A

24-hour urine collection (3500 ml) revealed a potassium level of 40 mEq/L, urinalysis shown 43 leukocytes and 23 red blood cells by Webb method. ECG showed normal sinus rhythm with a HR of 100/min, depressed left ST-segments of V1-V6, and prominent U waves with small upright T waves. The infusion of isotonic saline (1000 mL/24hrs), Ringer's lactated (1000 mL/24 hrs), 7.4% KCl (100 mL/24h), and antibiotic treatment (ceftioxone 2g/24h) established a good course for our patient with marked improvement in her general condition: BP=100/70 mmHg, HR of 78 bpm, suprapubic tenderness, positive Chvostek's sign, urinary volume of 700 ml/24hrs in conditions of the intake of 3000 ml (1000 ml per oral) but with normal serum natremia and kalemia.

Muscle weakness, polyuria, polydipsia, low blood pressure, urinary potassium loss of 40 mEq/L metabolic alkalosis, hypokalemia, hyponatremia, high urinary chloride level and the excellent response of clinical manifestations to the prescribed treatment, allowed us to consider the diagnosis of Bartter's syndrome in this case.

Despite regular therapy with oral KCL 15g/day, indomethacin 75mg/day during the next five years the patient had multiple hospitalizations with complaints of fatigue, wasting syndrome, myalgias, dehydration, hypotension, polyuria, and polydipsia. Dehydration and persistent hypotension were the clinical contraindications for ambulatory therapy with ACE-inhibitors and potassium-sparing diuretics. It is important to mention that during these admissions she often required intravenous supplementation with 7.4% KCl 100 mmol/L based on the potassium serum levels. She also presented frequent episodes of upper respiratory tract infections, and also many urinary tract infections; in 2000 she underwent emergency cholecystectomy for acute cholecystitis. It seems reasonable to assume that the associations of recurrent renal infections with Bartter's syndrome contributed to the progressive alteration in her renal function. Moreover, during one of the hospitalizations the serum urea level was of 77.6 mg/dL and serum creatinine was of 1.9 mg/dL, to a corresponding diuresis about of 1500 ml/day.

In the course of the last admission in our department (2007), she was admitted again for fever, chills, cough, wasting syndrome, polyuria,

and polydipsia. Physical examination revealed signs of dehydration (poor skin turgor, dry mucous membranes), cold extremities, muscle cramps with hypotonia; she presented normal respiratory examination, BP = 90/60 mmHg, HR=84 bpm, bradiphasia. Laboratory evaluation revealed an important inflammatory syndrome (ESR = 64 mm/1h; 84 mm/2h), leukocytosis (13.300/mm³), platelet count was 586.000/mm³, severe hypokalemia (1.84 mmol/L), a dilution hyponatremia (125.3 mmol/L), raised BUN and creatinine levels (urea=108.27 mg/

dL), and hypercholesterolemia. The ECG showed regular rhythm, HR=55 bpm, QRS axis of +25°, with minor right bundle block changes, and prominent U wave in all leads (secondary to hypokalemia). Surprisingly, CXR showed the existence of a round, well defined homogenous opacity of 4.5/5 cm, located in her upper left pulmonary lobe. (Figure 1, Figure 2) The diagnosis of pulmonary tuberculosis was also confirmed by positive smears and cultures. (Figure 3, Figure 4)

The patient was transferred in a specialized medical setting where she underwent specific treatment that lead to the favorable outcome of our patient with relieving of the presenting complaints (fever, weight loss, cough, severe chills and night sweats). The association of



FIGURE 1. CXR-homogenous opacity by 4,5/5 cm, with net circular shape to upper left pulmonary lobe

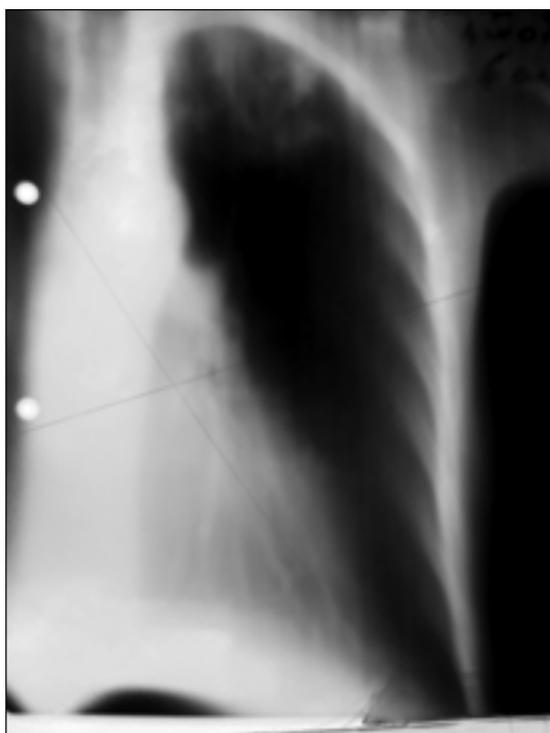


FIGURE 2. Plane tomography of left pulmonary lobe – the opacity 4.5/5 cm of upper left lobe

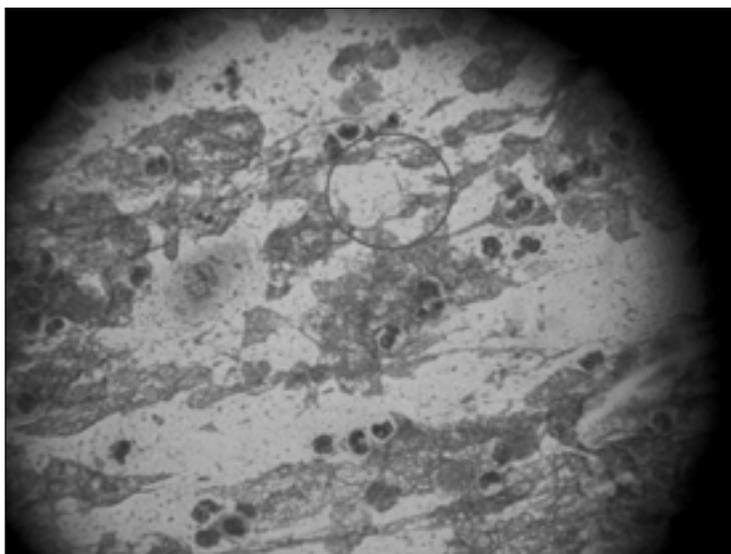


FIGURE 3. Mycobacterium Tuberculosis

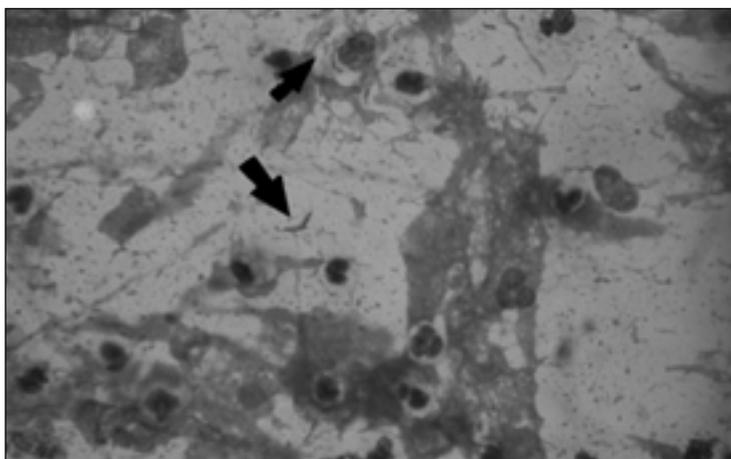


FIGURE 4. Mycobacterium Tuberculosis

tuberculostatics consisted of (Isoniazid 200 mg/day, Ciprofloxacin 1000 mg/day, Ethambutol 800 mg/day, Pyrazinamide 1500 mg/day) 7/7 days.

The hallmark features of this case are: late diagnosis of Bartter's syndrome in a 39-year-old patient, long course of disease associated with repeated admissions due to upper respiratory tract infections and urinary tract infections, and finally an unusual association with pulmonary tuberculosis. Immunodepression is a valid feature of long follow up tubulopathies, in this case Bartter's syndrome, with a high prognostic impact value. □

DISCUSSIONS

Most cases of Bartter's syndrome are discovered during early childhood with polyuria and weakness; however our case of a 51-year-old woman was diagnosed at the age of 39. This disorder has an autosomal recessive trait and the annual incidence is about 1 case per million people (3). Even so, over the last few decades the pathogenesis and causes of this syndrome still remain ambiguous. Conversely, it seems that the major defect of this disorder is the deficiency of sodium chloride reabsorption in the ascending loop of Henle. The thick ascending limb (TAL) is a major part of the nephron's urine concentration apparatus due to its water-resistant qualities and exclusive sodium chloride reabsorption capacities. Therefore, defects of TAL cause important polyuria with all its consequences, in particularly important in pregnant women (polyhydramnios) and in infancy. The decreased level of sodium chloride reabsorption in this portion of the loop causes reduced medullar hypertonicity with a concentration deficit. Because chloride reabsorption does not occur, more sodium chloride accumulates in the distal tubule. In this portion of the nephrons, the excess sodium can be reabsorbed and exchanged with potassium, resulting in increased K⁺ loss. Therefore, the resulting hypokalemia induces a vicious phase characterized by the prostaglandin synthesis and activation of the renin-angiotensin-aldosterone system (4). A confounding finding for clinician is also Gitelman's syndrome that tends to have milder symptoms and can be present in early adulthood. To further differentiate these two conditions it is known that Bartter's syndrome is associated with hypercalciuria, whereas

Gitelman's syndrome is associated with hypocalciuria and hypomagnesaemia.

It is important to outline that transepithelial transport of sodium chloride in the TAL requires the presence and function of at least 5 gene products. Therefore, the primary defect is the absence of sodium chloride (NaCl) reabsorption in the ascending loop of Henle (see **Table 1**). Overall, Bartter's syndrome is an absorption tubular defect in which the kidney cannot reabsorb chloride in the thick ascending limb of Henle and in the distal convoluted tubule, depending on the mutation. Our case of Bartter's syndrome reproduces genetically determined functional defects of kidney transporters and ion channels, leading to a confusing clinical picture characterized by hypokalemia, sodium depletion, activation of the renin-angiotensin-aldosterone system with increased plasma levels of Angiotensin II, yet normal or low blood pressure, reduced peripheral resistance, and hyporesponsiveness to pressor agents (5).

- sodium is reabsorbed via NKCC2- electroneutral bumetanide-sensitive Na-2Cl-K cotransporter encoded by SLC12A1 (defect in Bartter type I);
- potassium is recycled through the potassium channel ROMK1 (defect in Bartter type II);
- chloride exits through the chloride channels CLCNKB (defect in Bartter type III) and CLCNKA;
- both chloride channels require a subunit named Barttin (BSNN – defect in Bartter type IV).

A recently reported new form of Bartter syndrome (type 5 Bartter syndrome) is due to activating mutations of the calcium-sensing receptor (CaSR) (17, 18).

Table 1. Mutations in SLC12A1, ROMK1, CLCNKB, and Barttin (BSNN) which cause autosomal recessive Bartter's syndromes types I, II, III, and IV (15,16)

The syndrome is usually diagnosed based on several clinical and laboratory criteria: chloride resistant hypokalemia, hypochloremic metabolic alkalosis, normotensive hyperreninemic hyperaldosteronism, juxtaglomerular apparatus hyperplasia and an autosomal recessive inheritance. On the other hand, current data suggest that we can perform an antenatal diagnosis by ultrasound; in this respect if the fetus develops polyhydramnios or intrauterine growth retardation we should consider the diagnosis of Bartter's syndrome. Particularly,

polyhydramnios is detected at 26 weeks of gestation with coexisting high amniotic fluid chloride level (6). Prostaglandin E2, prostacyclin, kallikrein, and bradykinin production are frequently elevated. Unfortunately, the urinary prostaglandins levels were not measured in our case, but the measurements of urinary prostaglandins can help in diagnosis and treatment. Same to our case, growth and developmental retardation may be associated with Bartter's syndrome. Renal biopsy is rarely required for diagnosis, and it confirms hyperplasia of the juxtaglomerular apparatus with variable levels of interstitial fibrosis.

Hypokalemia and hiperkaliuria can be found in conditions associated with elevated renin production (>3,1 ng/ml/hr) caused by elevated aldosterone levels by the increased renal secretion of potassium. Malignant hypertension, renovascular hypertension, and renin-secreting tumors are the most common disorders associated with elevated renin levels. Increased aldosterone production of any etiology can cause hypokalemia by enhancing distal tubular secretion of potassium. The hypokalemia can develop, however, only if distal fluid delivery is adequate. Disorders associated with increased aldosterone production such as congestive heart failure, cirrhosis, and nephritic syndrome may also cause decreased renal perfusion, and the hypokalemia may not occur until diuretic therapy increases distal tubular fluid delivery. Pseudohyperaldosteronism, or Liddle's syndrome, has all the clinical manifestations of aldosterone excess including hypertension, metabolic alkalosis, and hypokalemia as a result of renal potassium wasting. The etiology, however, is tubular with hyperabsorption of sodium and volume expansion with resulting hypersecretion of potassium and proton. Hypokalemia is commonly associated with renal tubular acidosis (RTA). In proximal RTA; potassium loss is due to increased delivery of Na and HCO₃, to the distal tubule. In distal RTA, increased potassium secretion is due at least in part to decreased H⁺ secretion and the need to maintain cationic balance. Hyperaldosteronism is also seen in this disorder and may contribute to the hypokalemia. Protracted vomiting is a common cause of hypokalemia. The potassium loss, however, is not from the loss of gastric fluid itself. Because gastric fluid contains only 5 to 10 mEq/L of potassium, massive losses would be necessary to deplete the body's potassium stores. Vomiting

can cause volume contraction that stimulates aldosterone production and the development of hypochloremic metabolic alkalosis. Both of these factors increase the renal excretion of potassium. Hypokalemia is seen commonly in association with magnesium depletion. The mechanism is not known but like the hypocalcemia seen with Mg depletion, the hypokalemia cannot be corrected until the Mg is repleted. Diuretics, whose site of action is proximal to the sites of potassium secretion in the distal tubule, may cause profound potassium wasting. Several factors contribute to the mechanisms of potassium loss. These factors include increased delivery of fluid to the distal tubule, volume contraction with stimulation of aldosterone secretion, and the metabolic alkalosis seen with volume contraction (4,7). Hypokalemia can be seen in certain forms of both acute and chronic leukemia and is most commonly associated with lysozymuria. The most common drugs associated with hypokalemia are the semisynthetic penicillins such as carbenicillin, piperacillin, and ticarcillin. The hypokalemia is caused by the delivery of large quantities of Na and nonreabsorbable anions to the distal tubule. The aminoglycosides, most notable Gentamicin, can also cause renal potassium wasting. Intracellular potassium depletion in the renal tubule is thought to play a part in the mechanism of nephrotoxicity of these drugs. Osmotic diuresis, most commonly associated with glycosuria, may cause profound potassium wasting and hypokalemia.

The hypokalemia is secondary to increased delivery of fluid across the distal tubular potassium secretory sites, thereby increasing potassium loss. Diabetic ketoacidosis may be associated with a potassium deficit of as much as 200 to 300 mEq. The acidosis and insulin deficiency may mask this deficit, but severe life-threatening hypokalemia may develop if treatment is begun when potassium has not been adequately repleted. Alkalosis may cause mild hypokalemia by shifting potassium from the extracellular to the intra-cellular space. The effect is not nearly as profound as that seen with the hyperkalemia associated with acidosis. Respiratory alkalosis by itself causes little change in the serum potassium calcium (11).

Hypokalemic periodic paralysis is an uncommon and usually familial disorder. Sporadic cases have also been described, and there appears to be an occasional association with

thyrotoxicosis. Episodes of paralysis due to a rapid serum distribution of potassium into the cells can be precipitated by various factors known to have a direct or indirect effect on potassium balance. These include carbohydrate-rich food, insulin glucose, beta-adrenergic agonists, adrenocorticotrophic hormone (ACTH), and some mineralocorticoids. During an attack, plasma potassium may fall to 1 to 2 mEq/L. Diazoxide, propranolol, spironolactone and acetazolamide have been shown to abort attacks. Although the kidney is efficient at sparing potassium, prolonged decreased intake of potassium will lead to total body potassium depletion and hypokalemia. Protein- and calorie depletion diets will also be lacking in potassium. True starvation and decreased intake secondary to psychological causes (anorexia nervosa) may lead to profound potassium depletion. Elderly patients with limited access to food or unable to prepare balanced diets may become potassium depleted, hence the

maned-tea and toast syndrome. Large amounts of potassium can be lost in diarrheal stools. The stool water itself may be high in potassium. In addition, the volume contraction may increase renal potassium losses. Villous adenomas, which constitute 2 to 12 % of colonic tumors, are commonly associated with hypokalemia. Potassium concentration in the secreted mucus may be as high as 80 mEq/L. Volumes of diarrhea may reach 1 to 3 liters per day. This direct loss of potassium, along with the volume contraction seen in this disorder, leads to the hypokalemia. Ureterosigmoidostomy is known as an uncommon urinary diversion procedure in which the ureters are implanted in an isolated portion of sigmoid colon. Secretion of potassium and bicarbonate into the lumen of the sigmoid loop leads to both metabolic acidosis and hypokalemia. The now more common ileal loop allows for a more rapid transit time of the urine in the bowel loops and less potassium loss (Figure 5).

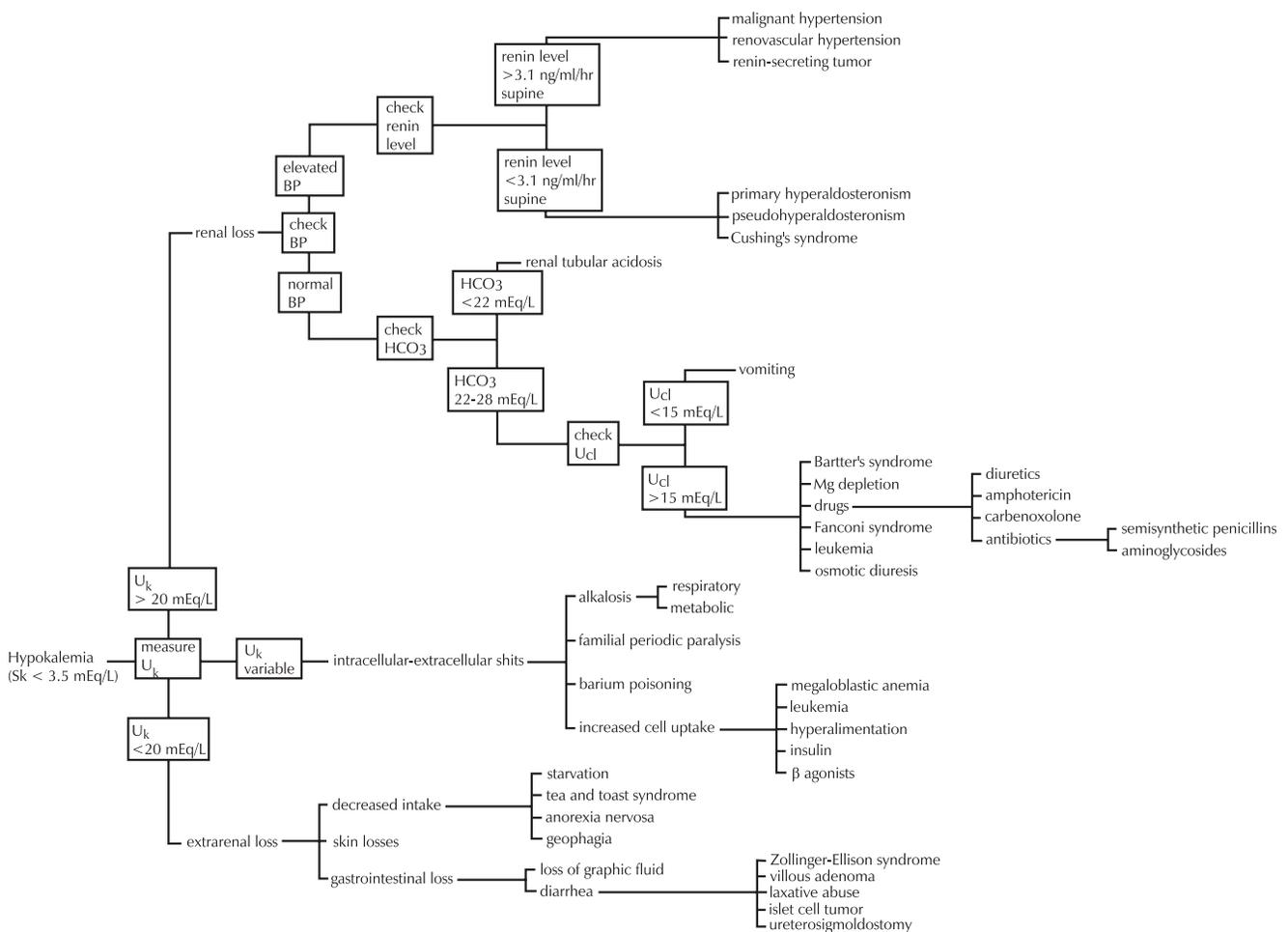


FIGURE 5. An Algorithmic Approach of Hipokalemia Diagnoses

Patients with Bartter's syndrome deal with some obstacles for treatment. Treatment options are mainly symptomatic but should have an improved quality of life and avoid long-term effects like nephrocalcinosis that characterize hereditary renal tubular disorders. As a result, the therapeutic management is focused on adjusting both the hypokalemia and the alkalosis.

Same to our presented case, medical care has also included potassium and sodium supplements for electrolyte loss; angiotensin-converting enzyme inhibitors to counteract angiotensin II and aldosterone; indomethacin or other prostaglandin synthetase inhibitors to decrease prostaglandin secretion; administration of growth hormone for children with short stature but not in our case; and additionally supplements with calcium and magnesium. Potassium-sparing agents (e.g., spironolactone) are always recommended to correct the excess K⁺ loss (2,4).

Likewise, the replacement of significant fluid and sodium chloride losses is more difficult in young patients. Similarly, metabolic alkalosis is strongly correlated with volume depletion. Same to our case, leukocytosis appears to be mostly a marker of volume depletion and demargination due to physical stress, rather than an infection like tuberculosis, while leucopenia is often a marker of a severe underlying disease. It seems reasonable to assume that hypokalemia should be suspected in case of patients with diuretic therapy, with chronic or severe diarrhea, or in those with chronic volume depletion. All the more, alkalemia, insulin, beta-adrenergic agonists, and hyperaldosteronism trigger potassium transferring into the intracellular space. Therefore, a urine potassium concentration over 20 mEq/L suggests new hypokalemia or excessive renal potassium loss; and a serum potassium concentration of 2.5 mEq/L generally reflects a total body potassium deficit of 200 to 400 mEq. Moreover, caution is needed for any treatment that promotes rather rapid shifting of extracellular potassium intracellularly, e. g. inhalative beta bronchodilators for the asthma.

One puzzling factor in the treatment of this syndrome is the risk of progressive renal damage. Chronic renal failure is reported in Bartter's syndrome cases; however the cause is not established. For that reason, severe and prolonged hypokalemia can cause tubulointerstitial injury with renal failure, as well as focal and segmental glomerulosclerosis (12, 13). Bartter's syndrome is a state associated with hyperprostaglandinemia and high urinary excretion of prostaglandin derivatives (14). Consequently, a rise in chemotaxis is described in Bartter's syndrome neutrophils, but with a normal immune function (14). The involvement of long-term chronic hyperaldosteronism or non-steroidal anti-inflammatory treatment is also involved but remains to be further established. On the other hand, the cases with Bartter's syndrome complicated with renal failure seem to be a rare incidence, despite nearly common hypokalemia, even with proper treatment in our presented case. It seems that the long follow up of our case with Bartter's syndrome to chronic renal failure favored the tuberculosis pulmonary process, a surprising diagnosis during the last admission of our patient.

In summary, it seems that acquired tubular disorders are not as rare as often assumed. Particularly, but not in our described case, autoimmune diseases may be involved in the triggering of Bartter's syndrome onset, and therefore an increased clinical awareness will lead to the identification of many cases in the future. Hopefully, more progress will be made in understanding the disorders affecting renal sodium transport that will finally lead to improved therapeutic strategies for these patients. The identification and detection of other possible triggering mechanisms is extremely important in these patients with Bartter's syndrome complicated with chronic renal failure and the absence of nephrocalcinosis, and advocate the need for systematic studies to delay the evolution of renal failure that favor immunosuppression, and even more, may favor the infections with pulmonary tuberculosis. □

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