VOLUME - 12, ISSUE - 01, JANUARY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Internal Medicine

A CASE SERIES OF ADULT ONSET BARTTER SYNDROME

Gurumoorthy A D* Junior resident, Internal medicine, Stanley Medical College, Chennai, India
*Corresponding Author

Thilakavathi R Professor of Internal medicine, Stanley Medical College, Chennai, India

ABSTRACT Bartter syndrome is a rare genetic salt wasting tubulopathy due to defect in ion transporters in the thick ascending limb of loop of henle with a prevalence of 1 in 1,000,000 in general population. Five types have been described based on the genetic mutation and the transporter which is involved. Type I-IV Bartter Syndrome are inherited as autosomal recessive, whereas type V Bartter Syndrome due to activating mutation in calcium sensing receptor (CaSR) is inherited in an autosomal dominant manner. Majority of the cases usually present in antenatal period or neonatal period. Based on age of onset, types I, II, IV have been classified as antenatal BS. Type III Bartter Syndrome, also called classic Bartter Syndrome usually presents in childhood and adolescence but the age of onset can be quite variable. However, cases of Bartter Syndrome have been reported even in adult patients but it is extremely rare. Here, we report a series of four cases of adult onset Bartter syndrome diagnosed in our hospital.

KEYWORDS : Bartter syndrome, calcium sensing receptor

INTRODUCTION:

Bartter syndrome was first described by Bartter and coworkers in 1962[1]. It is a tubulopathy affecting the thick ascending limb of loop of Henle leading to salt wasting. It is characterized by hypokalemia, hypocalcemia, hypercalciuria, mild hypomagnesemia, metabolic alkalosis, hyperreninemic hyperaldosteronism, and normal to low blood pressure[2]. In patients participated in Framingham Heart Study, the prevalence of BS was found to be 1 in 1,000,000[3]. Bartter syndrome is commonly seen in the prenatal or neonatal period. But, it has been reported even in adults either idiopathic or secondary to other causes. Here, we discuss a series of four cases of Bartter syndrome which we diagnosed in our hospital.

Case Report 1:

A 48 year old lady with no known comorbidity was brought with complaints of weakness of all 4 limbs, abdominal distention and constipation for 3 days. On examination, her blood pressure was 100/60 mm Hg, Power- 3/5 in all limbs, hypotonia, deep tendon reflexes 1+ and electrocardiogram showed U waves of hypokalemia. Serum potassium was found to be 1.3 mEq/L. She had a normal hemogram and renal function test. Computed tomography of abdomen showed dilated bowel loops suggestive of paralytic ileus. Serum magnesium was 1.6 mg/dl, calcium was 10.1 mg/dl and arterial blood gases showed metabolic alkalosis. Hypokalemia was corrected with intravenous and later oral potassium chloride. Her thyroid function test was normal. Urinary potassium excretion was found be 139mEq/gm of creatinine suggesting renal loss of potassium. Urine chloride was 52 mEq/L and calcium creatinine ratio was 0.38 which lead to diagnosis of Bartter syndrome. Her chest X-ray was normal and anti-nuclear antibodies were negative. She also denied consumption of any drugs. Hence a diagnosis of adult onset Classic Type III Bartter syndrome was made and patient was discharged with oral potassium supplementation and is on followup.

Case Report 2:

A 32 year old lady with history of migraine headache and 3 episodes of hypocalcemic tetany in the past came with complaints of carpopedal spasm for 2 hours. Chvostek sign and Trousseau sign were positive. Corrected serum calcium was 7.2 mg/dL and electrocardiogram showed QTc prolongation (510msec). Hypocalcemia was corrected with intravenous calcium gluconate. Investigations revealed serum potassium - 2.1mEq/L, serum magnesium- 1.1 mg/dL, serum phosphate - 2.8mg/dL, serum creatinine - 0.8 mg/dL and arterial blood gases revealed metabolic alkalosis. Hypokalemia and hypomagnesemia were corrected with intravenous potassium chloride and magnesium sulphate. Her thyroid function was normal. Serum parathormone was 15pg/ml which was inappropriately on the lower side of normal range. Ultrasound revealed normal parathyroid glands. 25-hydroxy vitamin D was 33 ng/mL which is normal. 24 hour urine collection revealed an increased calcium excretion of 264 mg/24 hours with calcium creatinine ratio of 0.26 and also increased potassium excretion of 42 mmol/24 hours. Her chest X-ray was normal and anti-nuclear antibodies were negative. A diagnosis of autosomal dominant hypocalcemia/Type V Bartter syndrome was made and patient is under followup with oral potassium and calcium supplementation.

Case Report 3:

A 40 year old gentleman came with complaints of abdominal pain, vomiting, perioral numbness and tingling sensation in bilateral hands after intake of alcohol. Trousseau sign was positive. Electrocardiogram showed QT prolongation (496msec) and serum corrected calcium was 6.8 mg/dl. He also had serum potassium - 2.9 mEq/L, magnesium - 0.8 mg/dl, phosphate - 2.9 mg/dl and arterial blood gases showed mixed respiratory and metabolic alkalosis. Hypocalcemia, hypokalemia and hypomagnesemia were corrected intravenously. His renal function test and thyroid function test were normal. Computed tomography of abdomen showed multiple microlith in bilateral kidneys. Serum parathormone was 20 pg/ml which was inappropriately normal. 24 hour urine collection revealed increased renal potassium loss of 18.5 mEq/ 24 hours and also increased renal loss of calcium (334 mg/24 hours), with urine calcium creatinine ratio of 0.35. There were no evidence of secondary causes of Bartter phenotype and hence patient was diagnosed to have autosomal dominant hypocalcemia / Type V Bartter syndrome and patient is under followup with oral potassium and calcium supplementation.

Case Report 4:

A 48 year old male was admitted in emergency department with complaints of cough with expectoration, weight loss for past 1 month and weakness of all 4 limbs for past 1 day. He had a similar episode 3 years back, when he was found to have hypokalemia and pulmonary tuberculosis for which he was treated with anti-tubercular treatment for 6 months and declared cured. He was advised to take potassium supplements regularly. Now, the patient had stable vitals, examination revealed tracheal deviation to right with

cavernous bronchial breath sound over right supraclavicular area, paresis of all 4 limbs and trunk muscles with normal tone and reflexes. Electrocardiogram showed U waves and serum potassium was 2.2 mEq/L. Hypokalemia was corrected accordingly. Thyroid function test, serum creatinine, calcium, magnesium were normal. Urine spot potassium creatinine ratio was 23mEq/g and arterial blood gases showed metabolic alkalosis. 24 hour urine excretion of calcium was 296 mg with calcium-creatinine ratio of 0.25. Chest X-ray showed fibrosis in right upper and middle zone with mediastinal shift to right side. Sputum was positive for acid fast bacilli and Mycobacterium tuberculosis was detected on CBNAAT. Hence, a diagnosis of Bartter syndrome was made, probably acquired secondary to pulmonary tuberculosis and patient was discharged with Anti-tubercular therapy and oral potassium supplements.

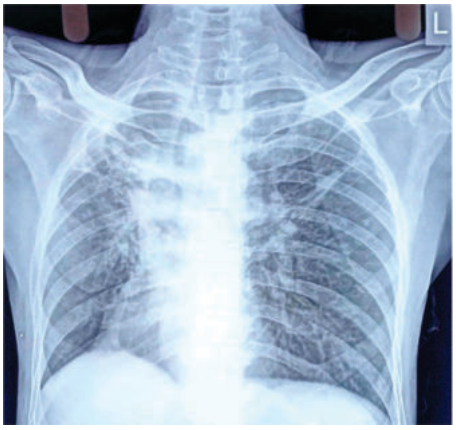

Figure 1. Chest X-ray showing right upper and middle zone fibrosis with trachea and cardiac shadow shifted to right side.

DISCUSSION:

The thick ascending limb of loop of henle is the most relevant nephron segment in terms of Bartter syndrome as it is critical for the electrically driven paracellular reabsorption of cations including calcium, magnesium, and sodium but impermeable to water. The required lumen-positive transepithelial voltage is generated by the charge separation resulting from electroneutral apical membrane entry of Na+, K+, and Cl- which is mediated by the cotransporter NKCC2, with the basolateral exit of Cl- and Na+ mediated by the chloride channel ClC-K/barttin and Na+/K+ ATPase, respectively, and the apical recycling of K+ through the renal outer medullary potassium channel (ROMK)[4]. Bartter syndrome mimics the clinical effects of chronic ingestion of loop diuretics and its use should be excluded in all the suspected individuals.

Bartter syndrome can occur due to various genetic defects leading to reduced activity of one of the several electron transporters in the thick ascending limb of loop of henle. To date, five types of Bartter syndromes have been described based on the transporter involved. Type I Bartter syndrome is due to a loss-of-function mutation of the apical sodium-potassium chloride cotransporter gene (*NKCC2*). Type II Bartter syndrome is caused by mutations in the apical renal outer medullary potassium channel gene (*ROMK*). Mutations in the basolateral chloride channel (*CLCNKB*) gene cause type III BS. Type IV Bartter syndrome results from a loss of-function mutation of *BSND*, which encodes barttin, the β subunit of CLC-K channels that is essential for their function and it is usually associated with deafness. Types I-IV are inherited in an autosomal recessive manner[5].

Autosomal dominant hypocalcemia type 1 is caused by autosomal dominantly inherited activating mutations of calcium sensing receptor (CASR) on the basolateral side of thick ascending limb of loop of henle, which plays an important role in calcium and magnesium homeostatsis. It is characterised by hypocalcemia, relative hypercalciuria and inadequate parathyroid hormone (PTH) secretion, and when it is associated with hypokalemia, it is referred to as Type V Bartter syndrome[6].

Several drugs are also reported to produce a Bartter syndrome-like phenotype, including aminoglycosides (capreomycin, gentamicin and viomycin), colistin, and amphotericin B. Acquired BS is reported in auto-immune conditions such as Sjögren's disease and granulomatous conditions like sarcoidosis and pulmonary tuberculosis[7]. Also, there are a few case reports of idiopathic Bartter syndrome in patients with type 2 diabetes but causal association is unproven.

The treatment of Bartter syndrome involves correction of hypokalemia with potassium supplements and reduction of further renal losses through using potassium sparing diuretics (spironolactone or triamterine) and angiotensin converting enzyme inhibitors like enalapril. Prostaglandin synthetase inhibitors like indomethacin, aspirin, and ibuprofen have all been tried in patients with Bartter syndrome and the best evidence comes from indomethacin[8]. Patients with autosomal dominant hypocalcemia with type V Bartter phenotype also require supplementation of calcium and magnesium in addition to potassium. Recombinant PTH(1-34) and calcilytics are under trials in those patients[9,10].

CONCLUSION:

Though Bartter syndrome is predominantly a disease of infancy and childhood, it can also occur sporadically in adults and it is often under-diagnosed. Hence we recommend to consider Bartter syndrome in the differential diagnosis of any patient with hypokalemia and metabolic alkalosis.

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