Srp Arh Celok Lek. 2015 Nov-Dec;143(11-12):748-751
ПРИКАЗ БОЛЕСНИКА / CASE REPORT
DOI: 10.2298/SARH1512748V
UDC: 616-008.9-053.3:544.6.018.4 : 616-056.7-053.3

Pseudo-Bartter's Syndrome in Patients with Cystic Fibrosis: A Case Series and Review of the Literature

Gordana Vilotijević-Dautović[1,2], Vesna Stojanović[1,2]

[1]Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

SUMMARY

Introduction Pseudo-Bartter syndrome (PBS) is characterized by hyponatremic, hypochloremic metabolic alkalosis that mimics Bartter syndrome but with no pathology in the renal tubules. We present five patients with cystic fibrosis (CF) and PBS.

Cases Outline Four children aged between three and five-and-one-half months with previously diagnosed CF and one aged 17 months with previously undiagnosed disease, were hospitalized during the summer season, with severe dehydration, oliguria, apathy and adynamia. Additionally, one of them had an ileostomy due to meconium ileus after birth. All children were on a diet without additional salt intake. Laboratory analysis on admission showed hyponatremia (115–133 mmol/L, mean 122.4 mmol/L), high plasma renin activity (229–500 pg/ml, mean 324 pg/ml) and metabolic alkalosis (pH 7.5–7.6, mean 7.56) in all the patients, and in four of them high blood level of aldosterone (74–560 pg/ml, mean 295.9 pg/ml), hypokalemia (2.3–2.8 mmol/L, mean 2.6 mmol/L), hypochloremia (59–71 mmol/L, mean 66 mmol/L) and low urinary sodium (5–12 mmol/L, mean 9 mmol/L). After intravenous rehydration followed by additional use of sodium and chloride in mean dosis of 1.78 mmol/kg per day, all the patients made a complete recovery. With advice for additional use of salt in the mentioned amount, the patients were discharged from the hospital.

Conclusion PBS is one of CF complications, especially in infants and young children in situations accompanied by increased sweating and/or other causes of additional loss of sodium and chlorine. Sometimes, as was the case with one of our patients, PBS may be the initial presentation form of the disease.

Keywords: cystic fibrosis; pseudo-Bartter syndrome; infants

INTRODUCTION

Cystic fibrosis (CF) is a disease of exocrine gland dysfunction caused by genetic mutation on chromosome 7, which results in abnormalities in the production and/or function of protein called cystic fibrosis transmembrane conductance regulator (CFTR) that acts as a chloride channel and regulator of epithelial chloride and bicarbonate transport [1, 2]. The widespread presence of CFTR throughout the body leads to multisystem involvement [1, 2]. Although it primarily affects the respiratory and gastrointestinal tracts, it can also involve other organs [1, 2]. It may also cause electrolyte and acid base disturbances, especially in countries with warm climate during hot summer months. However, the rare episode of dehydration, metabolic alkalosis and hypochloremia in CF patients is presented as pseudo-Bartter syndrome (PBS) [3, 4].

PBS is characterized by hyponatremic, hypochloremic metabolic alkalosis that mimics Bartter syndrome but with no pathology in the renal tubules [5]. Sometimes PBS may be the first manifestation of CF [6, 7, 8].

We present five patients with CF and PBS. In one of them PBS was the initial presentation of CF.

Correspondence to:
Vesna STOJANOVIĆ
Institute for Child and Youth Health Care of Vojvodina
Hajduk Veljkova 10
21000 Novi Sad
Serbia
vsnefro@gmail.com

REPORT OF CASES

During the summer period of 2012 and 2013, the PBS was diagnosed in five patients with CF. The reason for hospitalization in all patients was severe dehydration, oliguria, apathy and adynamia. The diagnosis of CF in four children is determined by the first month after birth (neonatal screening), while one, a 17-month-old girl, basic disease is diagnosed by the picture of PBS (Table 1). Basic data related to the age of children at the time of hospitalization, nutritional status, diet, factors that preceded dehydration and initial laboratory parameters are given in Tables 2 and 3. The important fact is that none of the children, except a two-month female infant who was fed unmodified cow's milk, had no additional salt intake. An additional risk factor for the development of PBS had a patient number five, which had an increased loss of water and electrolytes through ileostomy.

DISCUSSION

It is well known that CF patients may fail to thrive despite adequate intake of calories. In those cases it is important to think of the existence of electrolyte disturbances due to PBS.

PBS is a rare syndrome characterized with hypochloremic metabolic alkalosis, hyponatremia,

Table 1. Results of newborn screening (IRT level, sweat test), CFTR mutations and fecal elastase level

Patient	IRT (ng/ml)	CFTR mutation	Sweat test (mmol/L)	Fecal elastase (μg/g)
1	80 and 100	621+1G>T//2789+5G>A	79 and 85	200
2	/	F508 del homozygote	68 and 98	15
3	129 and 133	F508 del homozygote	58 and 62	146
4	236 and 175	F508 del homozygote	87 and 96	15
5	460 and 229	F508 del / G 542X	78 and 86	19

IRT – immunoreactive trypsinogen; CFTR – cystic fibrosis transmembrane conductance regulator

Table 2. Characteristics of patients with cystic fibrosis and pseudo-Bartter syndrome and therapy they received

Patient	Age (months)	Sex	Symptoms before onset of PBS	Predisposing factors	Feeding	Body weight at admission (g)	Substitution therapy
1	3	Female	Failure to thrive	High air temperature	Cow's milk	4250 (<3 pct)	NaCl 0.5 mmol/kg/day KCl 1 mmol/kg/day
2	17	Female	None	High air temperature	Standard diet	13500 (50 pct)	NaCl 2 mmol/kg/day KCl 1 mmol/kg/day
3	4	Female	Recurrent respiratory infections	High air temperature	Formula	5700 (<50 pct)	NaCl 1.7 mmol/kg/day KCl 1.5 mmol/kg/day
4	5.5	Male	Failure to thrive	High air temperature	Formula	5700 (3 pct)	NaCl 1.7 mmol//kg/day KCl 1.3 mmol/kg/day
5	5	Male	Meconium ileus, ileostomy, failure to thrive	High air temperature and ileostomy	Formula	5200 (3 pct)	NaCl 3 mmol/kg/day

pct – percentile

Table 3. Initial laboratory findings on admission of patients with cystic fibrosis and pseudo-Bartter syndrome

Patient	pH	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Urea (mmol/l)	SCr (umol/l)	PRA (IU/ml)*	Aldosterone (pg/ml)*	UNa (mmol/l)	UK (mmol/l)	UCl (mmol/l)
1	7.6	119	2.8	69	2.8	10.4	320	560	12	5.5	10
2	7.5	115	2.8	58.8	20	120	279	37.8	5	60	6
3	7.6	124	2.3	71	8.3	33.9	229	74	34	1.1	14
4	7.6	121	2.5	65	30	64	500	97.6	7	11	10
5	7.5	133	4.2	109	10	46	296	452	12	/	6

Na – sodium; K – potassium; Cl – chloride; SCr – serum creatinine; PRA – plasma renin activity; UNa – urinary sodium; UK – urinary potassium; UCL – urinary chloride

* Referent range: PRA to 46 IU/ml; Aldosterone 16–40 pg/ml

hypokalemia, hyperreninemia, hyperaldosteronism and persistent failure to thrive. Hypochloremic metabolic alkalosis with elevated aldosterone and rennin occur both in Bartter syndrome, as well as in PBS within the CF. The main difference is that in the PBS renal tubules are not affected, while in classic Bartter syndrome renal tubules are not able to reabsorb electrolytes. In classic Bartter syndrome chloride loss in urine is high, while in PBS chloride loss in urine is low (<10 mmol/l) [3, 4, 9].

The CFTR dysfunction in the sweat glands results in excessive loss of sodium and chloride. This is especially true during hot summer months. The excessive loss of sodium chloride leads to a significant loss of the extracellular volume and secondary activation of the rennin-angiotensin-aldosterone system. Hyperaldosteronism leads to an increased loss of potassium through sweat, as well as through urine, causes hypokalemia and stimulates sodium cation exchange (hydrogen, potassium) which in addition results with hypokalemia and alkalosis occurrence. In reduced extracellular space relative increase in the concentration of bicarbonate occurs, and low levels of chloride leads to an increased reabsorption of bicarbonate in kidneys. In addition, reduced extracellular volume decreases bicarbonate filtration in urine due to the reduction of glomerular filtration rate. All this leads to metabolic alkalosis. On the other hand, hypokalemia itself may cause metabolic alkalosis [9].

Yalcin et al. [10] found the incidence of PBS in patients with CF to be 12%, Ballestero et al. [11] 16.8%, and Fustik et al. [12] 16.5%. The first attack of PBS was most often before the age of one [9, 11]. In our patients only one patient had PBS beyond the first year of life (the patient was 17 months old at the time).

PBS is a usual complication in patients with established CF, but sometimes PBS can be the initial manifestation of CF [3]. In four of our patients the diagnosis of CF was based on neonatal screenings. In only one of our patients, in whom newborn screening was not performed, initial presentation of PBS and failure to thrive were followed by the diagnosis of CF. Marah [13] also described a case of an infant in which PBS was an initial manifestation of CF.

Risk factors for the development of PBS in CF patients include warm weather conditions (profuse sweating), severe respiratory or pancreatic disease and gastrointestinal losses (vomiting and diarrhea) [13]. Due to hyponatremia and hypochloremia, which appear in these diseases, the appetite is reduced, which additionally decreases the salt intake [14]. None of our patients had vomiting, but salt loss was caused by profuse sweating, and only a single patient had salt loss by ileostomy due to meconium ileus.

It is well known that PBS in patients with CF usually presents during warm summer months [15]. In four of our patients the trigger of PBS was high air temperature during

hot summer. In addition, in one patient with ileostomy, due to meconium ileus after birth, who had great losses through it, PBS appeared during winter.

In patients with PBS, differential diagnosis includes: cyclical vomiting (pyloric stenosis), congenital chloride-losing diarrhea, sustained gastric suction, misuse of laxatives, Gitelman syndrome, use of diuretics (in which case chloride in urine is low!) and primary hyperaldosteronism [9]. Igrutinović et al. [16] described a case of an infant with congenital chloride diarrhea and PBS.

All of our patients had a usual diet appropriate for their age, before the onset of PBS. Despite sodium intake being appropriate, they had extreme salt loss. The patient who was on cow's milk, which contains larger amounts of sodium, developed PBS as well. In most studies with CF PBS, majority of infants has been breast feeding. In a study by Fustik et al. [12], all the patients with CF PBS were breastfed. Kennedy et al. [5] described seven patients with CF PBS, all of who were on cow's milk.

After the initial intravenous fluid rehydration during one or two days, and electrolyte supplementation, oral substitution therapy with sodium and potassium was performed for all patients during further hospitalization. The substitution of potassium was performed for three to four days, because the stabilization of sodium homeostasis, that is elimination of secondary hyperaldosteronism, the cause of excessive renal loss, disappeared.

The substitution of sodium was continued for all patients after the hospital discharge (up to six months). Oral substitution with sodium and/or potassium can be carried out in all patients with CF PBS over months, and even years. To date there is no clear position on how long the supplementation with sodium chloride or potassium chloride should be applied. It is suggested that the treatment is recommended until normal growth of the child is restored and until serum electrolyte levels are satisfactory, even after the abolition of supplementary therapy [17].

Yalcin et al. [10] published a review of as many as 29 patients with PBS. The average age at diagnosis of CF PBS was four months. In 11 patients CF was not diagnosed until CF PBS occurred. There were no differences in age, gender, genotype or severity of PBS attacks between those with pre- and post-PBS-diagnosed CF. Nine of the 29 patients were being fed breast milk, and the rest were taking formula milk. In all patients acid-base status and serum electrolyte levels were normalized after two to four days. Most of the patients had a respiratory exacerbation when PBS occurred (profuse sweating, loss of appetite and high fever). All of them had vomiting, loss of appetite, failure to thrive during the PBS episode [10].

In all the patients the values of rennin were high. Aldosterone values were high in four patients and within borderline range in one patient. This can be explained by the fact that the low serum potassium suppresses the secretion of aldosterone.

In conclusion, PBS is one of complication of CF, especially in infants and young children in situations accompanied by increased sweating and/or other causes of additional loss of sodium and chlorine. Sometimes, as was the case with one of our patients, PBS may be the initial presentation form of the disease. Hence, patients with CF in a state of increased sweating or other situations accompanied by increased loss of electrolytes require appropriate compensation.

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Псеудо-Бартеров синдром код болесника са цистичном фиброзом: приказ случајева и преглед литературе

Гордана Вилотијевић-Даутовић[1,2], Весна Стојановић[1,2]

[1]Институт за здравствену заштиту деце и омладине Војводине, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

КРАТАК САДРЖАЈ

Увод Псеудо-Бартеров синдром (ПБС) се одликује хипонатремијском и хипохлоремијском метаболичком алкалозом, као и Бартеров синдром, али без поремећаја функције реналних тубула. Приказано је пет болесника са цистичном фиброзом (ЦФ) и ПБС.

Приказ болесника Четири детета узраста од три месеца до пет и по месеци са претходно дијагностикованом ЦФ и једно дете од 17 месеци са дотад недијагностикованом ЦФ примљена су на болничко лечење током летњег периода због тешке дехидратације, олигурије, апатије и адинамије. Једно дете је такође имало илеостому због меконијумског илеуса по рођењу. Сва деца су била на исхрани без додатног уноса соли. Лабораторијске анализе на пријему су код свих показивале хипонатријемију (115–133 *mmol/l*, просечно 122,4 *mmol/l*), повишену плазма-ренинску активност (229–500 *pg/ml*, просечно 324 *pg/ml*) и метаболичку алкалозу (*pH* 7,5–7,6, просечно 7,56), док су код четворо деце забележени висок ниво алдостерона у крви (74–560 *pg/ml*, просечно 295,9 *pg/ml*), хипокалемија (2,3–2,8 *mmol/l*, просечно 2,6 *mmol/l*), хипохлоремија (59–71 *mmol/l*, просечно 66 *mmol/l*) и снижена вредност натријума у мокраћи (5–12 *mmol/l*, просечно 9 *mmol/l*). Након интравенске рехидратације и наставка додатног уноса натријума и хлора у просечној дози од 1,78 *mmol/kg* дневно, сва деца су се потпуно опоравила. Са саветом за додатни унос соли у поменутој дози деца су пуштена кући.

Закључак ПБС је једна од компликација ЦФ, посебно код одојчади и мале деце, у условима појачаног знојења и/или постојања других разлога праћених повећаним губитком натријума и хлора. Некада, као у случају једног од наших болесника, ПБС може бити прва манифестација ЦФ.

Кључне речи: цистична фиброза; псеудо-Бартеров синдром; одојчад

Примљен • Received: 20/01/2015 **Прихваћен • Accepted:** 19/03/2015