



Paper Accepted*

ISSN Online 2406-0895

Case Report / Приказ болесника

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

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

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Received: August 11, 2017

Revised: November 20, 2017

Accepted: July 25, 2018

Online First: August 7, 2018

DOI: <https://doi.org/10.2298/SARH170811053F>

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

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

SUMMARY

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. Mean age was 6.3 ± 2.16 months at admission. All 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: 7.59 ± 0.06 , 41.73 ± 5.78 , 117.52 ± 2.88 , 66.0 ± 11.58 and 2.62 ± 0.37 , respectively. Sweat chloride test was pathological and range from 69 to 120 mmol/l. The determination of fecal elastase-1 proved that they were PS (values > 200 $\mu\text{g/g}$ stool). CFTR 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 mutation.

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

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

САЖЕТАК

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

Приказ случајева Приказани су шест случајева панкреасно суфициентних (ПС) пацијената са ЦФ који су имали као компликацију епизоде тешке хипонатремичне дехидрације са метаболичком алкалозом као одојчад. Просечна старост је била $6,3 \pm 2,16$ месеци на пријему. Сви случајеви нису имали симптоме који указују на ЦФ пре пријема. 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) били су, редом: $7,59 \pm 0,06$; $41,73 \pm 5,78$; $117,52 \pm 2,88$; $66,0 \pm 11,58$ и $2,62 \pm 0,37$. Знојни хлоридни тест био је патолошки и варирао од 69 до 120 mmol/l. Одређивање фекалне еластазе-1 показало је да су ПС (вредности > 200 $\mu\text{g/g}$ столице). ЦФТР генска анализа у свих шест случајева потврдила је дијагнозу ЦФ; наиме пацијенти су били сложени хетерозиготи за F508del и другу ретку мутацију или сложени хетерозиготи за две ретке мутације.

Закључак Карактеристично за ове случајеве је што су панкреасно суфицијентни и имају веома благу презентацију ЦФ. Без ових епизода дехидрације, ови пацијенти би остали недијагностиковани до каснијег узраста. ЦФ треба узети у обзир код одојчади и деце које манифестирају хипоелектролитијум и метаболичку алкалозу, чак и у одсуству респираторних или гастроинтестиналних симптома.

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

INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease caused by mutations in a gene on chromosome 7 that 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 2000 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 hyoelectrolytemia were pancreatic insufficient (PI). Respectively, they had severe mutations with regard to pancreatic exocrine function [7]. Last few years we have noticed the emergence of severe hyponatremic hypochloremic dehydration with metabolic alkalosis in pancreatic sufficient (PS) CF infants, which further in clinical course had very mild disease expression.

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.

The mean age of children was 6.3 ± 2.16 months (range, 3-9 months). Biochemical features of the patients at admission phase are summarized in Table 1. Mean values of blood pH, serum bicarbonate, sodium, chloride and potassium (mmol/l) at admission were: 7.59 ± 0.06 , 41.73 ± 5.78 , $117.5.2 \pm 2.88$, 66.0 ± 11.58 and 2.62 ± 0.37 , respectively. Urine chloride concentrations in all patients were below 20 mmol/l. For case 1 it was second episode, for case 4 third episode and for cases 2,3,5

and 6 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 get 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 from 69 mmol/L to 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 patients were compound heterozygotes for F508del (the most common CFTR mutation, class II) and other rare mutation or compound heterozygotes for two rare mutation (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 2-5 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 treatment of 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 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 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 is 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, that further in clinical course had mild disease expression, 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 missense mutation in exon 4 of CFTR gene, resulting in amino acid change (Glycine to Asparagine at 126) in CFTR chloride channel and 711+ 3A- >G is splicing mutation in intron 5, resulting in mRNA splicing defect. That may arouse doubt that certain genotypes are more predisposed for development of this metabolic disorder. Higher rate of sweating and electrolyte losses with sweat may be reason some CF individuals to be 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 episode of dehydration with metabolic alkalosis and hyoelectrolytemia, 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 as severe hyponatremic dehydration with hypovolemia [11] or diffuse bronchiectasis in later age.

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Table 1. Biochemical features of the PS CF patients with pseudo-Bartter's syndrome

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Mean \pm SD
pH	7.60	7.67	7.60	7.61	7.57	7.49	7.59 \pm 0.06
Bicarbonate (mmol/L)	42.9	49.1	42.8	44.6	39	32	41.73 \pm 5.78
Sodium (mmol/L)	113	121	117	116	118	120	117.52 \pm 2.88
Chloride (mmol/L)	61	65	54	56	78	82	66 \pm 11.58
Potassium (mmol/L)	2.1	2.7	2.4	2.6	3.2	2.7	2.62 \pm 0.37

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Table 2. Genotypes of the PS CF 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