

## Case report

# Pseudo-Bartter as an initial presentation of cystic fibrosis. A case report and review of the literature

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## Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by the mutation of the cystic fibrosis transmembrane regulator gene (*CFTR*) on chromosome 7. Although it primarily affects the respiratory and gastrointestinal tracts, it can also involve other organs. It may also cause electrolyte and acid base disturbances, rarely the mode of presentation. This can result in difficulty in making an early diagnosis in the absence of other characteristic clinical features.

We report here such a case which presented in infancy.

## Case report

A 6-month old Yemeni infant presented with an 8-day history of diarrhoea and vomiting. He was born at full term with an uneventful prenatal, perinatal and postnatal history. His parents, who are first-degree cousins, and his 4-year-old sister were healthy.

On presentation, he was febrile and had moderate dehydration (< 10%). His weight was 7.8 kg (just above the 5th percentile), length 69 cm (on the 10th percentile) and head circumference 43.8 cm (on the 5th percentile). His blood pressure fluctuated between 70/50 mmHg and 100/80 mmHg. The rest of his examination was unremarkable.

Analysis of serum electrolytes gave the following results: sodium 124 mmol/L, potassium 4 mmol/L,

chloride 84 mmol/L, bicarbonate 29 mmol/L and creatinine 0.4 mg/dL. He required intravenous fluid therapy and was discharged after correction of his biochemical abnormalities.

He was readmitted 5 more times over a 2-year period with episodes of diarrhoea and vomiting associated with similar biochemical abnormalities (Table 1). He never had significant respiratory problems throughout that period. The possibility of Bartter syndrome was raised, but the diagnosis was dismissed as his blood pressure was initially high, urinary chloride excretion was low with only slightly elevated levels of serum renin (320 ng/dL at rest and standing) and aldosterone (195 ng/dL at rest and 206 ng/dL while standing).

Further evaluation, around the age of 1 year and while he was clinically stable, revealed a thriving child with the following serum biochemical results: sodium 133 mmol/L, potassium 3.4 mmol/L, chloride 100 mmol/L and bicarbonate 22 mmol/L. The serum levels of aldosterone (99 ng/dL) and renin (84 ng/dL) were normal, so was urinary chloride excretion (20 mg/dL) but the fractional excretion of potassium was elevated at 67%. Hyponatraemia was interpreted as being secondary to prolonged diarrhoea and vomiting, hypokalaemia to stool losses, metabolic alkalosis to extra cellular compartment contraction and the initial but transient rise in blood pressure to secondary hyperaldosteronism. Tubulopathy was excluded in view of the absence

**Table 1 Biochemical results of the patient at various admissions**

Biochemical measure	Date				
	24/4/99	09/5/99	25/9/99	04/7/99	03/9/01
Plasma Na (mEq/L)	117	131	125	127	126
Plasma Cl (mEq/L)	84	88	85	82	89
Serum K (mEq/L)	3.1	3	4	3.2	2.7
Plasma HCO <sub>3</sub> (mEq/L)	30	28	28	28	29
Blood Urea (mg/dL)	8	6	25	34	23
Serum Creatinine (mg/dL)	-	0.4	0.6	0.7	0.9
Plasma pH	7.54	-	7.5	7.55	7.56
HCO <sub>3</sub>	31	-	29	30.3	31
Base excess	4	-	2	4	5
Urinary Na (mEq/L)	-	10	<10	-	<10
Urinary K (mEq/L)	-	43	-	-	54.7
Urinary Cl (mEq/L)	-	<10	<10	-	<10
Serum aldosterone (ng/dL)	99.2	-	-	-	-
Serum renin (ng/dL)	84	-	-	-	-

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of hypercalciuria, hypocalcaemia, hypomagnesaemia, hypermagnesuria or significant hypokalaemia. The patient was discharged on sodium chloride and potassium chloride supplementation.

After being lost to follow-up for several years, he was seen again at the age of 8 years when he presented with severe gastroenteritis, hypovolaemic shock and chest infection. His height and weight were below the 3rd percentile, temperature was 38.7 °C, heart rate 98/min, respiratory rate 30/min, blood pressure 70/50 mmHg, O<sub>2</sub> saturation 88% in room air and capillary refill 4 seconds. He had marked finger and toe clubbing, with bilateral crepitations heard on auscultation.

He underwent fluid resuscitation and investigations showed the following results: serum sodium 128 mmol/L, chloride 76 mmol/L, potassium 3.3 mmol/L, bicarbonate 28 mmol/L, anion gap 15.6 mmol/L, urea 35 mg/dL, creatinine 1.3 mg/dL, calcium 10.5 mg/dL, phosphorus 7.6 mg/dL and magnesium 2.3 mg/dL. Blood gas results were: pH 7.51, pCO<sub>2</sub> 48.4 mmHg, pO<sub>2</sub> 65 mmHg, base excess 6.1 mmol/L, bicarbonate 31.6 mmol/L. Urinary electrolytes results were: sodium < 10 mmol/L, chloride < 15 mmol/L, potassium 117 mmol/L, calcium excretion < 2 mg/day and magnesium excretion 2.3 mg/day. Bilateral streaky infiltrates were seen on chest radiography. Sputum culture grew *Pseudomonas aeruginosa* and blood and urine cultures revealed no bacterial growth. Fluid therapy led to gradual biochemical correction over 3 days.

The suspected diagnosis of cystic fibrosis was confirmed with a sweat chloride level of 120 mmol/L and homozygosity for the Delta F 508 gene on genetic studies. The child was started on standard CF therapy. He is currently doing well regarding weight gain and his blood chemistry remains normal.

## Discussion

CF is an inherited disorder affecting most organs, especially the exocrine glands. It is associated with a large number of mutations affecting the chloride channel, the commonest being mutation of the delta F508 on chromosome 7. The manifestation of the disease can appear at birth or later in the life according to the type of mutation, which also predicts the severity of the disease [1]. The most common systems affected are respiratory (where the typical presentation includes recurrent pneumonia and obstructive lung disease) and digestive (secondary to pancreatic insufficiency) leading to growth failure [1]. Other manifestations include renal agenesis [2] and absence of vas deferens [1,2]. Uncommonly, it can present as an acid-base and electrolyte imbalance, such as hypokalaemia, hyponatraemia and metabolic alkalosis.

Most children with CF presenting as hyoelectrolytaemia and metabolic alkalosis (so-called pseudo-Bartter) were under the age of 6 months [3,4]. Multiple inter-related factors have been incriminated in its pathophysiology. Normally, with the cystic fibrosis transmembrane regulator (*CFTR*) gene regulating sweat production, normal sweat glands produce iso-osmotic primary sweat, partly by chloride secretion across the apical *CFTR* [5]. The water-impermeable sweat duct reabsorbs sodium chloride transcellularly, leading to the excretion of hypotonic sweat, enabling the body to regulate its temperature with minimal loss of electrolytes [5]. The volume of sweat in CF patient is different from that in healthy people [6]. Although the production of primary sweat is relatively normal in CF patients [5], the dysfunctional *CFTR* in the sweat duct results in excessive sodium and chloride loss in the final sweat [5,6]. This loss in sodium chloride is more marked in hot weather where the rate of sweat production may reach up to 2 litres/hour [5–7], leading to

massive sodium chloride loss which results in significant extracellular volume contraction and secondary hyperaldosteronism. This hyperaldosteronism will lead to increased potassium losses both in the sweat and the urine, resulting in hypokalaemia [3,8–14].

The pathophysiology of metabolic alkalosis includes: volume depletion leading to a relatively high bicarbonate level in the contracted extracellular volume (haemoconcentration) [3,8,9,15], and low extracellular chloride leading to increased reabsorption of bicarbonate to replace the lost extracellular anions (chloride and bicarbonate) [3,9]. In addition, the extracellular volume depletion leads to decreased filtered load of bicarbonate in the urine due to decreased Glomerular filtration rate (GFR) [3,8] and the hypokalaemia itself can maintain and generate metabolic alkalosis [3,8,15,16]. The effect of these electrolyte losses is the activation of the renin–angiotensin system and stimulation of sodium cation (hydrogen, potassium) exchange, with resulting alkalosis and potassium depletion. Although hyperaldosteronism without distal sodium delivery will not cause alkalosis, an increase in mineralocorticoid with distal proton delivery would, as in the case of Bartter syndrome and chronic diuretic use. Studies have shown that some changes in renal sodium handling [17] and free water clearance [18] occurs in CF patients. Furthermore, the *CFTR* (or *CFTR*-like) gene or protein has been located in the proximal tubules of rabbits [19,20], rats [21], mice [20] and also in human distal tubules [22]. Thus, a volume-depleted CF patient can still maintain distal sodium delivery due to dysfunctional *CFTR*.

Gastrointestinal losses act as contributory factors, accentuating an underlying salt depletion and metabolic alkalosis. In all CF infants with acute or chronic fluid and electrolyte losses with sweating, their metabolic abnormalities and condition are aggravated by acute intercurrent episodes of vomiting,

diarrhoea, or respiratory symptoms [3,7,10]. These intercurrent illness acts as a precipitating event aggravating the underlying metabolic alkalosis and hyponatremia. In addition, infants with CF are prone to develop episodes of hyponatraemic hypochloaemic dehydration with metabolic alkalosis, due to excess salt loss with sweating, especially in regions with a hot, dry climate, during the warmer months [3,7,10]. Breastfed infants are more prone to have such electrolyte derangement especially in hot weather due to low salt content in the breast milk [10].

In our patient, the volume depletion was most likely secondary to many factors including: hot climate, episodes of gastroenteritis, recurrent vomiting and intercurrent infections. It led to contraction alkalosis due to the relative increase in serum bicarbonate concentration

and decrease in filter load of bicarbonate secondary to decreased GFR. This volume depletion led to activation of the renin-angiotensin system and secondary hyperaldosteronism (Table 1) with enhanced urinary and sweat potassium excretion. This resulted in hypokalaemia, which by itself could aggravate and maintain the metabolic alkalosis.

Hypochloaemic metabolic alkalosis with increased serum aldosterone and renin levels occurs in both Bartter and in CF (pseudo-Bartter) [12,13,15] syndrome. The main difference is that urinary chloride losses in Bartter syndrome are high, while they are low in CF (with elevated sweat chloride losses).

When faced with a child with hypochloaemic hypokalaemic metabolic alkalosis, causes other than Bartter syndrome need also to be considered. They include persistent vomiting (as in pyloric

stenosis), congenital chloride-losing diarrhoea, Gittelman syndrome, diuretic use and primary hyperaldosteronism [1,3,8,10,15]. A practical approach to deal with hypochloaemic metabolic alkalosis is suggested. First, urinary chloride level should be measured: if very high, Bartter syndrome is very likely. If it is not elevated, other non-urinary chloride losses, such as stool losses (congenital chloride diarrhoea or laxative abuse) or excessive losses in sweat (CF) should be considered.

## Conclusion

When confronted with hypochloaemic hypokalaemic metabolic alkalosis, the possibility of CF must always be considered, even in the absence of characteristic clinical features.

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