The Hypokalemia Mystery: Distinguishing Gitelman and Bartter Syndromes from 'Pseudo-Bartter Syndrome'

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Introduction:

The Gitelman and Bartter Syndromes (GS and BS, respectively) are characterized by the constellation of hypokalemia, hypochloremia, metabolic alkalosis, hyper-reninemic hyperaldosteronism, low to normal blood pressure and juxtaglomerular apparatus hypertrophy. These are due to pathogenic variants in the genes that encode the thiazide-sensitive sodium-chloride cotransporter NCC (*SLC12A3*) in the distal convoluted tubule or transporters involved in sodium chloride reabsorption in the loop of Henle. 'Pseudo-Bartter syndrome' (PBS) is caused by extra-renal or acquired renal salt losses and shares the same plasma electrolyte profile and acid-base disturbances, making the distinction from the genetic forms very challenging. PBS has various etiologies including diuretic and laxative abuse, self-induced vomiting and the side effects of some antimicrobials. Additionally, congenital chloride diarrhea, cystic fibrosis, Pendred syndrome and chloride deficient diet can manifest as PBS (1).

In this review, we focus on factitious PBS secondary to diuretic abuse, laxative abuse or self-induced vomiting, whereby we point out some clinical and laboratory clues to help clinicians make the correct diagnosis.

Patient's characteristics and clinical features of factitious PBS

Concealed diuretic abuse, laxative abuse and self-induced vomiting are the most common causes of PBS in adults. They are typically seen in women preoccupied with their body image and in patients with psychiatric eating disorders that include purging (2). Reported motives include slimming, edema, bloating, premenstrual symptoms and persistent constipation (3).

The ability of some patients to obscure their abuse or self-induced vomiting can make the diagnosis of factitious PBS challenging. There are reports of patients who misled their physicians and agreed to undergo invasive diagnostic procedures like kidney biopsy, renal arteriography and renal vein catheterization for assessment of differential renin secretion before a diagnosis of diuretics or laxative abuse was made (4). Interestingly, the severe

and even life-threating symptoms associated with hypokalemia and volume contraction sometimes may not stop these patients from continuing their dangerous purging behavior. Some of them tend to continue purgative habits despite having weakness, cramps, dizziness, polyuria and paralysis (5). Therefore, it is important to raise the differential of factitious PBS in patients with mysterious hypokalemia even if they deny any of the aforementioned behaviors.

Laboratory data of PBS secondary to diuretic abuse:

Urine sodium, potassium and chloride are usually high under the effect of recent diuretic intake and low after remote use. Indeed, the variability in urine sodium, potassium and chloride values should raise suspicion of PBS. A positive diuretic screen is diagnostic; however, a negative diuretic screen does not always rule out its abuse as the diuretic intake may be intermittent. Therefore, repeating the urinary screen is warranted when the diagnosis of factitious PBS is suspected. A concomitant measurement of the urinary fractional excretion of chloride (FE_{Cl}) can help interpret results of a diuretics screen: a negative screen in a sample with low urine chloride can be due to the absence of recent diuretic ingestion, while a negative screen associated with a high urine chloride (FE_{Cl} > 0.5%) favors a diagnosis of BS (3).

Nephrocalcinosis, secondary to hypercalciuria and hypokalemia-induced hypocitraturia, can be seen in both BS and loop diuretic abuse. However, one differentiating feature between the two is the variable urinary calcium excretion which points towards intermittent loop diuretic ingestion rather than BS. The development of nephrocalcinosis in PBS patients is a sign of long-term intake of large doses of loop diuretics (6).

Laboratory data of PBS secondary to laxative abuse:

Patients abusing laxatives develop hypokalemia because of the high content of potassium in the lower gastrointestinal tract. Urinary potassium is high in these patients as

a result of secondary hyperaldosteronism. Urinary sodium and chloride are typically low. Similar to diuretics, the intermittent intake of laxatives may lead to a negative screen result. Another diagnostic limitation is the unavailability of screening tests for all types of laxatives. Hypermagnesemia, when present, may be a clue to the abuse of magnesium-containing laxatives (7).

Laboratory data of PBS secondary to self-induced vomiting:

The pathophysiology of hypokalemia in vomiting is considered to be secondary to renal losses rather than direct gastrointestinal losses. The low potassium content in the gastric fluid (5 to 10 mEq/L) only contributes to a small proportion of potassium wasting in vomiting. Increased gastric acid secretion causes high bicarbonate generation with subsequent increase in the glomerular filtration of the bicarbonate load and its distal tubular delivery with an obligatory sodium load. This, coupled with hypovolemia-induced secondary hyperaldosteronism, causes urinary potassium wasting and thus explains the high urinary potassium in vomiting (8). The metabolic alkalosis in vomiting can be very severe with serum bicarbonate values exceeding 45 mmol/L.

While urinary chloride is typically low in self-induced vomiting, urinary sodium can be low if the event is remote or high if recent. The high urinary sodium seen with recent vomiting likely reflects metabolic alkalosis and increased $NaHCO_3$ urinary losses. Table 1 summarizes the serum and urine electrolyte differences between the three entities.

Kidney disease risk in PBS:

PBS secondary to diuretics, laxative abuse and self-induced vomiting is a risk factor for the development of chronic kidney disease. Deterioration of kidney function was initially thought to be secondary to chronic hypokalemia and thus is known as hypokalemic nephropathy. However, recent studies suggest that it may rather be a consequence of hyperaldosteronism. Histologically, this entity manifests as proximal tubular intracytoplasmic vacuolization with chronic interstitial nephritis and fibrosis (9).

Conclusion:

Unexplained hypokalemia should always raise suspicion ~~for a~~of factitious PBS even when the patient denies any diuretic or laxative misuse. Paying careful attention to the clinical and laboratory pieces of evidence when solving the puzzle of mysterious hypokalemia is crucial for making the correct diagnosis of factitious PBS and instigating appropriate treatment. Psychiatric evaluation and management are essential for treatment success and long-term purging cessation.

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Table 1: Serum and urine laboratory values in Bartter Syndrome and Pseudo-Bartter Syndrome secondary to diuretic abuse, laxative abuse and self-induced vomiting [*].

	Serum K	**Serum Co2**	**Urine Na**	**Urine K**	**Urine Cl**
Bartter Syndrome	Low	High[†]	High	High	High
Diuretic abuse	Low	High[†]	High under the effect of diuretics	High under the effect of diuretics	High under the effect of diuretics
			Low when diuretic effect weans off	Low when diuretic effect weans off	Low when diuretic effect weans off
Laxative abuse	Low	High[†♠]	Low	High	Low
Self-induced Vomiting	Low	High[†]	High in recent vomiting	High	Low
			Low in remote vomiting		

[*]The electrolyte and acid-base disturbances are more complex when a combination of these entities is present.

[†] Hypokalemia contributes to metabolic alkalosis through increasing intracellular shift of hydrogen ions, enhancing tubular generation and excretion of ammonium and stimulating the distal tubule H^+-K^+-ATPase pump which excretes hydrogen ions in exchange for potassium.

♠In laxative abuse, hypokalemia may further contribute to metabolic alkalosis by interfering with intestinal chloride reabsorption and impairing bicarbonate secretion through the intestinal chloride-bicarbonate exchanger (10).