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Neonatal Bartter syndrome: A case report from Northern India

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Abstract. *Bartter Syndrome is a rare genetic disorder affecting the renal tubular system causing a decreased absorption of sodium and chloride in the thick ascending limb of the Henle loop. Most children present in infancy with complaints of polyuria, polydipsia, vomiting, constipation and failure to thrive while older children present with recurrent episodes of dehydration, muscle weakness and cramps. The present study aimed to demonstrate a case of Bartter syndrome presenting as acute gastroenteritis.*

Key words: *Bartter syndrome, child, gastroenteritis.*

Conflict of interest statement. The authors declare no competing interest.

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Синдром Барттера новонароджених: клінічний випадок з Північної Індії

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Резюме. *Синдром Барттера – це рідкісне генетичне захворювання, яке пошкоджує систему ниркових канальців, що викликає зниження абсорбції натрію та хлориду в товстій висхідній частині петлі Генле. Синдром Барттера у більшості новонароджених дітей проявляється поліурією, полідипсією, блювотою, закрепом та відсталістю розвитку, тоді як у дітей старшого віку рецедивуючими епізодами зневоднення, м'язовою слабкістю та судомами. Метою цієї роботи було продемонструвати читачам випадок синдрому Барттера, який дебютував гострим гастроентеритом.*

Ключові слова: *синдром Барттера, дитина, гастроентерит.*

Introduction. Bartter syndrome (BS) is a rare genetic disorder affecting the renal tubular system causing a decreased absorption of sodium and chloride in the thick ascending limb of the Henle loop. Mutations in various genes lead to defective synthesis of transporter and channels leading to increased secretion of sodium, chloride and prostaglandins in urine resulting in salt wasting, hypokalaemia, metabolic alkalosis, hyperaldosteronism, hyperreninemia and normal blood pressure [1].

Most children present in infancy with complaints of polyuria, polydipsia, vomiting, constipation and failure to thrive while older children present with recurrent episodes of dehydration, muscle weakness and cramps [2].

Mild, nonspecific symptoms, signs, and a lack of awareness for BS are to blame for the delay in diagnosis [3]. However, early detection and treatment improve the prognosis and prevent a variety of complications. Prenatal diagnosis could be useful for initiating appropriate management, but studies on amniotic fluid to establish the diagnosis yielded contradictory results. The presence of clinical features and persisting hypokalemic metabolic alkalosis should raise the suspicion of BS and further diagnostic workup should be performed which includes: Evaluation of medical history including polyhydramnios, premature birth, growth failure, and family history; Biochemical parameters: serum electrolytes (sodium, chloride, potassium, calcium, magnesium), acid-base status, renin, aldosterone, creatinine, fractional excretion of chloride, and urinary calcium-creatinine ratio. Renal ultrasound to detect medullary nephrocalcinosis and/or kidney stones should also be performed. Confirming the clinical diagnosis of BS employing genetic analysis whenever possible is recommended (grade B, moderate recommendation) [4].

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Case Report. A 5 months old male child born of non-consanguineous marriage presented with complaints of 2-3 episodes of vomiting and lethargy, there is a history of similar complaints at age of 4 months for which hospitalization was required at a local nursing home. The baby was the first issue born by normal vaginal delivery at 39 wks of gestation with a weight of 3.5 kg and an uneventful perinatal course, there is a history of stillborn birth in a previous pregnancy. Antenatal ultrasound was normal.

On examination there is failure to thrive (Wt=4.5kg, length = 61cm, head circumference=39cm), developmental milestones were normal. At the time of presentation moderate dehydration was present and the patient was treated conservatively with intravenous fluids, anti-emetics and antibiotics.

Arterial blood gas evaluation showed metabolic alkalosis (pH = 7.8 bicarbonate =37.7mmol/L) was found while biochemical evaluations revealed hyponatremia (Na=110.7mmol/L), hypokalaemia (K=2.71mmol/L), hypocalcemia (Ca=0.63mmol/l) and hypochloremia (Cl= 68mmol/l) and U wave was noticed on ECG. Magnesium levels, kidney function tests, TLC, haemoglobin and platelet count were normal and urine output was noted to be 4.2 ml/kg/hr. Despite treatment with intravenous ringer lactate, H2-blockers, anti-emetics hydration status and general condition of patient improved but metabolic alkalosis and hypokalaemia persisted. At this stage due to the child's normotensive status and persistent hypokalaemia in absence of any relevant drug history, such as chronic loop diuretic use an inherited tubular disorder such as BS/Gitelman Syndrome was considered after ruling out the sub-acute obstruction and underlying gastroesophageal reflux.

Urine analysis revealed low osmolarity (136mOsm/kgH2O) with increased excretion of sodium(302.4meq/l) and chloride (356.1mEq/L) in 24 hrs urine, while serum aldosterone (83.1ng/dl) and serum renin (54.79ng/ml/hr) levels were also increased. A diagnosis of neonatal BS was made based on clinical history, examination and investigations. Due to the rarity of the condition, low awareness among treating physicians and rural areas it was the first case of BS reported at our institute. The patient was then started with oral potassium, sodium supplements and ibuprofen at a dose of 30mg/kg/day. Attendants were counseled regarding the genetic nature of the disease and advised genetic and mutational analysis of child at specialized center due to lack of specialized laboratory. After a month of the follow-up period, the child felt fine. BERA examination and USG of the abdomen revealed no significant abnormality. The patient's biochemical data are presented in Table 1.

Table 1

The patient's biochemical data at presentation and after the treatment

Biochemical parameter	Reference value	Parameters at presentation	Parameters after treatment
S. Sodium	135-145meq/l	110.7	142.3
S. Potassium	3.5-5.5meq/l	2.71	4.72
S. Calcium (ionised)	1.05-1.35mmol/l	0.63	1.26
S. Magnesium	1.7-2.8mg/dl	2.2	—
S. Chloride	96-108meq/l	68	75
Blood pH	7.35-7.45	7.8	7.56
Urinary osmolality	300-900mosm/kgh2o	136	—
Urinary potassium	20-125meq/l	90.3	—
Urinary chloride	2-10meq/l	27.6	—
Urinary calcium	50-150mg/kg/24hr	41	—
Urinary sodium	40-220meq/l	302.4	—

Discussion. BS is a rare autosomal disorder affecting 1 in 1,000,000 children [5], basic pathophysiology involves defective resorption of Na^+ and Cl^- due to mutation of ion channels and transporters leading to excessive loss of electrolytes in the urine. Increased delivery of Na^+ and Cl^- to the distal part of the nephron leads to salt wasting, hypokalaemia, polyuria, volume contraction and stimulation of the renin-angiotensin-aldosterone axis [6]. BS has various subtypes that have been reported depending upon phenotype and genotype (Table 2) [7, 8].

Table 2

Types of Bartter Syndrome

Disorder	Protein	Gene location	Inheritence
BS 1 (antenatal)	NKCC2	SLC12A1; 15q15-q21.1	AR
BS 2 (antenatal)	Kir1.1 or ROMK 1	KCNJI; 11q24	AR
BS 3 (classic)	Clc-Ka	CLCNKB; 1p36	AR
BS 4 (antenatal with sensorineural deafness)	4a- ClC-K 4b-ClC-Ka	BSND Deletion; 1p-31 ClCNKA-CLCNKB; 1p-36	AR AR
BS 5	CaSR	CASR; 3q13	AD

Type 1, 2 and 4 mostly presents during infancy and have more severe symptoms while classic BS manifests in childhood and has milder symptoms, pregnancy is complicated by polyhydramnios without gross congenital anomalies and spontaneous premature delivery. Presenting complaints include polyuria, failure to thrive, dysmorphism in form of triangular facies with prominent ears, vomiting, drooping mouth, strabismus, sensorineural deafness, convulsions and increased susceptibility to infection. Childhood presentation occurs around 2 years of age and includes polyuria, polydipsia, vomiting, salt craving, the tendency for dehydration, lethargy, developmental delay and failure to thrive [9].

Hypokalemia is a common clinical manifestation of vomiting. If it is difficult to correct after potassium supplementation therapy, it should be considered the primary cause of vomiting. Further investigation, in this case, revealed a significantly high level of urinary potassium, indicating renal potassium loss. If both blood pressure and potassium excretion from the kidneys increase, the primary disease is thought to be caused by an excess of mineralocorticoids, such as a peribulbar cell tumor, renal artery stenosis leading to primary renal failure, primary aldosteronism, Cushing's syndrome, or Liddle syndrome. In the absence of hypertension and low blood volume, diseases caused by excessive sodium transport from the distal nephron, such as diuretic use, BS, or Gitelman syndrome, should be considered [10]. In patients with hypokalemia, it is also critical to check for the presence of alkalosis or acidosis based on blood pH. Cushing's syndrome should be considered first in patients with renal potassium loss and metabolic alkalosis; this condition is characterized by hypertension and hypercorticism-like symptoms such as central obesity, elevated blood cortisol, and circadian rhythm disorder [11].

BS must be differentiated from non-renal causes of chloride loss e.g., chronic vomiting, chloride losing diarrhea, laxative abuse, dietary deficiency and cystic fibrosis. Other renal causes which may mimic BS includes Gitelman Syndrome, Sjogren Syndrome, Kearns-Sayre syndrome, Dent's Disease and chronic administration of diuretics [9].

Long-term treatment consists of potassium supplements (1-3meq/kg/day), prostaglandin inhibitors (indomethacin(2-3mg/kg/day) or ibuprofen (30mg/kg/day) in which the former is preferred) and potassium-sparing diuretics, such as spironolactone, eplerenone, or amiloride at later stages. Cyclooxygenase inhibitors inhibit increased levels of prostaglandins which causes fever and polyuria. ACE inhibitors, ARBs have been used to prevent loss of potassium in urine and prevention of proteinuria [12]. The use of rofecoxib, a COX2 selective inhibitor, suppressed hyperreninemia to the same level as indomethacin, albeit with fewer gastric side effects although the occurrence of cardiovascular side-effects limits its long term use [13]. Acetazolamide has recently been used successfully in children with BS [14]. Despite the treatment, hypokalemia usually persists due to aldosterone-mediated electrolyte derangements, but the low levels of serum potassium will be less pronounced than at the time of diagnosis [15].

Long-term complications include growth failure, chronic kidney disease, cardiac arrhythmias, QT prolongation and chronic side effects of prostaglandin synthesis inhibitors which include vomiting, abdominal pain, peptic ulcer and renal toxicity [16].

Conclusions. Due to low prevalence and awareness among clinicians, children with BS are frequently misdiagnosed, resulting in a delay in treatment initiation. When treating children who complain of recurrent vomiting, failure to thrive, lethargy, constipation, dehydration that does not respond to treatment, a high index of suspicion for BS should be maintained and proper investigations should be performed to rule out close mimickers. Although it is uncommon, BS should be considered in people who have hypokalemia, metabolic alkalosis, increased urinary potassium loss, and a poor response to potassium replacement.

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Authors Contributions.

Astitva Singh and Nishant Sharma: data collection, the study design; writing and submitting the manuscript and idea owner of this study;

Prachi Agarwal and Bolledu Swaroop Anand: data collection;

Akshay Shukla and Nishant Sharma: the manuscript editing and approval of the final draft.

References:

1. *Kumar PS, Deenadayalan M, Janakiraman L, Vijayakumar M.* Neonatal Bartter syndrome. Indian Pediatr. 2006;43(8):735-7.
2. *Choudhary D, Anand VR, Sachdev CP, Gulati D.* Hypotonia an unusual childhood presentation of Bartter syndrome. Int J Contemp Pediatr 2017;4:2237-2238. doi: 10.18203/2349-3291.ijcp20174766.
3. *Mali LP, Meena SS, Baniwal M.* Classical Bartter syndrome–A case report. Indian journal of medical specialties. 2015;6(3):116-118. doi: 10.1016/j.injms.2015.06.004
4. *Konrad M, Nijenhuis T, Ariceta G, Bertholet-Thomas A, Calo LA, Capasso G, et al.* Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations

from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders. Kidney Int. 2021;99(2):324-335. doi: 10.1016/j.kint.2020.10.035.

5. *Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, et al.* Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet. 2008;40(5):592-599. doi: 10.1038/ng.118.
6. *Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo S.* Harrison's Principles of Internal Medicine, vol. 2. 18th ed. USA: The McGraw Hill Companies; 2012. p. 2360–2361.
7. *Bartter FC, Pronove P, Gill JR Jr, MacCardle RC.* Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. 1962. J Am Soc Nephrol. 1998;9(3):516-28. doi: 10.1681/ASN.V93516.
8. *Proesmans W.* Threading through the mizmaze of Bartter syndrome. Pediatr Nephrol. 2006;21(7):896-902. doi: 10.1007/s00467-006-0113-7.
9. *Sinha A, Bagga A.* Tubular Disorders. In Srivastav RN, Bagga A, editor. Pediatric Nephrology. 6th ed. New Delhi: JAYPEE; 2016, p. 312-316.
10. *Wu X, Yang G, Chen S, Tang M, Jian S, Chen F, Wu X.* Bartter syndrome with long-term follow-up: a case report. J Int Med Res. 2020;48(8):300060520947876. doi: 10.1177/0300060520947876.
11. *Abcar AC, Kujubu DA.* Evaluation of hypertension with hypokalemia. Perm J. 2009;13(1):73-76.
12. *Cunha TDS, Heilberg IP.* Bartter syndrome: causes, diagnosis, and treatment. Int J Nephrol Renovasc Dis. 2018;11:291-301. doi:10.2147/IJNRD.S155397.
13. *Nascimento CL, Garcia CL, Schvartsman BG, Vaisbich MH.* Treatment of Bartter syndrome. Unsolved issue. J Pediatr (Rio J). 2014;90(5):512-7. doi: 10.1016/j.jped.2014.01.012.
14. *Mazaheri M, Assadi F, Sadeghi-Bojd S.* Adjunctive acetazolamide therapy for the treatment of Bartter syndrome. Int Urol Nephrol. 2020;52(1):121-128. doi: 10.1007/s11255-019-02351-7.
15. *Vaisbich MH, Fujimura MD, Koch VH.* Bartter syndrome: benefits and side effects of long-term treatment. Pediatr Nephrol. 2004;19(8):858-63. doi: 10.1007/s00467-004-1527-8.
16. *Bhat YR, Vinayaka G, Sreelakshmi K.* Antenatal bartter syndrome: a review. Int J Pediatr. 2012;2012:857136. doi: 10.1155/2012/857136.