

Recurrent Seizure: An Unusual Presentation of Bartter Syndrome in an Adult Female

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Abstract

A young lady presented with recurrent seizure. Examination revealed features suggestive of tetany. Investigation showed hypokalaemia, severe hypocalcaemia and hypercalcuria, hyper-reninaemia, hyperaldosteronism, and metabolic alkalosis. Adult onset, severe hypocalcaemia along with other biochemical features points towards type V Bartter syndrome. Seizure is an unusual presentation of Bartter syndrome making this case reportable.

Key words: *Bartter syndrome, hypokalaemia, hypocalcaemia, metabolic alkalosis, seizure.*

Introduction

Bartter syndrome was originally described by Bartter and colleagues in 1962¹. It is an autosomal recessive renal tubular disorder characterised by hypokalaemia, hypochloreaemia, metabolic alkalosis, hypercalcuria and hyporeninaemia with normal blood pressure². Bartter's syndrome mostly presents the in neonatal period with hypokalaemic metabolic alkalosis. Initial presentation of Bartter syndrome in adults is relatively less common. Here we report a case of Bartter syndrome in an adult female who presented with intractable seizure.

Case report

A 27-year-old female presented in emergency room in a drowsy state with history of generalised tonic clonic seizure one hour prior to admission. She had history of similar episodes twice in the last 1 month and was prescribed levetiracetam 500 mg thrice daily after the first episode. There was no history of headache, vomiting, visual disturbance, or fever in the recent past. Relatives stated that she was having perioral numbness and leg cramps for the last 2 months. She was not on any regular medication except the antiepileptic and did not have any history of addiction or substance abuse. She was a non-vegetarian and family history was non-contributory.

On clinical examination, the patient was found to be drowsy, but arousable. Her vitals were stable. Pupils were of normal size and reacting. There was no cranial nerve palsy, motor or sensory deficit. Meningeal signs were absent and reflexes were normal. Next morning, the patient recovered from postictal drowsiness. During measurement of blood

pressure, the patient developed spasmodic contraction of the hand. So, the patient was examined for Trousseau's sign which was found to be positive. Chvostek's sign was also positive. General and systemic examination including neurological findings were otherwise non-contributory.

Laboratory investigations revealed: Total leucocyte count: 4,600/mm³, differential leucocyte count:- neutrophils: 74%, lymphocytes: 22%, eosinophils: 2%, monocytes: 2%, basophils: 0%, fasting plasma glucose: 102 mg/dl, blood urea: 24 mg/dl, serum creatinine: 0.9 mg/dl, total bilirubin: 1.0 mg/dl, aspartate transaminase: 39 IU/L, alanine transaminase: 42 IU/L, alkaline phosphatase: 120 IU/L, total protein: 7.3 g/dl, serum albumin: 4.0 g/dl, serum globulin: 3.3 g/dl, serum sodium: 136 meq/l (normal value: 135 - 145 meq/l), serum potassium: 2.0 meq/l; (normal value: 3.5 - 5.0 meq/l), serum calcium: 6.6 mg/dl (normal value: 8.5 - 10.2 mg/dl), serum magnesium: 2.1 mg/dl (normal value: 1.7 - 2.3 mg/dl), serum phosphate: 3.3 mg/dl (normal value: 2.5 - 4.5 mg/dl), TSH: 2.34 mIU/L, 25 hydroxy vitamin D: 32 ng/ml (normal value: > 30 ng/ml), serum iPTH: 48 ng/l (normal value: 10 - 65 ng/l), 24 hours urinary potassium: 35 mmol/day (normal value: < 15 mmol/day, 24 hours urinary calcium: 923.5 mg/24 hours (normal value: 100 - 300 mg/24 hours), plasma renin: 35.2 ng/ml/hour (normal value: 0.6 - 4.3 ng/ml/hour), plasma aldosterone: 295 pmol/l (normal value: 55 - 250 pmol/l). Arterial blood gas analysis:- pH: 7.63, Pa O₂: 79 mmHg, Pa CO₂: 41 mmHg, HCO₃⁻: 39 mmol/l.

MRI brain was normal, and EEG was suggestive of seizure disorder.

On the basis of hypokalaemia, metabolic alkalosis, hypocalcaemia, hypercalciuria, normal blood pressure,

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hyperreninaemia and hyperaldosteronism, the patient was diagnosed as a case of adult variant of Bartter syndrome. She was treated with calcium gluconate infusion and oral potassium chloride syrup along with antiepileptic drug. After 72 hours, the patient stabilised and there was no further seizure. On 4th day, serum potassium was 3.5 meq/l and serum calcium was 8.0 mg/dl. Spironolactone 300 mg/day, indomethacin 75 mg/day and oral calcium 500 mg thrice daily were added before discharge on 5th day.

Discussion

Bartter syndrome is an autosomal recessive renal tubular disorder characterised by normal blood pressure, hypokalaemia, metabolic alkalosis, hyperreninaemia, secondary hyperaldosteronism, and usually high level of prostaglandin E2 (PGE2). Prevalence of Bartter syndrome is 1 in 1,000,000³. The low prevalence may be in part due to lack of diagnosis because of prenatal or neonatal death.

The primary defect is an impairment of one of the transporters involved in sodium chloride absorption in the loop of Henle and distal convoluted tubule^{1,4}. It produces a clinical disorder similar to that with chronic loop diuretic ingestion.

The underlying pathology results in excessive urinary losses of sodium and chloride leading to volume depletion followed by activation of renin-angiotensin-aldosterone system⁵.

Excessive distal sodium delivery increases distal tubular sodium reabsorption and exchange with electrically equivalent potassium or hydrogen ion which in turn, promotes hypokalaemia. At the same time, this promotes inadequate exchange of bicarbonate. Combined hypokalaemia and excessive bicarbonate retention lead to metabolic alkalosis.

Persons with Bartter syndrome also have hypercalciuria⁶. Normally, reabsorption of negative chloride ions promotes a positive voltage in the lumen, driving paracellular positive calcium and magnesium absorption. Dysfunction of chloride transporters in the loop of Henle prevents urine calcium reabsorption leading to hypercalciuria. Excessive urine calcium excretion may be one factor responsible for nephrocalcinosis observed in a few patients.

Along with volume depletion, renal release of prostaglandins (PGE2) result in relatively normal blood pressure in spite of secondary hyperaldosteronism⁷.

Bartter syndrome is classified into 5 types with the following genetic defects^{8,9,10}:-

1. Type I: Defective function of Na-K-2Cl (NKCC2, encoded

by *SLC12A1*) co-transporter.

2. Type II: Defective function of luminal potassium channel (ROMK encoded by *KCNJ1*).
3. Type III: Defective function of basolateral chloride channel (ClC-Kb, encoded by *CLCNKB*).
4. Type IV and IVb: Defective function of ClC-Ka and ClC-Kb (single mutation affecting Barttin subunit in IV and double mutation affecting both channels in IVb).
5. Type V: Gain of function mutation of calcium sensing receptor (CaSR).

Type I, II, IV and IVb Bartter syndrome present in antenatal period and the patients usually die in neonatal period. Type III and type V Bartter syndrome are less severe and present in adults with hypokalaemia, metabolic alkalosis, and hypercalciuria.

Type V Bartter syndrome is also called autosomal dominant hypocalcaemia (ADH). It is caused by gain of function mutation of calcium sensing receptor (CaSR) gene (ADH type 1) or gain of functions mutations of G alpha 11, a key mediator of CaSR signalling (ADH type 2)¹¹⁻¹³. Activation of CaSR blunts potassium efflux through ROMK channel and also may reduce activity of Na-K-2Cl co-transporter. Sporadic *de novo* mutation of CaSR have also been reported. Most of the patients are asymptomatic although few patients present with seizure¹⁴. The biochemical features include: serum calcium: 6 - 8 mg/dl, sometimes as low as 5 mg/dl, inappropriately normal serum PTH and high or high normal urinary calcium excretion. Severe hypocalcaemia with resultant seizure along with other relevant biochemical picture in an adult patient probably leads to the diagnosis of type V Bartter syndrome in this patient although genetic study could not be done.

Non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin production and potassium sparing diuretics which block sodium-potassium exchange in distal tubule are the main options of therapy. Potassium and calcium supplementation are the other modalities of treatment. Our patient responded to this combined therapeutic approach along with antiepileptic drug.

Conclusion

Adult onset Bartter syndrome itself is a rare entity. Its presentation with seizure due to hypocalcaemia is even rarer which makes the case reportable. The take home message is to look for hypokalaemia and metabolic alkalosis in a patient with symptomatic or asymptomatic hypocalcaemia, otherwise we may miss the diagnosis of a rare disease like Bartter syndrome.

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