

## CASE REPORT / ПРИКАЗ БОЛЕСНИКА

# Hyponatremic dehydration and metabolic alkalosis as dominant manifestation in cystic fibrosis infants with mild phenotype – a case series

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**Introduction** Due to increased losses of chloride and sodium in the sweat, children with cystic fibrosis (CF) are predisposed to develop episodes of hyponatremic/hypochloremic dehydration with hypokalemia and metabolic alkalosis when they sweat excessively. Even the patients with mild phenotype may have such episodes of dehydration and salt depletion.

**Outline of cases** Six cases of pancreatic sufficient (PS) CF patients complicated with episodes of severe hyponatremic dehydration with metabolic alkalosis in infancy are presented. The mean age was  $6.3 \pm 2.16$  months at admission. All the cases had no symptoms suggestive of CF before admission. The most common clinical symptoms at the time of hospitalization were vomiting, anorexia, weight loss, dehydration, irritation, or lethargy. Mean values of blood pH, serum bicarbonate, sodium, chloride, and potassium (mmol/l) were as follows:  $7.59 \pm 0.06$ ,  $41.73 \pm 5.78$ ,  $117.52 \pm 2.88$ ,  $66.0 \pm 11.58$  and  $2.62 \pm 0.37$ , respectively. Sweat chloride test was pathological and ranged 69–120 mmol/L. The determination of fecal elastase-1 proved that they were PS (values  $> 200 \mu\text{g/g}$  stool). CF transmembrane conductance regulator gene analyses in six cases confirmed the diagnosis of CF; namely, patients were compound heterozygotes for F508del and other rare mutation or compound heterozygotes for two rare mutations.

**Conclusion** Distinctive about these cases is that they were PS and had very mild presentation of CF. Without these episodes of dehydration, these patients would have remained undiagnosed until later age. CF should be considered in infants and children presenting with hypoelectrolytemia and metabolic alkalosis even in the absence of respiratory or gastrointestinal symptoms.

**Keywords** : cystic fibrosis; CFTR genotype; hyponatremic dehydration; metabolic alkalosis

**INTRODUCTION**

Cystic fibrosis (CF) is a multisystem disease caused by mutations in a gene on chromosome 7, which encodes the CF transmembrane conductance regulator (CFTR) protein. CFTR functions primarily as a chloride channel and controls the movement of salt and water into and out of epithelial cells in the affected organs. Almost 2,000 different CFTR mutations have been identified, resulting in different consequences on protein function, ranging from complete protein absence to defective protein activity at the plasma membrane [1, 2]. Hence, phenotypic expression of the disease varies widely among individuals with CF [3].

In countries without neonatal screening for CF, the disease is usually diagnosed during childhood by respiratory and/or gastro-intestinal symptoms. Hyponatremic hypochloremic dehydration with hypokalemia and metabolic alkalosis is a rare but typical presentation of CF in infants [4, 5, 6]. Dysfunctional CFTR in the sweat ducts are responsible for the excessive chloride and sodium losses, especially during warm months. The extracellular fluid volume contraction and salt depletion will lead to activation of renin-angiotensin system and

secondary hyperaldosteronism. The resulting effect is increased renal potassium and hydrogen losses for the exchange with sodium in the distal tubule. The consequenced hypokalemic alkalosis is a metabolic mimicry of Bartter's syndrome; therefore, the condition is known as pseudo-Bartter's syndrome in CF.

In our previous study of pseudo-Bartter's syndrome in CF, all patients with metabolic alkalosis and hypoelectrolytemia were pancreatic insufficient (PI). Respectively, they had severe mutations with regard to pancreatic exocrine function [7]. Over the last few years, we have noticed the emergence of severe hyponatremic hypochloremic dehydration with metabolic alkalosis in pancreatic sufficient (PS) CF infants, which had very mild disease expression further on in the clinical course.

**REPORT OF CASES**

Clinical records of six patients, three boys and three girls, presenting in infancy with metabolic alkalosis and electrolyte abnormalities such as hyponatremia, hypochloremia, and hypokalemia, which were later found to have CF, were analyzed.

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**Table 1.** Biochemical features of the pancreatic sufficient cystic fibrosis patients with pseudo-Bartter's syndrome

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	M ± SD*
pH	7.6	7.67	7.6	7.61	7.57	7.49	7.59 ± 0.06
Bicarbonate (mmol/L)	42.9	49.1	42.8	44.6	39	32	41.73 ± 5.78
Sodium (mmol/L)	113	121	117	116	118	120	117.52 ± 2.88
Chloride (mmol/L)	61	65	54	56	78	82	66 ± 11.58
Potassium (mmol/L)	2.1	2.7	2.4	2.6	3.2	2.7	2.62 ± 0.37

\*Mean values ± standard deviation

**Table 2.** Genotypes of the pancreatic sufficient cystic fibrosis patients with pseudo-Bartter's syndrome

Case No.	Mutation I cDNA name / legacy name	Mutation II cDNA name / legacy name
1	c.377G>A / G126D	c.1366G>T / V456F
2	c.377G>A / G126D	c.1753G>T / E585X
3	c.1521_1523delCTT / delF508	c.579+3A>G / 711+ 3A- >G
4	c.1521_1523delCTT / delF508	c.579+3A>G / 711+ 3A- >G
5	c.1521_1523delCTT / delF508	c.349C>T / R117C
6	c.1521_1523delCTT / delF508	c.1070C>T / A357V

The mean age of children was  $6.3 \pm 2.16$  months (range being 3–9 months). Biochemical features of the patients at the admission phase are summarized in Table 1. Mean values of blood pH, serum bicarbonate, sodium, chloride, and potassium (mmol/L) at admission were as follows:  $7.59 \pm 0.06$ ,  $41.73 \pm 5.78$ ,  $117.52 \pm 2.88$ ,  $66 \pm 11.58$ , and  $2.62 \pm 0.37$ , respectively. Urine chloride concentrations in all the patients were below 20 mmol/l. For case 1 it was the second episode, for case 4 the third episode, and for cases 2, 3, 5, and 6 the first episode of dehydration. All episodes of dehydration occurred during the summer and early autumn months. The most common clinical symptoms in these patients were vomiting, anorexia, weight loss, dehydration, irritation, or lethargy. We did not obtain a history of recurrent chest infection or loose stools in any child. Therefore, all cases had no symptoms suggestive of CF before admission.

After rehydration and correction of metabolic abnormalities in the blood, a subsequent sweat chloride test and genotyping confirmed the diagnosis of CF in these infants. Sweat chloride tests were pathological and ranged 69–120 mmol/L. Assessment of the pancreatic functional status by determining the values of fecal elastase-1 showed that all six infants were PS (fecal elastase values were over 200 µg/g stool). CFTR gene analyses determined that the patients were compound heterozygotes for F508del (the most common CFTR mutation, class II) and other rare mutation or compound heterozygotes for two rare mutations (Table 2). A new mutation c.1070C>T (A357V) was detected in case 6.

Monitoring the clinical course of the disease in these children within the next two to five years showed that they have mild expression of CF mainly manifested as recurrent sinusitis and nasal polyps in case 3. Only case 4 had another hospitalization for treating acute exacerbation of lung disease with *Pseudomonas aeruginosa* infection. Very mild pulmonary involvement was found on the chest X-ray in all six cases.

## DISCUSSION

Metabolic alkalosis in association with low serum electrolyte concentration is not a common metabolic disorder in infancy. Conditions associated with repeated vomiting, especially pyloric stenosis, continuous gastric drainage without appropriate electrolyte replacement, chloride-losing diarrhea, potassium-losing nephropathy, Bartter's syndrome, the use of thiazide diuretics, and salt depletion by sweating in CF can lead to such a disturbance [8, 9].

Metabolic abnormalities in the so-called pseudo-Bartter's syndrome in CF can have mimicking biochemical features of Bartter's syndrome. Although the biochemical hallmark of both Bartter's and pseudo-Bartter's syndrome is abnormally low plasma electrolyte concentrations, there are important differences between the two diseases. In Bartter's syndrome, the sweat electrolyte profile is normal and the renal handling of electrolytes is defective. In CF, sweat electrolyte losses are increased, and intensive electrolyte reabsorption occurs in the renal tubules. In all our CF infants presenting with electrolyte depletion and metabolic alkalosis, the initial diagnosis of Bartter's syndrome was excluded by hypochloruria (< 20 mmol/L). Determination of urinary chloride before therapy is especially useful to distinguish these two conditions.

In our previous study, all CF infants with pseudo-Bartter's syndrome were PI [7]. We considered that biochemical abnormalities due to insufficient CFTR chloride canal function are more pronounced in CF patients with "severe" disease-caused mutations (class I, II, and III). Compared to the "severe" CFTR mutations, certain "mild" mutations tend to be associated with significantly lower sweat chloride concentrations [10]. However, the emergence of severe hyponatremic hypochloremic dehydration with metabolic alkalosis in PS CF infants, which had mild disease expression in the further clinical course, indicated that neither the CFTR genotype nor sweat chloride levels are correlated with the occurrence of dehydration episodes. Our present analysis showed that two rare mutations (G126D and 711+ 3A- >G) were found

in two cases, each. G126D is a missense mutation in exon 4 of the CFTR gene, resulting in amino acid change (glycine to asparagine at 126) in CFTR chloride channel and 711+3A->G is a splicing mutation in intron 5, resulting in an mRNA splicing defect. This may arouse doubt that certain genotypes are more predisposed to the development of this metabolic disorder. Higher rate of sweating and electrolyte losses with sweat may be the reason why some CF individuals are biochemically more vulnerable, but the risk factors for the development of dehydration with electrolyte depletion in CF are still not defined.

In conclusion, any CF patient, even a patient with a mild form of the disease, may experience an episode of dehydration with metabolic alkalosis and hyponatremia, particularly during the hot weather conditions. CF should be considered in the differential diagnosis of infants and children presenting with these biochemical abnormalities, even in the absence of respiratory or gastrointestinal symptoms. Missing the diagnosis of mild forms of CF may lead to life-threatening complications, such as severe hyponatremic dehydration with hypovolemia or diffuse bronchiectasis at a later age [11].

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## Хипонатремична дехидратација и метаболичка алкалоза као доминантна манифестација код одојчади са цистичном фиброзом и благим фенотипом – серија случајева

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### САЖЕТАК

**Увод** Због повећаних губитака хлора и натријума у зноју, деца са цистичном фиброзом (ЦФ) предиспонирана су да развију епизоде хипонатремичне/хипохлоремичне дехидрације са хипокалемијом и метаболичком алкалозом када се претерано зноје. Чак и болесници са благим фенотипом могу имати такве епизоде дехидрације и исцрпљивање соли.

**Приказ болесника** Приказано је шест случајева панкреасно суфицијентних (ПС) болесника са ЦФ који су као одојчад имали као компликацију епизоде тешке хипонатремичне дехидрације са метаболичком алкалозом. Просечна старост је била  $6,3 \pm 2,16$  месеци на пријему. Нису сви случајеви пре пријема имали симптоме који указују на ЦФ. Најчешћи клинички симптоми у време хоспитализације били су: повраћање, анорексија, губитак тежине, дехидрација, иритација или летаргија. Средње вредности рН крви, серумских бикарбоната, натријума, хлора и калијума ( $mmol/l$ ) биле су,

редом:  $7,59 \pm 0,06$ ;  $41,73 \pm 5,78$ ;  $117,52 \pm 2,88$ ;  $66 \pm 11,58$  и  $2,62 \pm 0,37$ . Знојни хлоридни тест био је патолошки и варирао је од 69 до 120  $mmol/l$ . Одређивање фекалне еластазе-1 показало је да су ПС (вредности  $> 200 \mu g/g$  столице). ЦФТР генска анализа код свих шест случајева потврдила је дијагнозу ЦФ; наиме, болесници су били сложени хетерозиготи за *F508del* и другу ретку мутацију или сложени хетерозиготи за две ретке мутације.

**Закључак** Карактеристично за ове случајеве је то што су панкреасно суфицијентни и имају веома благу презентацију ЦФ. Без ових епизода дехидрације, ови болесници би остали недијагностиковани до каснијег узраста. ЦФ треба узети у обзир код одојчади и деце код којих се манифестују хипоелектролитемија и метаболичка алкалоза, чак и у одсуству респираторних или гастроинтестиналних симптома.

**Кључне речи:** цистична фиброза; ЦФТР генотип; хипонатремна дехидрација; метаболичка алкалоза