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Karan Jaykrushna Pandya

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Case report

Late Presentation of Bartter Syndrome as Refractory Hypokalemia

Karan Pandya [1], Parth Adrejiya [2], Jaya Pathak [3], Radhay Parikh [4], Bansari Parmar [5], Meghal Varma [6], Jugal A. Parikh [7]

[1] Third year Resident Doctor,Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[2] Intern Doctor, Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[3] Associate Professor, Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[4] Third year Resident Doctor, Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[5] Undergraduate, Final Year MBBS, Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[6] Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

[7] Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India

***Corresponding Author:** Karan Jaykrushna Pandya, Third year Resident Doctor, Dept. Of Medicine, S.S.G Hospital, Medical College Baroda, Vadodara, Gujarat, India.

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Abstract

Bartter syndrome is a rare salt-wasting nephropathy characterized by sporadic or inherited genetic defects in transporters and channels in the thick ascending limb of the loop of Henle and distal tubule of Nephron leads to renal potassium wasting with hypokalemia, metabolic alkalosis, increased renin-angiotensin-aldosterone system, normal blood pressure. Most of the cases have been noted in the pediatric age group and adult-onset cases are very rare. Here we report an unusual case report of Bartter's syndrome in a 52 years old male patient.

Background:

Hypokalemia is a common electrolyte derangement in approximately 20% of hospitalized patients and 2-3% of patients in outpatient clinics. Many diseases alter the equilibrium of K^+ between the Extracellular compartment and intracellular spaces by causing excess K+ loss, sequestration inside cells, or under influence of hormones, or drugs. Hence, it is more common to find hypokalemia as a single episode in such cases. Treatment of the disease and K^+ correction will help to achieve normal homeostasis. However, unusual is to find cases of recurrent hypokalemia where despite treatment of predisposing factor & K^+ correction, hypokalemia persists and episodes recur. These are relatively uncommon incidences that not only pose diagnostic challenges but also increase morbidity and mortality due to life-threatening cardiac conduction disturbances and neuromuscular dysfunction hence appropriate emergency management and diagnosis and treatment of underlying etiology becomes very important.

Bartter et al. in 1962 described a clinical syndrome characterized by hypokalemia, metabolic acidosis, hyperreninemia, hyperaldosteronism, normal blood pressure, and resistance to the pressor effects of norepinephrine and angiotensin ll. Histologically, there is hyperplasia of the juxtaglomerular cell. It occurs mostly in childhood or adolescence, and initial presentation over 40 years of age was very rare.

This case report is highlighting the diagnostic approach and management of the rare causes of recurrent hypokalemia in an older aged male with persistent hypokalemia, metabolic alkalosis, normotension, hyperreninemia, and hyperaldosteronism eventually diagnosed with Bartter's syndrome.

Key words: sporadic; inherited genetic; limb; nephron; hypokalemia

Case history:

A 52-year-old male presented to the SSG hospital complaining of acute onset of weakness in both lower limbs in the form of not being able to get up from the bed and walk for one day. It is non-progressive and symmetric in both limbs and no such complaints in the upper limbs. Additionally, there were no complaints of breathlessness, speech, deglutition, or urinary or bowel incontinence. There were no complaints of paresthesia or impaired sensations in the lower limbs and upper limbs. There was no history of trauma, backache, vomiting, diarrhea, fever, or headache. There was no previous history of stroke and no known case of hypertension and diabetes mellitus, no chronic prescription use (like Thiazide or Loop diuretics, theophylline, chloroquine). Looking at previous medical history, we found that the patient had 7-8 similar episodes of recurrent weakness in all limbs over 2 years.

Out of which 2 episodes were precipitated following diarrhea and vomiting and the symptoms resolved with the administration of intravenous fluids. Periodic follow-up with Serum K+ levels reveal persistent hypokalemia. No family history of such symptoms was elicited. An initial general examination was done which revealed intact sensorium, normal body temperature, pulse was 80 beats per minute (bpm) with normal characteristics, respiration was 14/min and regular, Blood pressure was 100/78 mmHg, RBS:104mg/dl. Central nervous system examination showed intact higher functions, no abnormalities in cranial nerves, and reactive pupils. Upper limb nervous system examinations were normal. There was hypotonia, and power was 2/5 in both lower limbs, absent deep tendon reflexes, and flexor plantar response. Cerebellar examinations were normal. Sensory examination in all four limbs was normal.

Cardiovascular, Gastrointestinal, and Respiratory system examinations were normal and yielded no diagnostic clues. Initial history and examination implied acute flaccid areflexic motor paralysis mostly likely due to electrolyte imbalance.

Initial investigations were done. The results were as follows:

Tests	Reported Values	Reference Values
Hemoglobin	13.3 g/dL	13.2 – 16.6 g/dL
RBC Count	4.64 million/mm3	4.0-5.9 million/mm3
WBC Count	8,510/mm3	4,500 – 11,000/mm3
Platelet count	3,23,000/mm3	2,50,000 – 3,50,000/mm3
Serum Potassium	**1.5 mEq/L**	**3.5 – 5.5 mEq/L**
Serum Sodium	126 mEq/L	135 – 145 mEq/L
Serum Creatinine	1.30 mg/dL	0.74 – 1.35 mg/dL

Table 1: Preliminary Laboratory Investigations

Immediately, Electrocardiogram (ECG) was done. ECG revealed PR prolongation and T-wave flattening. Despite the symptomatic improvement of flaccid paralysis after intravenous potassium correction, K^+ values were low (2.5 mEq/L) after 2 days. This along with past clinical history, Serum Sodium, Urine K^+, TTKG (Trans tubular potassium gradient), S. Mg2+, ionized and normal calcium were done for further evaluation of persistent hypokalemia. TTKG was 20.53 (normal value 8-9) suggesting renal potassium wasting. Serum sodium was 126 mEq/L, serum magnesium (2.20 mg/dL), total calcium was 5.0mEq/l and ionized calcium was 2.0mEq/L. Urinary K+ excretion could be falsely low in a spot sample, so the Urine K+/Creatinine ratio was done. This ratio (816.8mEq/gm Creatinine) was significantly higher (indicating renal K^+ wasting) in this patient. 24 hours urinary excretion of potassium was 70 mEq, sodium 185 mEq, chloride 248 mEq, calcium 120 mg, protein 150 mg, glucose 40 mg/dl, and urine amounts 2500cc. Serum osmolarity was reduced(257mOsmol/kg) while urine osmolarity was 116mOsmol/kg (hypoosmolar urine). On further evaluation, Arterial Blood Gas analysis was done which showed Metabolic alkalosis (pH: 7.541) with high normal serum Bicarbonate levels (30.8 mEq/L). This along with normal Blood pressure excludes mineralocorticoid excess and Metabolic acidosis. There was no proteinuria, hematuria, or abnormality of urinary sediment. The plasma renin activity was 48.1 ng/ml/hr and the aldosterone level was 34.3 ng/dl.

Looking at the clinical history, examination, and lab investigation of persistent hypokalemia with high TTKG, normotension, metabolic alkalosis, normocalciuria, normal magnesia, high renin, and aldosterone activity with no use of laxatives or any diuretics would suggest the presence of Bartter's syndrome (BS). Thus, it was a very unusual case of BS with late onset of presentation. Investigations to look for coexisting complications and systemic defects were carried out. USG of the kidney, ureter, and Urinary bladder to look for nephrocalcinosis and audiometric testing to exclude Sensorineural Hearing Loss (SNHL) was done. No SNHL and Nephrocalcinosis were noted. Thyroid function tests (TFTs) were within normal limits.

Outcome and follow-up:

Emergency management of severe hypokalemia was started with 2 large bore IV (intravenous) lines placed for fluid replacement and K^+ correction was initiated. A total deficit of 400mEq/L was estimated which reflects a drop in serum from 3.5mEq/L to 1.5mEq/L. So, KCL diluted in Normal Saline at 40mEq/L concentration was administered at the rate of 40 mEq/hr intravenously under cardiac monitoring carefully. Response to therapy was assessed by improvement of symptoms and measuring S. K^+ levels. Our patient showed rapid and complete reversal of symptoms over 48 hours.

So for bartter syndrome diagnosis patient had been treated with potassium chloride 40 mEq

twice daily, Spironolactone 50 mg two times a day, indomethacin 25 mg three times a day, and enalapril 2.5 mg day followed up with serum and urinary K^+ as a marker for prognosis. On further follow-up every month for 6 months there was a normal range serum K^+(3.5-4.5 mEq/L) with improved muscle strength and no further episode of acute limb paresis.

Discussion:

In most cases of neuromuscular weakness secondary to electrolyte imbalance etiology of hypokalemia can be derived from the clinical presentation and

relevant history, and routine laboratory investigations. However, it poses a significant challenge in cases of recurrent episodic paresis with persistent hypokalemia when neither the history examination points to the diagnosis.

Our preliminary clinical examination and history ruled out GI (gastrointestinal) and Integumentary losses. There was no history of drug use, no previous history of DM, or hyperthyroidism and our investigations confirm the same (TFT is normal, RBS:104 mg/dl). Serum Magnesium levels were normal(2.2mg/dl) ruling out refractory hypokalemia. This curtails the differential diagnosis of renal potassium wasting. Urinary potassium levels in a 24-hour urine sample can differentiate renal (>15 mmol/L or >15-20mmol/day) from extrarenal causes (<15 mmol/day). Since it's not practical, spot urine samples can be used before instituting potassium supplementation. As K^+ concentration depends both on the amount of K+ excreted and urine volume [1], spot urine samples in patients with polyuria, salt-wasting nephropathies, and chronic hypokalemia can falsely show low/normal K^+ levels. Hence, we need a marker not dependent on urine volume [2].

Trans tubular potassium gradient (TTKG) is a superior marker of renal K+ wasting as compared to urinary potassium levels [3] a d also differentiates renal potassium wasting according to its pathophysiology [4]. TTKG (<2 indicates increased tubular flow and intracellular shifts whereas >4 indicates excess K^+ secretion from the cortical collecting tubules). TTKG of our patient was 20.53.

Another marker Urinary K^+/Cr ratio can be used to differentiate renal vs extrarenal loss and it especially becomes important since it's not affected by urine volume [2]. Studies by Lin C et al. [2] found this ratio effective in distinguishing renal potassium wasting from hypokalemic periodic paralysis (HPP).

HPP is an autosomal dominant ion channelopathy characterized by the transient intracellular shifting of K^+ inside cells manifesting as periodic weakness in muscle groups. The urine K/Cr ratio is lower in extra renal disorder (HPP) and higher in Renal disorders. This is necessary before initiation of K^+ correction because transient K+ shifts reverse following K^+ replacement which increases the risk of rebound Hyperkalemia and its complication. Thus, it is necessary to differentiate HPP from Renal K+ wasting disorders. In our patient, this ratio was significantly higher (816.8mEq/gm Creatinine). This along with the absence of clinical findings and persistent hypokalemia in between attacks of weakness ruled out HPP.

Normal Blood pressure and normovolemia rule out high mineralocorticoid activity which can cause excess Renal K^+ wasting from DCT. Further, ABG analysis revealed metabolic alkalosis which negates the possibility of hypokalemia due to Renal tubular acidosis (RTA). Metabolic alkalosis can be due to chronic diuretic use, Bartter's syndrome, Gitelman's syndrome, and GI loss (vomiting, diarrhea). There is no history of diuretic ingestion, negative GI complaints, and urinary chloride [5] (differentiate causes hypokalemia with metabolic alkalosis due to renal loss) excretion >20 mmol/L brings down the differential to Bartter's and Gitelman's syndrome which can be differentiated by Urinary Calcium excretion and serum magnesium levels. Normocalciuria and normal magnesium levels in our patient exclude Gitelman's syndrome.

Gitelman's syndrome typically presents in adolescence and late adulthood, and since our patient presented to us within this age group, this becomes an essential differential to Bartter syndrome. The clinical presentation of GS is similar to chronic thiazide ingestion and is milder in severity as compared to Bartter's syndrome [6].

Bartter syndrome-like presentation i.e Pseudo Bartter's syndrome had been reported with abuse of agents like laxatives, Furosemide, in eating disorders like Bulimia nervosa, Gentamicin nephrotoxicity, Sjogren's syndrome, and Cystic fibrosis. Since our patient lacked history and clinical features indicative of these causes.

In bartter's syndrome, the primary defect occurs in Sodium, Potassium Chloride cotransporter, or Potassium chloride in the thick ascending limb of the loop of Henle which results in increased delivery of solutes to the distal segment, where selective absorption of Na+ and excretion of K^+ occurs. Traditionally Barter's syndrome (BS) is sub-classified into five different categories based on genetic defects [7] which is summarized in the table below:

FEATURES	**Type 1BS:**	**Type 2BS:**	**Type 3BS:**	**Type 4BS:**	**Type 5BS:**	**GS**
Age of Presentation	Antenatal	Antenatal	<1year (Infancy)	Antenatal /Infancy	Variable	Late childhood, Adulthood
Mode of Inheritance	AR	AR	AR	AR	AD	AR
Involved Genes /Protein		KCNJ1/ ROMK	CLCNKB/ ClC-Kb, Distal tubular chloride channel	BSND/ Bartt in, Chloride channel Beta subunit	CASR/ Ca^{2+}-Mg2+ sensing receptor	SLC12A3/ NCCT
Pregnancy	Polyhydramnios	Polyhydramnios	-	Polyhydramnios, failure to thrive	-	-

Electrolyte Imbalance	Hypochloremic, hypokalemic alkalosis with high urinary Prostaglandins E2	Hypochloremic, Hypokalemicalkalosis with high Urinary Prostaglandins E2	Hypo chloremic, hypokalemic alkalosis	Hypochloremic, hypokalemicalkalosis		Hypochloremic, hypokalemicalkalosis
Serum K+	Low	Low	**Low**	Low	Low	**Low**
Urine CA2+	High	High	**Norm al**	High	High	**Low**
Serum MG2+	Norm al	Normal	**Normal/low**	Normal		**Low**
Nephrocalcinosis	Yes	Yes	No	No	Yes	No
		Prematurity		Sensorineural hearing loss.		

Table 2: Differentiating features between Subtypes of Bartter Syndrome and Gitelman's Syndrome:

The therapeutic goal is to correct the K^+ deficit and minimize ongoing losses through the treatment of underlying causes. Presently, there is no cure for BS and GS. Studies by Walsh et. al. [8] show that degree of hypokalemia (a marker of chronic K^+ depletion) doesn't correlate well with GFR. Ongoing sodium and water losses and consequent high renin-angiotensin aldosterone activation (RAAS) are responsible for chronic renal impairment. Therefore, blockade of aldosterone receptors to decrease the effects of RAAS or prostaglandin-kinin system will provide better renal protection than correcting hypokalemia per se. Hence, potassium supplementation, Spironolactone, ACE Inhibitors, and prostaglandin inhibitors are important treatment modalities.

Learning points:

1. Classical Bartter's syndrome (type 3), is a rare disease that may lead to unnecessary diagnosis delay.
2. Persistent hypokalemia and recurrent hypokalemic periodic paralysis in advanced age bartter syndrome should also be a differential diagnosis.
3. The cornerstone in treatment is long-term potassium chloride supplementation, Spironolactone, ACE Inhibitors, and prostaglandin inhibitors to improve long-term prognosis.

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