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ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

Clinical features and accompanying findings of Pseudo-Bartter Syndrome in cystic fibrosis

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Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFRT, Cystic Fibrosis Registry of Turkey; PBS, Pseudo Bartter syndrome.

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Abstract

Background: Pseudo-Bartter syndrome (PBS) is a rare complication of cystic fibrosis (CF) and there are limited data in the literature about it. We aimed to compare clinical features and accompanying findings of patients with PBS in a large patient population.

Methods: The data were collected from the Cystic Fibrosis Registry of Turkey where 1170 CF patients were recorded in 2017. Clinical features, diagnostic test results, colonization status, complications, and genetic test results were compared in patients with and without PBS.

Results: Totally 1170 patients were recorded into the registry in 2017 and 120 (10%) of them had PBS. The mean age of diagnosis and current age of patients were significantly younger and newborn screening positivity was lower in patients with PBS ($P < .001$). There were no differences between the groups in terms of colonization status, mean z-scores of weight, height, BMI, and mean FEV_1 percentage. Types of genetic mutations did not differ between the two groups. Accompanying complications were more frequent in patients without PBS.

Conclusion: PBS was detected as the most common complication in the registry. It could be due to warm weather conditions of our country. It is usually seen in younger ages regardless of mutation phenotype and it could be a clue for early diagnosis of CF.

KEYWORDS
cystic fibrosis, Pseudo-Bartter syndrome, registry

1 | INTRODUCTION

Pseudo-Bartter syndrome (PBS) is a known complication of cystic fibrosis (CF) which is consisted of hyponatremic, hypochloremic dehydration with metabolic alkalosis without renal pathology.[1] It is usually reported in infancy and warm climate countries.[1-3] Although exact mechanisms are not well known there are some explanations for mechanisms of PBS. Excessive salt and chloride loss from the sweat especially in hot environment, inadequate salt intake usually in infants who have breastfeeding, contributing gastrointestinal loss such as vomiting, diarrhea, or acute respiratory infections can aggravate metabolic alkalosis and hypoelectrolytaemia.[1,3,4] There are some small patient groups' results in the literature however larger series are not common.

We aimed to investigate the clinical features of CF patients with PBS. And also we want to compare clinical findings of CF patients with and without PBS.

2 | METHODS

All data was obtained from CF Registry of Turkey (CFRT) in 2017. Data of CF patients with and without acute exacerbation of PBS in 2017 who were recorded in CFRT was evaluated. CF diagnosis was based on ECFS Patient Registry inclusion criteria and included patients who fulfilled the diagnostic criteria: (a) two sweat tests greater than 60 mmol/L chloride, and (b) one sweat test greater than 60 mmol/L chloride and DNA analysis—two identified disease-causing CF mutations. If the sweat value was less than or equal to 60 mmol/L: (a) DNA analysis—two identified disease-causing CF mutations, and (b) clinical presentation—typical features of CF.[5] Data input to the registry was approved by local ethics committee and all patients and/or their parents were signed written consent for the data input. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Totally 15 demographic and 79 annually data compatible with ECFS Patient Registry were recorded in the registry consisted of demographic features, diagnostic tests, pancreatic sufficiency/insufficiency status, complications, colonization status, treatments, and transplantation status.

Age of diagnosis, current age, gender was noted. Weight and height measurements and body mass index (BMI) and their z-scores

by using reference values issued by the Centre for Disease Control were recorded.[6] History of meconium ileus, newborn screening results, sweat chloride test, and genetic test results were noted.

Pancreatic sufficiency/insufficiency status according to fecal elastase level and steatorrhea, accompanying complications such as chronic liver disease, CF-related diabetes, allergic bronchopulmonary aspergillosis, pneumothorax, hemoptysis, malignancy, osteoporosis, gastroesophageal reflux, sinusitis, malignancy, colonization results of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacia complex*, *Stenotrophomonas maltophilia*, *non tuberculosis mycobacterium* were noted if present. Pulmonary function tests were noted in patients who could perform, mean FEV_1 was recorded as percentage of predicted.

The CFTR genotype was noted and classified as severe if both mutations were class I, II, or III, as mild if ≥1 mutation was class IV or V, based on previously published classifications.[7,8]

Clinical features of all patients with and without PBS were compared. Since the current ages of the two groups were significantly different, age and gender matched 120 patients without PBS whose patient number in the registry ended with an even number were selected randomly and age and gender-matched patients with and without PBS were compared. Comparison of clinical features of newborn screening test positive patients with PBS and newborn screening test negative patients with PBS was done.

SPSS v.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. A *P*-value of less than .05 was considered significant.

3 | RESULTS

Totally 1170 CF patients were included in the registry in 2017 and 120 of them (10%) had PBS. Among all patients, 535 (46%) were females and 635 (54%) were males. The mean age of diagnosis was 1.92 ± 3.82 years, the median was 0.42 years (min, 0.08; max, 41 years) and 274 (23%) of them were diagnosed with neonatal screening, and 65 (5.5%) of patients had meconium ileus.

In 120 patients with PBS, seventy-one (59%) of them were male. The mean age of diagnosis was 0.77 ± 1.70 years, median 0.25 years (min, 0.08; max, 11 years). Pancreatic insufficiency was present in 90.8% of them and six of them (5%) had meconium ileus history. Newborn screening test was performed in 63 patients and 74.6% of them was resulted as positive, 8 of them were negative and 8 of them was resulted as unknown or not known if it was done. There were 1050 patients without PBS and 564 (50%) of them were male. The mean age of diagnosis was 2.09 ± 3.99 years, median 0.42 years (min, 0.8, max, 41 years), and the current age was 8.77 ± 6.37 years. Meconium ileus history was present in 59 (5.6%) of them and 87% of them had pancreatic insufficiency. The newborn screening test was performed in 211 patients and 88.6% of them was resulted as positive.

Mean z-scores for weight, height, and BMI and mean FEV_1 percentage of patients were similar in patients with and without PBS. First sweat chloride tests results were similar in two groups, however second sweat chloride test results were lower in patients with PBS ($P < .05$).

Thirty-three of the patients with PBS had *S. aureus*, 23 had *P. aeruginosa*, 4 had *S. maltophilia* colonization. No other colonization was detected in patients with PBS. Chronic liver disease accompanied in five patients and diabetes in one patient in patients with PBS and no other complication was recorded in patients with PBS. In patients without PBS, sinusitis was present in 110 patients, gastroesophageal reflux in 47, osteoporosis in 29, allergic bronchopulmonary aspergillosis in 19, major hemoptysis in 7 and pneumothorax in 2 and malignancy was present in 1 patient. Comparison of demographic features, meconium ileus history, pancreatic sufficiency/insufficiency status, newborn screening results, mean z-scores for weight, height and BMI, mean FEV_1 percentage, sweat chloride tests results, colonization status, and accompanying complications were shown in Table 1.

TABLE 1 Comparison of patients with PBS and without PBS

	Patients with PBS, n = 120 (%)	Patients without PBS, n = 1050 (%)	*P*
Age of diagnosis, y[a]	0.77 ± 1.70	2.09 ± 3.99	.001
Median of age (min-max), y	0.25 (0.08-11)	0.42 (0.08-41)	
Current age, y[a]	4.15 ± 3.59	8.77 ± 6.37	.001
Gender (M/F)	71/49	564/486	.256
Pancreatic insufficiency	109 (90.8)	914 (87.0)	.493
Meconium ileus	6 (5.0)	59 (5.6)	.624
Newborn screening positivity	47 (74.6)[b]	187 (88.6)[c]	.001
z-score for weight[a]	−1.05 ± 1.91	−0.89 ± 1.21	.372
z-score for height[a]	−1.21 ± 2.54	−1.08 ± 1.70	.577
z-score for BMI[a]	−0.15 ± 1.49	−0.46 ± 1.11	.111
FEV_1 percentage[a]	78.05 ± 23.29	81.56 ± 26.09	.511
1st sweat chloride test, mmol/L[a]	82.64 ± 28.45	87.68 ± 42.19	.104
2nd sweat chloride test, mmol/L[a]	74.66 ± 27.66	87.81 ± 27.15	.007
Colonization			
Staphylococcus aureus	33 (27.5)	262 (24.9)	.114
Pseudomonas aeruginosa	23 (19.1)	222 (21.1)	.110
Stenotrophomonas maltophilia	4 (3.3)	23 (2.1)	.469
Complications			
Chronic liver disease	5 (4.1)	88 (8.3)	.262
Diabetes	1 (0.8)	39 (3.7)	.139

Abbreviations: BMI, body mass index; PBS, Pseudo-Bartter syndrome.
[a]Mean ± standard deviation.
[b]Performed in 63 patients.
[c]Performed in 211 patients.

Clinical features of patients with PBS were compared with age and gender-matched patients without PBS. There were no significant differences in terms of newborn screening positivity, sweat chloride test results, meconium ileus history, pancreatic insufficiency, z-scores of weight, height and BMI, mean FEV_1 percentage, colonization status, and accompanying complications ($P > .05$). A comparison of the clinical features of patients with PBS and age and gender-matched patients without PBS was shown in Table 2.

Clinical features of patients with PBS who had positive newborn screening and negative newborn screening were compared and shown in Table 3. Pancreatic insufficiency was more common in patients with positive newborn screening (*P*:.001). First and second sweat chloride tests were lower in patients with negative newborn screening ($P = .025$, $P = .033$, respectively).

Forty-five different mutations and polymorphisms were detected in 65 patients in 120 alleles in patients with PBS. No mutation was detected in the others' genetic tests or not resulted yet. The most common mutation was DF508 in 19 alleles and it was homozygous in 5 (4%) patients. N1303K, D110H, G542X, and E92K were the other common mutations, respectively. In patients with PBS group, 44 patients (36%) had severe, 14 (11%) patients had mild mutations and the others had only polymorphisms or unclassified mutations. In patients without PBS, 413 (39%) patients had severe and 119 (11%) patients had mild mutations. There was no difference in terms of mutation classification between the two groups ($P > .05$).

TABLE 2 Comparison of patients with PBS and age- and gender-matched patients without PBS

	Patients with PBS, n = 120 (%)	Patients without PBS, n = 120 (%)	*P*
Age of diagnosis, y[a]	0.77 ± 1.70	0.45 ± 0.74	.309
Median of age (min-max), y	0.25 (0.08-11)	0.25 (0.08-6)	
Gender (M/F)	71/49	71/49	
Pancreatic insufficiency	109 (90.8)	103 (85.0)	.365
Meconium ileus	6 (5)	4 (3.3)	.301
Newborn screening positivity	47 (74.6)[b]	56 (88)[b]	.443
z-score for weight[a]	−1.05 ± 1.91	−1.14 ± 1.91	.726
z-score for height[a]	−1.21 ± 2.54	−1.21 ± 2.40	.977
z-score for BMI[a]	−0.15 ± 1.49	−0.23 ± 1.18	.734
FEV_1 percentage[a]	78.05 ± 23.29	83.70 ± 19.40	.403
1st sweat chloride test, mmol/L[a]	82.64 ± 28.45	78.90 ± 32.61	.378
2nd sweat chloride test, mmol/L[a]	74.66 ± 27.66	81.64 ± 27.76	.256
Colonization			
Staphylococcus aureus	33 (27.5)	29 (24.1)	.663
Pseudomonas aeruginosa	23 (19.1)	13 (10.8)	.094
Stenotrophomonas maltophilia	4 (3.3)	1 (0.8)	
Complications			
Chronic liver disease	5 (4.1)	10 (8.3)	.171
Diabetes	1 (0.8)	2 (1.6)	

Abbreviations: BMI, body mass index; PBS, Pseudo-Bartter syndrome.
[a]Mean ± standard deviation.
[b]Performed in 63 patients.

4 | DISCUSSION

Pseudo Bartter syndrome was reported in 10% of CF patients as the most common complication the CFRT and its frequency was similar with previous studies which are mostly reported from Turkey and Middle East countries.[2,3,9] However there is no data related with PBS incidence in Northern Europe.[1] PBS frequency was not reported in annual data reports of French, UK, Dutch, and ECFS CF registries in 2016 and 2017.[10-13] Turkey has more warmer climate than these countries.[14] Only there is a report from Spain where weather is more warmer from Northern Europe, PBS frequency was reported as 16.8%.[15] A previous study from our country showed that the frequency of PBS increased in the summer with the highest temperature.[16] Warmer climates of Turkey and Middle East countries may increase the incidence of PBS. Although chronic liver disease or CF-related diabetes were reported as common complications in many papers, we found PBS as the common complication.[17-19] Young age of our patients and the warm climate of our country may predispose it.

Age of CF diagnosis and current age of patients with PBS were significantly younger than the others. Inadequate salt intake due to breastfeeding, inability to meet their increased salt needs by own at this age group may predispose it.[1,3] It could also be possible that either the patients died due to PBS, without the diagnosis of CF being made are not reported in the registry in previous years or they are no longer present in the 2017 data because of death. PBS was reported as an important clinical finding of CF patients with persistent lower respiratory tract infection and severe malnutrition in low-income countries where newborn screening is not available.[20] The fact that the age of diagnosis is younger in patients with PBS may be due to the emergence of PBS in early ages which provide a clue for diagnosis.

Newborn screening for CF was implemented on January 2015 in Turkey and this is why only 23% of the CF patients diagnosed by newborn screening in this study. Elevated immunoreactive trypsinogen (IRT) level on the first week and then repeated on the second week of life (IRT\IRT) are used in screening algorithm. As soon as the CF diagnosis is made, routine salt supplementation is recommended for all infants aged under 2 years in Turkey. Newborn screening positivity was lower in patients with PBS, however no difference was observed when compared according to age and gender. Supplementation of salt in the newborn period as soon as they were diagnosed could be the reason of the lower frequency of PBS in these patients. This may be an explanation for the low incidence of PBS in

TABLE 3 Comparison of newborn screening positive and negative patients with PBS

	Newborn screening positive patients with PBS, n = 47 (%)	Newborn screening negative patients with PBS, n = 8 (%)	*P*
Age of diagnosis, y[a]	0.27 ± 0.30	0.45 ± 0.21	.054
Median of age (min-max), y	0.25 (0.08-2)	0.46 (0.08-0.83)	
Current age, y[a]	1.77 ± 1.08	1.50 ± 0.70	.448
Gender (M/F)	24/23	5/3	.549
Pancreatic insufficiency	45 (95)	2 (25.0)	.001
Meconium ileus	3 (6)	0 (0)	
z-score for weight[a]	−1.45 ± 2.16	−0.67 ± 1.6	.252
z-score for height[a]	−1.50 ± 2.67	−0.40 ± 2.50	.079
1st sweat chloride test, mmol/L[a]	78.63 ± 23.20	51.63 ± 26.78	.025
2nd sweat chloride test, mmol/L[a]	72.44 ± 21.71	34.67 ± 16.25	.033
Colonization			
Staphylococcus aureus	9 (19.1)	0 (0)	
Pseudomonas aeruginosa	6 (31.9)	1 (12.5)	
Complications			
Chronic liver disease	3 (6.3)	0 (0)	

Abbreviation: PBS, Pseudo-Bartter syndrome.
[a]Mean ± standard deviation.

countries where neonatal screening is established. In our study, although newborn screening which could provide early diagnosis and early salt supplementation to reduce the frequency of PBS, this was not enough to protect CF patients to develop PBS. Care should be taken in terms of PBS, and infants with CF should be closely followed in this regard.

Isolated PBS might be considered a CFTR-related disorder in infancy in cases where diagnostic criteria are not met, at least in selected-newborn screening negative- cases,[21] however, all patients in our study fulfilled the CF diagnostic criteria with sweat chloride test and/or genetic analysis.

Patients with PBS who had newborn screening test positivity had more common pancreatic insufficiency and higher sweat chloride test results, which might be related with CFTR dysfunction severity.

Pancreatic insufficiency was reported as a risk factor for PBS.[1] However, it was similar and more than 85% in two groups in this study which is compatible with the literature.[22] Lower mean z-scores of height, weight and BMI were observed in all patients and no differences detected between two groups. We should care more about nutrition in all CF patients in our country.

First sweat chloride tests were lower in patients with PBS and second sweat chloride tests were significantly lower in patients with PBS rather than patients without PBS. No relevant data could be found in the literature and we can speculate that chronic chloride loss in the sweat and reduced chloride concentration in the serum may cause the lower sweat chloride test results in patients with PBS.

Dahabreh et al[23] reported that *Pseudomonas* colonization was higher in patients with PBS in the first year of life. However we did not compare colonization status according to age. Total colonization status with *Pseudomonas spp* ve other microorganisms were similar in two groups and lower than the mentioned study.[23] It could be related with younger age of our patients. Although no significant difference was detected, accompanying diabetes and chronic liver disease and other complications such as sinusitis, osteoporosis, etc. were more frequent in patients without PBS and these could be related with older age of these patients.

Class I and class II mutations were seen more frequently in two groups and there were no differences in terms of mutation phenotype in this large cohort. And this shows that PBS could be detected in every CF patient regardless of mutation.

Since PBS can lead to severe neurological sequelae, and its treatment can be costly, the implementation of newborn screening of all newborns after 2015 in Turkey provides a significant contribution to the prevention of this potentially lethal situation.

Although we had a large patient population, our study had some limitations. It was a registry based study, therefore limited data were used in the study. We do not have the data about the frequency of PBS episodes of our patients and the number of patients who had PBS as a sole manifestation of CF. Besides, the season which PBS occurred was not recorded in our registry and we were not able to compare clinical data according to age groups. But with the continuation of data entry in our registry, we will be able to compare the data year by year in the future years.

In conclusion, PBS is a common complication of CF especially in countries with warm weather regardless of mutation phenotype. It is usually seen in younger ages and it could be a clue for early diagnosis of CF.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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