Bol Med Hosp Infant Mex. 2016;73(5):331–334

Boletín Médico del
Hospital Infantil de México

www.elsevier.es/bmhim

CLINICAL CASE

Pseudo-Bartter syndrome as manifestation of cystic fibrosis with DF508 mutation☆

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Received 26 January 2016; accepted 18 April 2016
Available online 6 December 2017

KEYWORDS
Pseudo-Bartter syndrome;
Cystic fibrosis;
Hyponatremic dehydration;
Metabolic alkalosis;
DF508

Abstract
Background: Pseudo Bartter syndrome (PBS) is defined as hypokalaemic hypochloraemic metabolic alkalosis in the absence of renal tubular pathology. Children with cystic fibrosis (CF) are at risk of developing electrolyte abnormalities and even PBS may occur.
Case report: A 5-month-old female infant with a history of two events of dehydration with vomit, refusal to eat, chronic cough, polyuria, malnutrition, metabolic alkalosis, hypokalemia, hyponatremia, hypochloremia and acute renal failure. Chronic cough study was performed, discarding pulmonary tuberculosis, gastroesophageal reflux disease and impaired swallowing. PBS was diagnosed due to hypokalaemic hypochloraemic metabolic alkalosis in the absence of renal tubular pathology. CF was corroborated by electrolytes in sweat and through molecular analysis of the delta F508 mutation. This is one of the few reported cases linking PBS and this mutation.
Conclusions: In patients with hyponatremic dehydration episodes with hypokalaemic hypochloraemic metabolic alkalosis, PBS should be considered as differential diagnosis. CF could be presented as PBS, mainly in patients younger than 2 years.

☆ Please cite this article as: Galaviz-Ballesteros MdJ, Acosta-Rodríguez-Bueno CP, Consuelo-Sánchez A, Franco-Álvarez I, Olalla-Mera OI, Vázquez-Frias R. Síndrome de pseudo-Bartter como presentación de fibrosis quística con mutación DF508. Bol Med Hosp Infant Mex. 2016;73:331–334.

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https://doi.org/10.1016/j.bmhime.2017.11.001

PALABRAS CLAVE
Síndrome pseudo-Bartter;
Fibrosis quística;
Deshidratación hiponatrémica;
Alcalosis metabólica;
DF508

Síndrome de pseudo-Bartter como presentación de fibrosis quística con mutación DF508

Resumen
Introducción: El síndrome de pseudo-Bartter (SPB) se define como una alcalosis metabólica hipoclorémica con hipocaliemia en ausencia de tubulopatía. Los pacientes con fibrosis quística (FQ), al presentar alteraciones hidrolectrolíticas, pueden llegar a presentarlo.
Caso clínico: Lactante femenino con antecedente de 2 eventos de deshidratación. Se presenta a los 5 meses de vida con vómito, rechazo al alimento, tos crónica, poliuria, desnutrición, alcalosis metabólica, hipocaliemia, hiponatremia, hipocloremia y falla renal aguda. Se realizó estudio de tos crónica, con lo que se descartó tuberculosis pulmonar, enfermedad por reflujo gastroesofágico y alteración en la mecánica de la deglución. Ante la alcalosis metabólica sin tubulopatía se diagnosticó SPB; por la historia de desnutrición y tos crónica se sospechó de FQ, la cual se corroboró con medición de electrolitos en sudor y mediante análisis molecular de la mutación delta F508. Este es uno de los pocos casos reportados con SPB y esta mutación.
Conclusiones: En pacientes con cuadros repetitivos de deshidratación hiponatrémica con alcalosis metabólica hipoclorémica o SPB debe considerarse como diagnóstico diferencial FQ. La FQ pude presentarse como SPB, principalmente en pacientes menores de 2 años.

1. Introduction

The pseudo-Bartter's syndrome (PBS) is defined as a hypochloremic metabolic alkalosis with hypokalemia in the absence of tubulopathy[1] that can occur in all ages, mostly in the neonatal period.[2] The difference between PBS and Bartter syndrome is the absence urinary chlorine loss. Patients with cystic fibrosis (CF) may present hydroelectrolytic alterations, who may develop PBS upon the excessive loss of fluids and electrolytes.

CF is an autosomal recessive disease caused by mutations in the gene that encodes the transmembrane regulatory protein (CFTR). Clinically, it is characterized by chronic suppurative lung disease and exocrine pancreatic dysfunction.[3] In children, CF typically emerges as a combination of failure to thrive, steatorrhea, respiratory symptoms, and less frequently as an acid-base and electrolyte imbalance.[4] The diagnosis should be suspected by the typical clinical presentation (lung disease, pancreatic insufficiency) and confirmed with the determination of chlorine in sweat (> 60 mEq/l) and the presence of two mutated alleles of the gene that encodes the CFTR protein.[3]

This article presents the case of a female infant who showed PBS as a manifestation of CF.

2. Clinical case

The patient is a 5-month-old female infant product of the fourth pregnancy after one miscarriage and three births—the first corresponds to a healthy sister, the second died after two days of life with multiple malformations. She presented gastrointestinal disturbances, gastroschisis, polydactyly, cleft palate, and heart disease, but a symptomatic diagnosis was not possible to integrate. The mother had a normoevolutive pregnancy and normal childbirth. At the time of birth, the patient presented a weight of 3.4 kg, a length of 50 cm, and an Apgar score of 8; she was exclusively breastfed. She presented two previous episodes of dehydration at three and four months of age, respectively, triggered by vomiting and poor intake, developing a water-electrolyte imbalance for which she required hospitalization and parenteral hydration. A probable diagnosis of Bartter syndrome was integrated based on hyponatremia, hypokalemia, and metabolic alkalosis. She was treated with ibuprofen and indomethacin.

The patient was hospitalized at five months of age due to a third episode of dehydration, characterized by vomiting of 24 hours of evolution (gastric content one time) and the refusal to feed. She also had a 5-month evolution history of cough, which was intermittent, without predominance of schedule, dry, cyanosis with coughing spasms, for which she received intermittent treatment with nebulization and multiple antibiotic schemes. The patient presented regular bowel movements with pasty evacuations from one to three times per day with no mucus or blood, and without steatorrhea or diarrhea. Polyuria and malnutrition were also present—with a weight of 5.18 kg and a length of 63.4 cm. According to the Centers for Disease Control and Prevention (CDC) tables, she presented a weight-for-age of 69.5%, height-for-age of 95.8%, and weight-for-height of 77.3%. Dehydration was clinically diagnosed.

Blood tests revealed metabolic alkalosis (pH 7.69, PCO_2 41.2 mmHg, PO_2 46.3 mmHg, HCO_3^- 51.9 mmol/l), hypokalemia (K^+ 2.4 mmol/l), hyponatremia (Na^+ 120 mmol/l), and hipocloremia (Cl^- 72 mmol/l). The values of serum creatinine were 1.1 mg/dl, urea nitrogen (BUN) 42 mg/dl, magnesium 2.2 mg/dl, phosphorus 4.1 mg/dl; urinary electrolyte values were sodium 6.0 mmol/l, potassium 30.1 mmol/l, chlorine 26.0 mmol/l, creatinine 87.1 mg/dl, calcium 1.9 (Ca/Cr 0.02), FENa 0.04%. Urinalysis showed pH 5.5, SG 1.012, absence of proteins or erythrocytes,

0-2 leukocytes per field, urine anion gap + 10. Upper gastrointestinal (UGI) series was performed, with proper passage of contrast material from stomach to duodenal arch, excluding pyloric stenosis as a cause of vomiting.

Based on the clinical manifestations of severe dehydration and vomiting, as well as metabolic alkalosis, hypokalemia, hypochloremia and potassium levels in urine greater than other electrolytes despite the reinstatement of initial volume, Bartter syndrome was suspected, particularly type III Bartter syndrome of moderate severity and with hypocalciuria since the symptoms arose after the first month of age, without any prenatal history of polyhydramnios or prematurity. However, the result of plasma renin activity was 2.6 ng/ml/h (reference values: 0.5-5.7 ng/ml/h), and serum aldosterone was 257 pg/ml (reference values: 10 to 300 pg/ml). Thus, the diagnosis of type III Bartter syndrome was unlikely.

Considering a chronic cough and being a patient in contact with people with TB, the following tests were performed: three bacilloscopies in gastric juice, which turned out to be negative; purified protein derivative (PPD) skin test of 7 mm; and X-ray of thorax and UGI series with swallowing mechanics without alterations. A 24-hour esophageal pH test was performed, which turned out negative for gastroesophageal acid reflux. Considering malnutrition, a urine culture was performed, negative. Despite having no macroscopic steatorrhea, a fecal fat test with Sudan stain was performed, which resulted positive (++). Consequently, a 72-hour fat balance study was performed, with a lipid absorption rate of 97.9%.

CF was suspected based on a chronic cough, as part of the phenotypic features of chronic sinopulmonary disease, chronic metabolic alkalosis, salt-losing phenotype and malnutrition as part of nutritional-gastrointestinal syndrome, electrolytes in sweat were analyzed in the laboratory of nutrition and gastroenterology by conductivity. The results showed Cl^- 103.3 mEq/l, Na^+ 82.6 mEq/l, K^+ 20.7 mEq/l. Through the determination of electrolytes in sweat by chlorimetry, Cl^- 69 mmol/l was confirmed, and by conductivity, Cl^- 90 mmol/l. The molecular analysis identified the delta F508 mutation.

The patient received nutritional support, and she initiated supplemental feeding and showed improvement in her weight and height; hence, the treatment with indomethacin and ibuprofen was suspended. To the present date, the patient shows pancreatic sufficiency data, eutrophic without the use of pancreatic enzymes. The study of fecal fat (Sudan stain test) proved negative.

3. Discussion

This case illustrates the unusual presentation of CF manifesting as PBS. The patient had a history of at least three events of dehydration without apparent cause. Thus, it is important to suspect of PBS and CF as a differential diagnosis.

Cystic fibrosis is a disease inherited as an autosomal recessive disorder, which fundamental defect is the regulatory transmembrane protein CFTR decreased or absent function. CFTR is encoded in the long arm of chromosome 7.[2] The clinical presentation is characterized by chronic pulmonary disease, pancreatic deficiency and high levels of electrolytes in sweat. However, in some patients, it is uncommonly present as a depletion of electrolytes, secondary to excessive sweat loss of salts and other fluids. As it can produce a severe depletion of electrolytes and metabolic alkalosis, a Bartter syndrome is mimicked. This is known as pseudo-Bartter syndrome,[1] which is usually present in patients younger than 2 years old.

Metabolic alkalosis in children is rare and can be observed in patients with infantile hypertrophic pyloric stenosis, persistent vomiting, hyperaldosteronism and, to a lesser extent, in Bartter syndrome. In this patient, the latter was the initial approach due to the metabolic alkalosis, hypochloremia, hypokalemia and the potassium levels in urine higher than the other electrolytes, despite the reinstatement of the initial volume. Patients with Bartter and Gitelman syndromes, two congenital defects in the renal tubules, usually arise with problems of constipation, muscle cramps and weakness secondary to chronic hypokalemia, which may be asymptomatic but can be aggravated by the presence of diarrhea or vomiting. Patients with Bartter syndrome begin in early childhood, and the failure to thrive is more serious than in the Gitelman syndrome.[5] The biochemical finding is a hypochloremic metabolic alkalosis with hypokalemia associated with elevated plasma renin and high aldosterone concentration activity. These last two were found within normal ranges in this patient, making the initial diagnosis less likely.

In CF, the excessive loss of sodium, chlorine and water through sweat can condition hyponatremia and hypochloremic dehydration, which results in reduced glomerular filtration and activates the renin-angiotensin-aldosterone system, which in turn leads to an increase in the reabsorption of sodium and potassium without affecting tubular excretion, known as PBS.[4] The hyponatremic and hypochloremic dehydration and metabolic alkalosis are a usual presentation of CF in children. In the literature, the majority of children with CF and PBS are diagnosed around six months of age.[1] Vomiting and loss of appetite are data suggestive of PBS in patients with CF simptoms.[6]

CF should be considered as a differential diagnosis in any child with biochemical manifestations of Bartter syndrome, especially in countries with no screening programs for CF since it can be monosymptomatic for many years.[7] No data about the incidence of PBS related to CF are available, although some reports from Jordan, Turkey and Saudi Arabia indicate a frequency of 12 to 18.3% in the pediatric population, mostly in the first year of life.[1,6,7] It has been reported that PBS usually occurs in during the warm seasons of the year.[4] However, it should be considered that it may also occur in adolescence, with hypertension as a clinical manifestation.[8]

Several mutations in the CFTR gene, such as F311L, D110E, D110H, T3381, N1303K, 2.789 + 5G-A, S13F and 3849 + 40 A/G have been associated with hyponatremic dehydration and metabolic alkalosis.[9–16] The patient described in the present paper showed the DF508 mutation, which is one of the most common mutations associated with CF. Interestingly, it has not been often reported as associated with PBS since it usually is diagnosed early due to its prompt clinical caracteristics.[17]

PBS management consists of hydration and electrolyte imbalance control. It is important to identify other factors that contribute to the metabolic alkalosis, such as classic Bartter and Gitelman syndromes, renin producing tumors, excessive use of diuretics and laxatives, eating disorders, and the obstruction of the gastrointestinal tract.[4] The administration of supplemental electrolytes (Na^+ and ^+K) should continue to maintain normal serum levels. Moreover, the essential improvement in growth curves should be noticed. Fluid management depends on the degree of dehydration and the severity of the electrolyte imbalance, considering serum and urinary electrolytes. Children with CF who live in warm places must be supplemented with sodium chloride during strong heat climate.

In patients with repetitive episodes of hypochloremic metabolic alkalosis with hypokalemia or PBS dehydration, CF should be considered as differential diagnosis. CF could associate with PBS, mainly in patients younger than two years old.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors declare no conflict of interest of any nature.

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