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Case Report

From electrolyte disturbance to diagnosis: pseudo-Bartter syndrome in cystic fibrosis

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ABSTRACT

Pseudo-Bartter syndrome (PBS) is an uncommon but well recognized extraintestinal manifestation of cystic fibrosis (CF), characterized by hypochloremic, hypokalemic metabolic alkalosis with hyponatremia and volume loss secondary to excessive salt loss because of CFTR dysfunction. It mimics Bartter syndrome biochemically but the primary pathology is extrarenal salt loss, and not a congenital renal tubular defect. In regions without routine newborn screening, PBS may be the initial presentation and mimic inherited renal tubular disorders, thus delaying diagnosis. A 4-month-old male infant presented with recurrent vomiting, lethargy poor feeding and severe hypokalemic hypochloremic metabolic alkalosis. Despite rehydration and correction of electrolyte imbalance, he experienced recurrent episodes of similar nature. Bartter syndrome was initially suspected because of persistent electrolyte abnormalities and elevated renin and aldosterone levels. However, intermittent chest infections and poor weight gain prompted further evaluation, where a possibility of CF was considered. Whole exome sequencing identified pathogenic CFTR variant, including the F508del and an elevated sweat chloride concentration (78 mmol/l). The child was started on pancreatic enzyme replacement, nutritional supplementation, airway clearance therapy, and electrolyte supplementation, which showed marked clinical improvement on follow up. CF should be considered in any infant presenting with recurrent hypochloremic, hypokalemic metabolic alkalosis, even in the absence of classical respiratory symptoms. Recognition of PBS as a potential presentation of CF can facilitate early diagnosis, helping to bridge the diagnostic gap created by the absence of universal NBS. Early recognition of PBS facilitates timely diagnosis and initiation of disease-specific therapy which is crucial for improving long-term outcomes.

Keywords: Cystic fibrosis, Pseudo Bartter syndrome, CFTR, Sweat chloride, electrolyte imbalance, Salt losers

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive multisystem disorder caused by pathogenic variants in the *CFTR* gene (CF transmembrane conductance regulator) located on chromosome 7 responsible of transport of chloride ions across the apical membrane of epithelial cells and other anions such as bicarbonate and thiocyanate.[1] Until now, more than ≥2000 different mutations have been reported to cause CF among which F508del being the commonest, affecting about two-thirds of CF patients worldwide.[2]

India is said to have the greatest number of undiagnosed CF patients, dismissing popular belief that it is extremely rare. Although the exact prevalence of CF among Indians is unknown, it is estimated to be around 1:40,000 to 1:100,000.[3] The frequency of the F508del mutation among Indian patients is reported to be 19-34%.[4]

Although pulmonary disease and pancreatic insufficiency are the classical manifestations, the clinical spectrum is heterogeneous, and many patients may initially present with extrapulmonary features.[5]

One such manifestation is PBS, characterized by hypochloremic, hypokalemic metabolic alkalosis resulting due to excessive extrarenal salt loss through sweat. PBS has been reported in approximately 12-16% of children with CF, particularly during infancy and in hot climates.[6] Excessive sweating, fever, vomiting, diarrhea, or inadequate salt intake may precipitate episodes of dehydration and electrolyte imbalance.[5] Because these biochemical abnormalities closely resemble Bartter syndrome, diagnosis may be delayed, especially when respiratory symptoms are absent or minimal.

In India, where newborn screening for CF is not universally implemented and awareness remains limited, infants presenting primarily with electrolyte disturbances may undergo extensive evaluation for renal tubular disorders before CF is considered.[7] We report an infant with recurrent PBS in whom the diagnosis of CF was missed initially and established only after re-evaluation of history and confirmation by genetic testing.

CASE REPORT

A 4-month-old male infant presented with a short history of recurrent vomiting, poor oral intake, and lethargy. He was second child born to a consanguineous marriage delivered at term, with an uneventful antenatal, perinatal, and neonatal period. Newborn screening had not been performed. His elder sibling was healthy.

On examination, the infant was lethargic but hemodynamically stable with normal blood pressure and features of mild dehydration. At 4 months, his weight was 3.5 kg and length was 60 cm suggesting failure to thrive. Rest of his examination was normal.

Initial investigations revealed severe hypokalemic hypochloremic metabolic alkalosis with hyponatremia. Serum sodium was 126 mEq/l, potassium 1.8 mEq/l, chloride 80.6 mEq/l, ionized calcium 1.1 mmol/l, magnesium 1.8 mEq/l, bicarbonate 47.3 mEq/l, arterial pH 7.68, and base excess +29.2. Despite intravenous fluid resuscitation and electrolyte replacement, persistent metabolic alkalosis prompted urinary electrolyte evaluation. Urinary sodium was 12 mEq/l, potassium 23 mEq/l, chloride 17 mEq/l, urinary calcium 6.8 mg/dl, urinary calcium-creatinine ratio 127 mg/g, and urinary magnesium 25 mg/dl.

The child improved following intravenous therapy, potassium supplementation and was discharged. Soon after, he was readmitted twice with recurrent episodes of vomiting associated with similar biochemical abnormalities. Between these admissions, he also had recurrent episodes of fast breathing being managed conservatively in the outpatient department with no history of persistent productive cough, or hospitalization for respiratory illness.

Recurrent episodes of hypokalemic metabolic alkalosis raised the possibility of Bartter syndrome, however there was no history of polyuria. Plasma renin and serum aldosterone levels were borderline elevated. Audiological evaluation was normal. Ultrasonography of abdomen was unremarkable. However, considering recurrent episodes of dehydration with failure to thrive, and intermittent respiratory symptoms, CF was also considered as a rare possibility. Whole-exome sequencing demonstrated compound heterozygous pathogenic variants in the *CFTR* gene, including c.1521_1523delCTT (F508del) and 3'splice site defect. Sweat chloride was measured to be 78 mmol/L, thus confirming the diagnosis of CF.

The patient was started on pancreatic enzyme replacement therapy, fat-soluble vitamin supplementation, medium-chain triglyceride oil, oral potassium supplementation, inhaled salbutamol, nebulized 3% normal saline, inhaled budesonide, chest physiotherapy, and antibiotics as required.

On follow-up, the child demonstrated good compliance with therapy, improved nutritional status, and no further hospital admissions for severe electrolyte disturbances.

Table 1: Difference between Bartter syndrome and PBS.

Features	Bartter syndrome	PBS
Pathophysiology	Primary renal salt wasting due to defective tubular ion transport	Extrarenal salt loss
Genetic basis	Present (mutations in genes such as SLC12A1, KCNJ1, CLCNKB, BSND etc.)	Absent; underlying disease may be genetic (e.g. CF due to CFTR mutation), but renal tubules are structurally normal
Urine chloride	Inappropriately high (>20 mmol/l)	Usually low (<20 mmol/l) because kidneys conserve chloride in response to extrarenal losses
Urine calcium	Hypercalciuria common (especially antenatal forms)	Usually, normal
Nephrocalcinosis	Common	Uncommon
Polyuria/ polydipsia	Common	Usually, absent
Sweat chloride test	Normal	Elevated in CF-related PBS

Continued.

Features	Bartter syndrome	PBS
Treatment	Lifelong electrolyte supplementation, NSAIDS, indomethacin, potassium-sparing agents, and targeted management	Correction of dehydration and electrolyte imbalance with treatment of the underlying cause (e.g. CF management and salt supplementation)
Prognosis	Chronic disorder requiring long-term follow-up	Generally, resolves after correction of the underlying cause, although recurrence may occur if salt losses persist

DISCUSSION

PBS is a potentially life-threatening but reversible complication of CF. Unlike classical Bartter syndrome, the electrolyte disturbance results from excessive extrarenal salt loss rather than a primary renal tubular defect.[3] Consequently, correction of electrolyte abnormalities without recognition of the underlying diagnosis often leads to recurrent episodes and delayed institution of disease-specific therapy as in our case.

Our patient initially fulfilled many biochemical criteria suggestive of Bartter syndrome, including severe hypokalemic metabolic alkalosis, hyponatremia, and borderline activation of the renin-angiotensin-aldosterone system. However, there was no persistent polyuria, nephrocalcinosis, hearing impairment, or sustained renal tubular dysfunction.

The diagnosis of CF was ultimately established by elevated sweat chloride and identification of pathogenic *CFTR* variants. Early recognition allowed initiation of nutritional support, pancreatic enzyme replacement, airway clearance therapy, and preventive respiratory care, leading to favourable clinical outcome.

Pathophysiology of PBS in CF

The CFTR protein regulates chloride transport across epithelial surfaces. In sweat glands, defective CFTR function prevents normal reabsorption of sodium and chloride from sweat, resulting in excessive salt loss.[7] During hot weather, fever, or dehydration, substantial sodium chloride depletion occurs.

Extracellular volume contraction activates the renin-angiotensin-aldosterone system, increasing distal sodium reabsorption in exchange for potassium and hydrogen ion secretion. This leads to hypokalemia and metabolic alkalosis. Unlike Bartter syndrome, renal tubular transport mechanisms remain intrinsically normal; therefore, the disorder is secondary to extrarenal electrolyte loss.

The most common differential of PBS is Bartter syndrome as both can have metabolic alkalosis, hypokalemia, hypochloremia, increased aldosterone and renin level and recurrent dehydration. Consequently, infants with CF may initially receive a diagnosis of Bartter syndrome, particularly when respiratory manifestations are absent.

The differentiation between Bartter syndrome and PBS is clinically important because both present with hypokalemic hypochloremic metabolic alkalosis; however, the underlying mechanisms, urinary electrolyte profile, associated clinical features, and management differ substantially (Table 1). Our case had hypokalemic hypochloremic metabolic alkalosis but urinary electrolyte profile raised the possibility of PBS. Urine chloride will be less (<20 mEq/day) in PBS while its level increased (>20 mEq/day) in Bartter syndrome as was seen in our case.[6] Patients with CF have excessive salt loss in sweat, positive sweat chloride testing, and pathogenic *CFTR* mutations, whereas patients with Bartter syndrome have pathogenic variants involving renal tubular ion transport proteins.

PBS has been described worldwide as the initial presentation of CF, particularly during infancy.[8] Most reported infants, as also in our case, present between 2 and 12 months of age with vomiting, lethargy, dehydration, and severe hypochloremic metabolic alkalosis.[9] Persistent vomiting can be an important diagnostic yield.[10] In several reports, diagnosis was delayed because respiratory symptoms were absent or mild, leading initially to consideration of Bartter syndrome or gastrointestinal disorders.[11,12]

Hot climates increase insensible water and salt losses through sweating, predisposing infants with CF to recurrent episodes of PBS. This is particularly relevant in India, where prolonged summers, delayed recognition of CF, and lack of universal newborn screening contribute to diagnostic delay.

CONCLUSION

PBS may be the first manifestation of CF during infancy and can closely resemble Bartter syndrome. In countries without universal newborn screening, recurrent episodes of hypochloremic hypokalemic metabolic alkalosis should prompt evaluation for CF even in the absence of significant pulmonary disease. Early diagnosis enables timely initiation of disease-specific therapy, prevents recurrent hospitalizations, and improves long-term outcomes.

Recognition of PBS as a possible initial manifestation of CF is crucial for pediatricians, nephrologists, and emergency physicians. Sweat chloride testing should be considered in any infant with unexplained recurrent hypochloremic metabolic alkalosis, especially when accompanied by poor weight gain or recurrent respiratory symptoms.

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