DOI: 10.4274/buchd.galenos.2023.44520
J Dr Behcet Uz Child Hosp 2023;13(2):94-100

Original Article

Pseudo-Bartter Syndrome in Patients with Cystic Fibrosis and Clinical Features

Kistik Fibrozis Hastalarında Psödo-Bartter Sendromu ve Klinik Özellikleri

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ABSTRACT

Objective: Pseudo-Bartter syndrome (PBS) is a complication of cystic fibrosis (CF) accompanied by electrolyte disorders. We aimed to compare the clinical features of patients diagnosed with CF with or without PBS in our clinic.

Method: One hundred twenty-eight patients with the diagnosis CF data was recorded. Clinical features, diagnostic test results, colonization status, complications and genetic test results were compared in patients with and without PBS.

Results: Totally 128 patients who were regularly followed diagnosis CF January 2017 and May 2022 and 18 of them (14%) developed PBS. Median age of CF diagnosis was significantly lower in patients with PBS (p<0.003). There was a significant difference between the two groups in terms of colonization. In the group with PBS, the chronic respiratory tract colonization was detected more. There were no significant differences for age, gender, weight, height, sweat test. The most common genetic mutation was c1521_1523delCTT (p. F508Del).

Conclusion: PBS was the most common finding in our patients with CF. It may be exacerbated by the warm weather conditions in our country. It may be a clue for early diagnosis of CF.

Keywords: Cystic fibrosis, Pseudo-Bartter syndrome, complications

ÖZ

Amaç: Psödo-Bartter sendromu (PBS) kistik fibrozis (KF) hastalığının elektrolit bozukluğu ile seyreden bir komplikasyonudur. Kliniğimizde KF tanısı olan, PBS gelişen ve gelişmeyen hastaların klinik özelliklerini karşılaştırmayı hedefledik.

Yöntem: Kistik fibrosis tanısı olan 128 hastanın verileri kayıt edildi. PBS gelişen ve gelişmeyen hastaların klinik özellikleri, tanısal test sonuçları, kolonizasyon durumları, komplikasyonları ve genetik sonuçları karşılaştırıldı.

Bulgular: Kistik fibrozis tanısıyla Ocak 2017-Mayıs 2022 tarihleri arasında kliniğimizde düzenli takip edilen 128 hastamız olup bunların 18'inde (%14) PBS gelişti. Hastaların ortalama tanı yaşı PBS olanlarda anlamlı olarak daha düşüktü (p<0,003). Yaş, cinsiyet, ağırlık, boy, ter testi, kronik solunum yolları bakteriyel kolonizasyonları ve KF komplikasyonlar arasında anlamlı farklılık yoktu. En sık görülen genetik mutasyon deltaF508 idi.

Sonuç: PBS kistik fibrozis hastalarımızda en sık görülen bulguydu. Ülkemizde sıcak hava koşulları buna neden olabilir. Kistik fibrozis hastalığının erken tanısı için ip ucu olabilir.

Anahtar kelimeler: Kistik fibrozis, Psödo-Bartter sendromu, komplikasyon

Received: 22.12.2022
Accepted: 26.01.2023

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Cite as: Özaslan MM, Duman Şenol H, Barlık M, Çoksüer F, Dindar B, Demir E, Gülen F. Pseudo-Bartter Syndrome in Patients with Cystic Fibrosis and Clinical Features. J Dr Behcet Uz Child Hosp. 2023;13(2):94-100

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessively inherited disease with an incidence of on in every 2,000-3,000 births[1]. In the United States, the mean life expectancy for the patients born with CF in 2018 was 47.4 years. According to 2017 data from the Turkish National Cystic Fibrosis Data Registry System, in 1,170 of patients, 23% of diagnoses were made by the neonatal screening program[2]. Mutation of the CF transmembrane conductance regulator (CFTR) protein, which is a complex chloride channel regulator protein that exists in all exocrine tissues, causes CF. Irregular transportation of ions like sodium, chloride and bicarbonate (HCO_3) results in thick viscous secretions in lungs, pancreas, liver, intestines and genital system and increases the amount of salt in sweat glands[3,4]. Chronic cough, phlegm and

wheezing are among respiratory tract findings. As the disease progress, it causes damage to the walls of the bronchus and bronchiectasis develops[5].

Respiratory tract infections due to pathogenic bacteria occur at early ages. *Staphylococcus aureus, Hemophilus influenza* and *Pseudomonas aeruginosa* are type of microorganisms that frequently colonize the respiratory tract[6]. Pseudo-Bartter syndrome (PBS) is a known complication of cyctic fibrosis the clinical presentation of hyponatremia, hypokalemia, hypochloremia and metabolic alkalosis[6]. Unlike Bartters syndrome, chloride excretion in urine is low. PBS is generally seen in infancy and in regions with warm climate[7]. Risk factors for developing PBS include warmer climate conditions, vomiting, diarrhea and respiratory tract infections[7]. Individuals with CF lose the increased amount of sodium and chloride, they cannot compensate for this loss due to reasons like malnutrition and this causes development of PBS. The purpose of this study was to compare the clinical features of patients with and without PBS to determine the risk factors for PBS development[8].

MATERIALS and METHODS

All data were recorded for 128 patients who were diagnosed with CF and regularly followed between January 2017 and May 2022. The diagnosis of CF was made with two criteria: (a) chloride concentration higher than 60 mmol/Lin two sweat-tests, and (b) one sweat-test higher than 60 mmol/L and two mutations related to the disease in DNA sequence analysis. If the sweat-test was lower or equal to 60 mmol/L, two different disease-related mutations with typical clinical features of CF were considered CF. If patients had hyponatremia (<134 meq/L) (severe <125, light-medium >125), hypochloremia (<100 meq/L), hypopotassemia (<3.4 meq/L) and metabolic alkalosis (HCO_3 >27) with dehydration but without renal tubulopathy, they were diagnosed with PBS.

Sex, present age, age at the time of diagnosis, height, weight and body mass index (BMI) z-scores were recorded. Accompanying complications (bronchiectasis, allergic broncho-pulmonary aspergillosis, diabetes mellitus, chronic liver disease), culture from sputum and existence of colonization were studied. Genetic results were scanned taking Clinical and Functional Translation of CFTR (CFTR2) and CFTR France database as references. Arterial blood gas and biochemical parameters (sodium, potassium, chlorid). Informed consent was obtained from all the patients and/or their parents and ethics committee approval was provided by Ege University Ethical Committee for Medical Research for the study (decision no: 22-6.1T/49, date: 23.06.2022) were recorded for patients who developed PBS.

Statistical Analysis

The IBM SPSS statistics 20.0 for Windows (Chicago, IL) was used for the statistical measurements. The χ^2 test was used for nominal variables. The data was expressed as mean ± standard deviation. Student t-test was used if parametric conditions were obtained if not, the Mann-Whitney U test was used. The Kolmogorov-Smirnov/ Shapiro-Wilk test was applied to test the normal distribution of the numerical variables. P-value of less than 0.05 was considered significant.

RESULTS

In our clinic, 18 (14%) of 128 CF patients who were followed developed PBS. Of all patients, 70 (55%) were male and 58 (45%) were female. Of the 18 patients with PBS 11 (61%) were male. The median age of diagnosis for CF was median 24 months [minimum (min): 1; maximum (max): 86]. The age of patients median PBS was 18 months. The median age of patients without PBS was median 49 months (min 1; max 168). Between the two groups, the mean age of CF diagnosis was significantly lower for the group with PBS (p=0.003). There was no statistical difference between the current age of patients (p=0.060). The age of patients median PBS was 18 months.

Mean Z-score for weight was -1.25±2.50 in the group with PBS and -1.08±1.63 in the group without PBS (p=0.782). Mean Z-score for BMI was-0.93±2.5 in the group with PBS and -0.81±1.71 in the group without PBS (p=0.719). There were no differences between weight and BMI of the groups. Sweat-test results were lower in the group with PBS, but there was no significant difference. When the immunoreactive trypsinogen screening test was compared between the two groups, it was positive in 4 patients (22.2%) in the PBS group, while it was positive in 27 patients (24.5%) in the non-PBS group (p=0.072).

There was a significant difference between the two groups in terms of bacterial colonization of chronic respiratory tract. While the colonization rate was 50.0% in the PBS group, it was 21.8% in the non-PBS group (p=0.021). Colonization distribution was *P. aeruginosa* for 22.2% of patients with PBS while 10.0% non-PBS patients (p=0.041), colonization was *S. aureus* for 16.7% of patients with PBS while 9.1% non-PBS group (p=0.061), *S. aureus* and *P. aeruginosa* colonization together rate was 11.1% PBS patients while 2.7% non-PBS patients

(p=0.032), there was a significant difference between the two groups.

Although not statistically meaningful, male patient rates were higher, weight, height, BMI Z-scores were lower and development of ABPA and diabetes were more frequent in patients with PBS. When the drugs that both groups use regularly are examined, they included dornase alpha, multi-vitamin, pancreatic enzymes, B2 agonist, inhaler steroids and inhaler antibiotics. There were no significant differences detected. Table 1 presents the comparison of clinical and demographic features of PBS and non-PBS patients.

When the complaints related to PBS are investigated, they included nausea-vomiting in 14 (48.2%), fever in 9 (31.0%), diarrhea in 6 (20.7%), stomachache in 4 (13.8%) and cough in 2 cases (6.9%). Hospitalization duration for the PBS group was 5.2±2.1 days and acute pulmonary exacerbation accompanied the clinical representation of PBS in three patients (16.6%). Culture from sputum of three patients (16.6%) had breeding and there was also acute pulmonary exacerbation accompanying PBS. All of the patients administered had parenteral fluid therapy. The patients with breeding in sputum culture were administered 14 days of antibiotic treatment along side fluid therapy. Sputum culture of two patients had *P. aeruginosa* growth; therefore, they were treated with meropenem and amikacin. One patient had *S. aureus* growth and was treated with ceftazidime and amikacin. Acute pulmonary exacerbation diagnosis was made with respiratory distress, increased cough and sputum. Four patients (3.12%) attended with PBS clinical findings and

Table 1. Clinical and demographic comparison of Pseudo-Bartter syndrome and non- Pseudo-Bartter syndrome patients

	Patients with PBS, (n=18)	**Patients without PBS, (n=110)**	**p-value**
Age of CF diagnosis (months)[a]	24 (1-86)	49 (1-168)	0.003
Current age (months)[a]	84 (4-144)	96 (5-189)	0.060
Sex (M/F)	11/7	59/51	0.061
z-score for weight[b]	-1.25±2.50	-1.08±1.63	0.782
z-score for height[b]	-1.28±1.75	-1.24±1.60	0.921
z-score for BMI[b]	-0.93±2.5	-0.81±1.71	0.719
1st sweat chloride test mmol/L[b]	75.22±24.96	86.50±32.20	0.126
2nd sweat chloride test mmol/L[b]	69.66±28.44	82.30 ±29.11	0.110
Neonatal screening positivity, n (%)	4 (22.2)	27 (24.5)	0.072
Colonization, n (%)	9 (50.0)	24 (21.8)	0.021
Pseudomonas aeruginosa, n (%)	4 (22.2)	11 (10.0)	0.041
Staphylococcus aureus, n (%)	3 (16.7)	10 (9.1)	0.061
P. aeruginosa and *S. aureus*, n (%)	2 (11.1)	3 (2.7)	0.032
Complication			
Bronchiectasis, n (%)	2 (11.1)	14 (12.7)	0.651 0.464
Chronic liver disease, n (%)	1 (5.5)	7 (6.3)	
Diabetes mellitus, n (%)	1 (5.5)	2 (1.8)	
ABPA, n (%)	1 (5.5)	2 (1.8)	
Drugs used			
Dornase alpha, n (%)	15 (83.3)	77 (89.5)	0.544
Multivitamin, n (%)	15 (83.3)	75 (87.2)	0.496
Pancreatic enzyme, n (%)	14 (77.7)	74 (86.0)	0.532
B2 agonist, n (%)	9 (50.0)	34 (39.5)	0.461
Inhaled steroid, n (%)	3 (16.6)	12 (13.9)	0.472
Inhaled antibiotic, n (%)	3 (16.6)	21 (13.9)	0.634

[a]median, interquartile range, [b]mean ± standard deviation, CF: Cystic fibrosis, PBS: Pseudo-Bartter syndrome, BMI: Body mass index, ABPA: Allergic bronchopulmonary aspergillosis, M/F: Male/female

were diagnosed with CF. The majority of attendances due to PBS occurred during the summer season (72%).

During admission, mean serum levels were sodium 125.5 meq/L (min: 112.4; max: 132.3), potassium 2.4 meq/L (min: 1.9; max: 3.2) and chloride 71.4 (min: 56.2; max: 86.3). Mean pH of arterial blood gas was 7.50 (min: 7.46; max: 7.65) and mean HCO_3 levels were 35.9 (min: 28.1; max: 48.6). Of patients, 72.2% (n=13) had their PBS exacerbations in the summer.

Severe hyponatremia (Na <125) was detected in 10 (55.6%) of the patients with PBS at the time of admission. Two patients with serum sodium levels of 120 meq/L and 115 meq/L were admitted to hospital with hyponatremic convulsions. When the demographic and clinical characteristics of patients with and without severe hyponatremia were compared, the number of hospitalization days and chronic bacterial colonization were found to be higher in patients with severe hyponatremia, but there was no statistically significant difference. Clinical features patients according to their sodium levels shown in Table 2.

With the PBS table, 18 patients attended 29 times. Of patients, 72.2% (n=13) had PBS attacks in the summer months. For the 29 PBS attendances in the table, information about salt use was accessed during attendance for 20 cases and 60% of patients did not use salt. One patient had PBS recur four times, one had PBS recur three times and 6 patients had PBS recur twice. When patients with and without recurrent PBS are compared, the chronic bacterial colonization rates were significantly high for patients with recurrent PBS (p=0.031). The annual mean pulmonary exacerbation number for patients with recurrent PBS attacks was four, while it was two for patients with a single attack.

There were 17 different mutations in 34 different alleles in patients with PBS. The most common mutation was homozygote c.1521_1523delCTT (F508del) with 4 (11.76%) alleles. The other common mutations were c.2052delA (2184delA), and c.3131A>G (E1044G). Genetic mutations of the patients with PBS are shown in Table 3.

DISCUSSION

PBS can be the first form of hospital admission for CF. PBS frequency was 14% in our study. This rate was 10% in a study in our country using Cystic Fibrosis Data Registry System data, while Dahabreh et al.[9] found 9% and 16.8% in another study in Spain.

Age of CF diagnosis and current age of patients with PBS were significantly younger than non-PBS cases. The study found mean age of diagnosis of the patients with PBS was 0.77±1.70 years using the Cystic Fibrosis Data Registry System in our country, which was similar to our study. In this age group, feeding with low-sodium breast milk may be associated with increased tendency toward dehydration[9]. In countries without a newborn screening program, PBS may be an early symptom that indicates CF, before patients develop permanent pulmonary defect[10,11]. Educating physicians about differential diagnosis for patients admitted with hypokalemic metabolic alkalosis is a necessity[12].

Z-score weight, height and for BMI was higher in the non-PBS group. Patients with PBS have more diarrhea and vomiting, which causes feeding disorder and their increased metabolic requirements which affects growth and development. Additionally, as *P. aeruginosa* and *S. aureus* colonization was more frequent in the PBS group, frequent pulmonary infections may be associated with disrupted nutrition.

Beginning in 2015, heel lance blood samples began to be scanned for immune reactive trypsinogen because CF causes serious pulmonary and metabolic problem our country. The first and second sweat-test results of

Table 2. Clinical features of Pseudo-Bartter syndrome patients according to their sodium levels

	Sodium <125 (n=10)	Sodium >125 (n=8)	p-value
Age of CF diagnosis (months)[b]	6.4±1.2	12.2±2.2	0.302
Sex (M/F)	6/4	5/3	0.522
Colonization (n, %)	5 (50)	4 (50)	0.264
z-score for height[b]	-1.79±2.11	-1.52±1.72	0.567
z-score for weight[b]	-1.22±1.90	-1.12± 1.63	0.361
1st sweat test mmol/L[b]	72.21±24.61	68.12±22.54	0.384
2nd sweat test mmol/L[b]	65.45±19.11	66.33±21.36	0.435
Hospital stay/day[a]	11 (4-18)	6 (3-8)	0.061

[a]median, interquartile range, [b]mean ± standard deviation, CF: Cystic fibrosis, M/F: Male/female

patients with PBS were low. In a multi-center study in our country, chloride levels were low on the 1st and 2nd sweat tests, similar to our study. The authors speculated that the reason could be chronic chloride loss from sweating and this may result in low serum chloride concentration. We think that chronic chloride loss from sweat is higher in patients with PBS.

Opportunistic pathogens like *S. aureus* and *P. aeruginosa* colonize the respiratory tracts of CF patients[13,14]. In all of the CF patients, the *P. aeruginosa* colonization rate was 11.8%, *S. aureus* colonization rate was 10.2% and the *P. aeruginosa* and *S. aureus* colonization rate was 4%. These rates are similar to another study in our country. In Europe, the chronic *P. aeruginosa* infection rate was between 14.29% and 62.16%. The group with PBS syndrome had higher chronic bacterial colonization in the lungs. For this, increased mucous density and viscosity with electrolyte changes and dehydration and the higher accompanying complications in the PBS group may be associated with the higher regression in growth development. According to 2019 European data, the chronic *Pseudomonas* infection rate changes between 15.38% and 67.5%. *P. aeruginosa* and *S. aureus* colonization was more frequent in the group with PBS compared to non-PBS cases. This may be related to patients diagnosed at early ages and being younger. Bronchiectasis and chronic liver disease were more frequent among the non-PBS group. There were no significant differences for complications between the two groups.

The majority of attendances due to PBS occurred during the summer season. This may be associated with our country being located in a hot climate belt and greater tendency for dehydration due to patients not increasing fluid and sodium intake during the summer months.

Eight patients had repeated PBS attacks and bacterial colonization rates were higher in these patients. Also annual numbers of exacerbations and hospitalization of these patients were higher. They were admitted to hospital with severe hyponatremia. In these patients, often dehydration attacks may increase the viscose secretions in the respiratory tract and may cause more bacterial colonization. As colonization increases, nutrition of the patients may worsen, which can disrupt the salt balance.

PBS is a fatal complication of CF that may cause electrolyte abnormalities, seizures, hypoventilation and arrhythmia[15-17]. It is difficult to provide strict rules about electrolyte supplements needed and the dose and duration of therapy[18-20]. The purpose of the therapy is to ensure normal electrolyte balance. When pulmonary exacerbation, gastroenteritis or over activity is seen, salt

Table 3. Genetic results of patients with Pseudo-Bartter syndrome

C DNA name	Protein name	Legacy name	Phenotype	Genotype information	n	%
c.1521_1523delCTT	Phe508del	deltaf508	disease-causing	homozygote	2	11.76%
				heterozygote	3	8.82%
c.2052delA	Lys684Asnfs*38	2184delA	disease-causing	homozygote	1	5.88%
				heterozygote	2	5.88%
c.3131A>G	p.Glu1044Gly	E1044G	unknown	homozygote	2	11.76%
c.328G>C	p.Asp110His	D110H	disease-causing	heterozygote	2	5.88%
c.3909C>G	p.(Asn1303Lys)	N1303K	disease-causing	heterozygote	2	5.88%
c.1624G>T	p.(Gly542*)	G542X	disease-causing	heterozygote	2	5.88%
c.274G>A	p.(Glu92Lys)	E92K	disease-causing	heterozygote	1	2.94%
c.2988+1G>A	No protein name	3120+1G>A	disease-causing	homozygote	1	5.88%
c.2834C>T	p.(Ser945Leu)	S945L	disease-causing	heterozygote	1	2.94%
c.1399C>T	p.(Leu467Phe)	1531C/T (L467F)	unknown	heterozygote	1	2.94%
c.2195T>G	p.(Leu732*)	L732X	disease-causing	homozygote	1	5.88%
c.254G>A	p.(Gly85Glu)	G85E	disease-causing	heterozygote	1	2.94%
c.1186A>T	p.Asn396Tyr	N369Y	unknown	heterozygote	1	2.94%
c.2339delG	p.Gly780	ValfsX23	unknown	heterozygote	1	2.94%
c.1202G>A	p.(Trp401*)	W401X (TAG)	disease-causing	homozygote	1	5.88%
c.1040G>C	p.Arg347Pro	R347P	disease-causing	heterozygote	1	2.94%

intake should increase. PBS patients were classified as severe (<125) and mild-moderate (>125) according to their sodium levels at admission and the two groups were compared. Mean duration of hospitalization and pulmonary colonization rate of the severe hyponatremia group were insignificantly higher. In the same group, acute bacterial exacerbation was present in patients and it was thought that this situation also lowered the sodium levels.

It is known that recombinant human DNAase (rhDNase) and inhaler hypertonic saline are used to increase mucociliary clearance, improve pulmonary function and decrease pulmonary exacerbations regardless of the severity[21-23]. Studies showed that these are related to decreased pulmonary function. The rates of use for inhaler antibiotics, steroids and B2 agonists were higher in the PBS group. This may be related to the higher chronic bacterial colonization rates and the more frequent pulmonary flare-ups. There were no significant differences between the two groups regarding the drugs they used.

The most common mutation in patients with PBS was F508. In a study using the National Cystic Fibrosis Data Registry system, the deltaF508 rate in our country was 28.4%. Other common mutations were c.2052delA and c.3131A>G. Three (10.8%) patients with PBS but also with normal CFTR genetic scanning were diagnosed with CF by using multiplex ligation-dependent probe amplification. The deltaF508 frequency in non-PBS group was 21.4%. Research in China observed the most frequent mutation in CF patients with PBS was c290G>A, while this mutation was not observed in our PBS patients. Mutation rates between the two groups were similar. This suggests that PBS is independent of mutations[24-26].

Study Limitations

Although all of the follow-up patients in our clinic were included the study, there are some limitations. Since our study is one centered, we have few patients. However as the patient count increases we will continue our work. Due to the data being analyzed by scanning files retrospectively, only limited information was reached.

CONCLUSION

In the conclusion PBS is a common finding of CF. Since CF is included in the newborn screening program, it should be kept in mind that asymptomatic patients are also followed in our country and the first clinical finding in these patients may be PBS. It is seen often in warm climate countries. CF should be considered for patients that attend with clinical manifestations of PBS and further examinations should be performed if suspected. Patients with CF diagnosis should be informed about PBS and warned about regular salt intake.

Ethics

Ethics Committee Approval: Ethics committee approval was provided by Ege University Ethical Committee for Medical Research for the study (decision no: 22-6.1T/49, date: 23.06.2022).

Informed Consent: Informed consent was obtained from all the patients and/or their parents.

Peer-review: Externally peer reviewed.

Author Contributions

Surgical and Medical Practices: M.M.Ö., H.D.Ş., M.B., F.Ç., B.D., E.D., F.G., Concept: M.M.Ö., H.D.Ş., M.B., F.Ç., B.D., E.D., F.G., Design: M.M.Ö., H.D.Ş., M.B., F.Ç., B.D., E.D., F.G., Data Collection or Processing: M.M.Ö., M.B., F.Ç., B.D., E.D., Analysis or Interpretation: M.M.Ö., H.D.Ş., F.Ç., B.D., E.D., F.G., Literature Search: M.M.Ö., H.D.Ş., M.B., F.Ç., E.D., Writing: M.M.Ö., H.D.Ş., M.B., E.D., F.G.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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