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CASE REPORT

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Pseudo-Bartter syndrome in infant with cystic fibrosis screen positive, inconclusive diagnosis: A case report

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Key Clinical Message

The introduction of newborn screening for cystic fibrosis (CF) increased diagnosis of cystic fibrosis screen positive inconclusive diagnosis (CFSPID). We described the case of a 12-month-old boy with CFSPID who, during summer, presented Pseudo-Bartter syndrome with no diagnostic criteria for CF.

KEYWORDS

chronic diseases, pediatrics and adolescent medicine

1 | INTRODUCTION

Worldwide many countries include cystic fibrosis (CF) in the panel of newborn bloodspot screening (NBS).[1] The main goal of these programs is to early detect infants at risk of CF in order to promptly treat them, according to current guidelines. Nowadays, there is a wide variety of NBS programs. In Campania, Italy, all newborns are screened for CF at the third day of their life through a Immunoreactive trypsinogen (IRT-IRT-DNA) algorithm.[2]

Asymptomatic patients with a positive NBS were defined as CF screen-positive, inconclusive diagnosis (CFSPID) in presence of a normal sweat chloride test (<30 mmol/L) and two CFTR variants, of whose at least one with unclear phenotypic consequences, or intermediate sweat chloride value (30–60 mmol/L) and one or zero CF causing variants.[3] Recently an increased number of CFSPID has been described as a consequence of the higher detection rate of CFTR molecular analysis used in some NBS algorithms.[4] During follow-up most children remain asymptomatic but, a variable percentage, may later develop a diagnosis of CFTR-related disorder (CFTR-RD) or CF. The range of progression to CF varied widely from 6% to 48%[5] as reported in retrospective or registry database studies. Terlizzi et al. have described a cohort of 336 Italian children with diagnosis of CFSPID. During follow-up in 80.7% CFSPID persisted while 5.3% and 1.2% progressed to CF and CFTR-RD, respectively.[6]

Here we report a case of a patient with CFSPID who developed metabolic alkalosis, referred to as Pseudo–Bartter syndrome (PBS), after 12 months of follow-up.

2 | CASE REPORT

We describe the case of a 12-month-old boy with CFSPID in follow-up at CF Center of AOU. Federico II of Naples. At diagnosis: IRT were 94.8 ng/mL (n.v. <48 ng/mL) and 38 ng/mL (n.v. <37 ng/mL) on the third and 30th day of life, respectively; the sweat chloride test was normal and CFTR molecular analysis showed the genotype *N1303K/G194V in trans*. According to the *CFTR2* database, *N1303K* is classified as a causing mutation while G194V is a mutation with variable clinical consequences.[7] The child started regular follow-up and during the first 11 months no sign or symptoms occurred, and the sweat tests were persistently in the normal range. As the weight appeared at 5°percentile, the main causes of malabsorption, including pancreatic insufficiency, were ruled out while a low caloric intake was found.

During summer, the child presented generalized weakness, fatigue and anorexia without diarrhea, nausea or vomiting. On clinical examination he showed severe dehydration (clinical dehydration scale 7 with, refill time 3 s), weight loss, heart rate 129 bpm, blood pressure 92/64 mmHg, SpO_2 98%, T36.2°C. Laboratory features showed metabolic alkalosis with hypochloremia and hypokalemia as follows: pH 7.52, HCO_3 48.5 mEq/L, base excess 21.9, Na 129.5 mEq/L, K 2.02 mEq/L, Cl 72 mEq/L, Lac 5.26 mEq/L. No history of diuretics drugs. Urinary chloride excretion was 7 mEq/L (normal value 64–176 mEq/24 h). ECG showed a long QT 460 ms. Magnesium, creatinine, glucose, and albumin were normal in serum. Exocrin pancreatic function was investigated: fecal elastase and steatocrit were in the normal range. A rehydrating fluid therapy with saline and intravenous potassium with cardiac monitoring was made.[8] The patient responded appropriately to intravenous therapy and 48 h later he was well hydrated, appetite increased and laboratory parameters were in the normal range. QT came back to normal. The main causes of metabolic alkalosis were ruled out. Once the dehydration had been resolved, a sweat test was performed twice and chloride was 54 and then 75 mEq/L, respectively. Therefore, based on metabolic alkalosis with hypochloremia and abnormal sweat chloride tests, CF diagnosis was discussed. The patient started salt supplementation according to guidelines. During the follow-up, sweat tests were repeated while the boy was healthy and chloride was 26 and 35 mEq/L, respectively. Actually, our patient carries out regular follow-up; no definitive CF diagnosis has been made.

3 | DISCUSSION

The introduction of NBS has led to earlier diagnosis and better outcomes for children with CF. Regardless of the algorithm used, all CF NBS programs can identify CFSPID cases, though their frequency increases in cases of more extensive DNA analysis, such as gene sequencing.[2] A CFSPID diagnosis requires a great deal of attention by the clinician and the management of these infants is evolving with increased experience. It is crucial that strategies are based, whenever possible, on evidence of clinical and psychological benefit for the child and the family.[9]

Our case points out the need of a closer follow-up when the patient with CFSPID develops symptoms suggestive of CF.

It is well known that defective CFTR results in excessive loss of NaCl in the sweat and consequent salt depletion. Hyponatremia, hypochloremia, hypokalemia, and metabolic alkalosis, in presence of normal function of kidney tubules, are referred to as Pseudo-Bartter Syndrome (PBS) which may occur frequently in CF during infancy and early childhood. Furthermore, it is well known that PBS may occur in patients with CF during warm weather or gastroenteritis, if supply of water and salt is inadequate. Given the overlapping symptoms (dehydration, failure to thrive), in patients with PBS CF, Bartter and Gitelman syndromes may be ruled out. Electrolyte abnormalities are more common in children less than 2.5 years old[10] and they may be subacute or chronic as well recurrent even before the diagnosis of CF.

We describe a child with CFSPID and normal sweat tests through a 11-month follow-up who developed PBS during a warm month. This did not allow CF diagnosis as subsequent sweat tests were normal/borderline, and no other CF symptoms were observed. Nevertheless, previous data reported that PBS in 9% of children may represent the first clinical manifestation of CF.[10] Likewise, Kumar et al. described eight patients with PBS as the first clinical manifestation of CF without increased sweat chloride concentration.[11] Knowledge about variability of sweat chloride over time within the subject is useful for clinicians to correctly interpret its changes. While small changes of repeated sweat chloride value above 60 mmol/L are not relevant, in the intermediate range more caution is needed for repeat measurements, in particular during malnutrition, dehydration, or serum electrolyte anomalies,[12] as the case of the child described in this report. Close follow-up and repeated sweat tests are indicated also in subjects with PBS that may further develop other symptoms suggestive of CF.

Given the possibility of progression from CFSPID to CF or CFTR-RD, the management of infants with CFSPID is challenging. Currently no standardized protocols are available for follow-up beyond infancy, nor

established predictors to stratify this population as high or low risk of reclassification to CF or CFTR-related disorder. In particular, no definitive recommendations about metabolic and nutritional therapies for asymptomatic infants with CFSPID are reported. Infants with CF are at risk for salt depletion when they do not receive adequate supplementation. Although the extent of salt loss is not likely to be as great in infants with CFSPID as in infants with CF, the amount of salt in the sweat for those with sweat chloride values in the intermediate range is by definition greater than three standard deviations above the normal.[13]

Salt supplementation in CFSPID patients is much more debated. Previous guidelines underline that when sweat chloride is more than 30 mmol/L, sodium supplementation must be increased when there is a risk for excessive perspiration and dehydration, that is, at high room temperatures or in subjects with fever. This supplementation should be adjusted based on the urinary Na/K ratio.[14]

In conclusion CFSPID patients may not have the typical features and severity of CF but they have been revealed as being at risk through their progression.[15] Therefore, they should be followed up at a tertiary CF care center in order to early evaluate the onset of suggestive signs and symptoms of CF. Most importantly, these children should receive appropriate care regardless of diagnosis. Clinicians have to be prepared to identify these infants and communicate with parents about this challenging and stressful situation for both healthcare professionals and families.

AUTHOR CONTRIBUTIONS

Angela Sepe: Conceptualization; project administration. **Camilla Romano:** Data curation; writing – original draft. **Ivana Landi:** Data curation; writing – original draft. **Alice Castaldo:** Data curation. **Chiara Cimbalo:** Data curation. **Federica Farina:** Investigation. **Manuela Scorza:** Writing – review and editing. **Laura Salvadori:** Investigation; supervision. **Valeria Raia:** Supervision; writing – review and editing. **Antonella Tosco:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from patient's parent to publish this report in accordance with the journal's patient consent policy.

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