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Early diagnosis of pseudo-Bartter syndrome in a hot climate region. Importance of suspecting the possibility of this diagnosis

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We report on a very young infant with cystic fibrosis diagnosed with pseudo-Bartter syndrome by neonatal screening at a reference center in a very hot climate region. She presented scarce clinical manifestations but showed all the corroborative laboratory changes. Although the clinical manifestations were not obvious, suspecting the possibility of this diagnosis in a hot climate region was essential for early diagnosis and subsequent intervention. We consider this an important aspect, since there is a current increase in the survival of patients with cystic fibrosis and in the ways to improve their health, so that they can enjoy better prognosis and quality of life.

Keywords: cystic fibrosis; neonatal screening; infant

INTRODUCTION

Cystic fibrosis (CF), a lethal homozygous genetic disease, causes alteration of the CFTR protein, which acts as a chloride channel. Its clinical manifestations are varied, the major ones being pulmonary and gastroenterological involvement and/or metabolic disorder.

Pseudo-Bartter syndrome (PBS) is a severe complication of cystic fibrosis, which presents in the form of hypochloremic alkalosis as a consequence of elevated loss of chloride, potassium and sodium in sweat (1). Vomiting, loss of appetite and dehydration are important warning signs of the possible PBS in CF patients, with a prevalence of up to 12% (2). Untreated patients can develop acute hypovolemic shock or chronic 'failure to thrive'. Both conditions compromise nutritional status and nutrition is an important component of clinical care (3).

Is important to note that PBS must be differentiated from Bartter syndrome, which is of renal origin. Although both conditions have abnormally low plasma electrolyte concentrations, in Bartter syndrome the sweat electrolyte profile is normal and the renal handling of electrolytes is defective. In CF, sweat electrolyte loss is increased, and intensive reabsorption occurs in renal tubules. The effect of this electrolyte loss is contraction of the extracellular space and activation of the renin-angiotensin system (1).

Neonatal screening for CF has opened the possibility of early identification of the possible clinical manifestations of the disease, thus contributing to improving the quality of life and survival of patients, especially in tropical regions. In the state of São Paulo (Brazil), after a pilot study (4), neonatal screening for CF was started in February 2010 using the immunoreactive trypsinogen method (reference value <70 ng/mL).

We report on a very young infant with CF diagnosed with PBS by neonatal screening at a reference center in a region of very hot climate, who presented scarce clinical manifestations but showed all the corroborative laboratory changes.

CASE REPORT

A 44-day-old girl was received at the outpatient clinic for neonatal screening for CF in May 2012 after two altered measurements of immunoreactive trypsinogen (105 and 116 ng/mL, respectively) performed on the 5th and 29th day

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of life, and of sweat chloride (69.0 and 79.2 mEq/L) performed on the 42nd and 44th day of life, respectively.

The mother reported that since one month of life, her daughter had been showing slight 'tiredness while nursing', although her appetite was preserved, with no digestive complaints. She was being exclusively breastfed. She was born at term by natural delivery, with no intercurrences, with a birth weight of 3510 g and birth length of 50.5 cm. Her parents denied consanguinity or CF among their relatives.

Physical examination revealed a well, active, hydrated infant with a length of 53.5 cm and weight of 4070 g, with a mean weight gain of 13.3 g/day in relation to birth weight. Her respiratory rate was 43/min, pulmonary semiology was normal, heart rate was 129 bpm, and peripheral O_2 saturation was 98%.

Because of the insufficient weight gain and the complaint of slight 'tiredness' when nursing, laboratory examinations were requested, as shown in detail in Figure 1. The tests revealed hypochloremic alkalosis, normal serum total proteins, hypokalemia, hyponatremia, normal fractional sodium and chloride urinary excretion, indicating that the losses were not of renal origin and permitting confirmation of the diagnosis of PBS.

Oral replacement of Na+ (3 mEq/kg/day) and K+ (2 mEq/kg/day) was started. Maternal milk was complemented with a starting feeding formula at the appropriate concentration for age, 20 mL/8 times a day. Metabolic adjustment (Table 1) and weight increase to 4520 g (increment of 75 g/day) was observed on day 6 of hospitalization. Steatocrit was determined after day 6, with the result equal to zero (reference value <10%); nevertheless, it was decided to start a small oral replacement dose of pancreatic enzymes (5900 U/kg/day).

TABLE 1. **Results of laboratory investigations performed at diagnosis and after 6 days of treatment**

Serum	Reference values	At diagnosis	After 6 days
Total proteins (g/100 g/dL)	>6.0	7.1	
Albumin (g/100 g/dL)	>3.5	4.3	
Sodium (mmol/L)	>135	121	133
Potassium (mmol/L)	>3.5	2.6	4.7
Chloride (mmol/L)	>98	85	104
pH	<7.45	7.51	7.46
Bicarbonate (mmol/L)	<24	33.3	26
Base excess (mmol/L)	<+2	+ 9.6	+2.6
Urea (mg/dL)	<40	28	
Creatinine (mg/dL)	<1.0	0.24	
Fractional sodium excretion (%)	<1	0.3	
Fractional chloride excretion (%)	<1.3	0.4	

DISCUSSION

Pseudo-Bartter syndrome may be confused with the true Bartter syndrome, i.e. genetic renal tubulopathy (5). Both disorders manifest with low weight-height gain, loss of appetite, vomiting, abdominal distention, muscle weakness, and a tendency to dehydration. Many authors have pointed out that severe clinical manifestations of PBS should be remembered as elements for diagnostic suspicion of CF, while others support the importance of suspected PBS in the presence of worsened signs and symptoms in individuals with CF (6-8).

Because we are working in a neonatal screening center located in a hot climate and in a developing country, we decided to report our experience of an active search for clinical manifestations already on the first visit with a confirmed diagnosis of CF obtained by neonatal screening. In the present case, the infant was found to be well, active, hydrated, with normal pulmonary semiology and with vague complaints of 'tiredness' while nursing, reported only after medical questioning, and a low weight gain.

The first issue to think about is that the low weight gain of an oligosymptomatic infant with CF tends to reflect pancreatic insufficiency, but even with the infant without typical symptoms, the fact that this center of newborn screening is located in a tropical climate region led us to think of PBS as a differential diagnosis. In the present report, the patient showed that the initial manifestation of PBS can be insidious.

Without intervention, the more serious consequences would probably appear after a period of evolution when the damage caused to the child by the metabolic disorders would be more evident, such as acute hypovolemic shock or chronic 'failure to thrive', with both conditions compromising nutritional status.

To our knowledge, this is the youngest CF patient diagnosed with PBS in the literature (44 days of life), presenting the lowest level of signs and symptoms, but with the presence of all the confirming laboratory manifestations. The high degree of suspicion and the early diagnosis permitted us to observe the natural history of the disease still in its phase of transition between laboratory changes and the onset of the first clinical manifestations.

We emphasize the need to include PBS in the differential diagnosis of weight impairment, even though discrete, in infants with CF. There should be greater vigilance mainly at

locations with a tropical climate like ours, with special attention directed to exclusively breastfed infants with CF due to the low sodium content of maternal milk.

We conclude that, although the clinical manifestations were not obvious, thinking of this diagnosis in a hot climate region was essential for the early diagnosis and subsequent intervention in PBS. We consider this an important aspect, since there is current increase in the survival of patients with CF and in the ways to improve their health, so that they can enjoy better prognosis and quality of life.

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SAŽETAK

Rana dijagnostika pseudo-Bartterova sindroma u području s vrućom klimom – važnost sumnje na ovu dijagnozu

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Opisuje se slučaj vrlo mladog ženskog dojenčeta s cističnom fibrozom kod kojega je pseudo-Bartterov sindrom otkriven neonatalnim probirom u referentnom centru u regiji s vrlo vrućom klimom. Dijete je pokazivalo malo kliničkih manifestacija, ali su u prilog dijagnozi govorile sve laboratorijske promjene. Iako kliničke manifestacije nisu bile očite, sumnja na mogućnost ove dijagnoze u području s vrućom klimom bila je bitna za rano postavljanje dijagnoze i intervenciju. Smatramo da je ovo važan aspekt, jer je preživljenje bolesnika s cističnom fibrozom u porastu, kao mogućnosti poboljšanja njihova zdravlja, kako bi imali što bolju prognozu i kvalitetu života.

Ključne riječi: cistična fibroza; neonatalni probir; dojenče