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PSEUDO-BARTTER'S SYNDROME IN PATIENTS WITH CYSTIC FIBROSIS

KİSTİK FİBROZİSLİ HASTALARDA PSÖDO-BARTTER SENDROMU

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ABSTRACT

Background: Pseudo-Bartter's syndrome (PBS) is a clinical entity characterized by hypokalemia, hypochloremia associated with metabolic alkalosis. It is different from Bartter's syndrome, in which hypokalemic metabolic alkalosis may develop without primary renal disease. Cystic fibrosis (CF), pyloric stenosis, continuous gastric drainage, cyclic vomiting, chloride loosing diarhea, and inappropriate laxative use can cause PBS. PBS can be an initial manifestation of CF or develops during follow-up of CF.

Aim: In this study, we aimed to evaluate patients with CF with respect to the development of PBS during diagnosis and follow-up period.

Methods: Patients with CF who were following up in our pediatric pulmonology and gastroenterology departments were evaluated with respect to PBS diagnosed at the beginning or during the course of the disease. Patients' demographic characteristics, duration of hospitalization, and biochemical values were presented.

Results: PBS was diagnosed in **7** (41.2%) of the total 17 patients with CF. Four were girls (57.1%) and the mean age was 3.1±1.3 months (1-5 months). While, 5 (29.4%) out of 7 patients were diagnosed as PBS at diagnosis of CF, 2 (11.7%) developed PBS during follow up.

Conclusion: PBS as the initial manifestation of CF has been reported in 6.4-16.8% of patients with CF. PBS has been detected in 41.2% in our patients, and PBS has been the initial manifestation in 29.4% of our patients. In conclusion, PBS is not a rare clinical picture and it should be considered in the evaluation of patients with CF.

Key words: Children, cystic fibrosis, Pseudo-Bartter's syndrome, metabolic, alkalosis

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ÖZET

Giriş ve Amaç: Psödo-Bartter sendromu (PBS), hipokalemik, hipokloremik metabolik alkaloz ile karakterize klinik bir tablodur. Bartter sendromundan farklı olarak, elektrolit kaybı böbrek dışı yollardan olmaktadır. Kistik fibrozis (KF), pilor stenozu, devamlı gastrik drenaj, siklik kusma, klor kaybettiren diyare ve uygunsuz laksatif kullanımı PBS'ye neden olabilmektedir. KF'li hastalarda PBS, tanı esnasındaki ilk klinik bulgu olabilmekte ya da hastalık sürecinde gelişebilmektedir. Bu çalışmada, KF'li olguların tanı ve izlem sürecinde PBS gelişimi açısından değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Kliniğimiz Çocuk Göğüs Hastalıkları ve Çocuk Gastroenteroloji Polikliniklerinden KF tanısı ile takipli olan hastalar başvuru anında veya takip sürecinde gelişen PBS açısından retrospektif olarak irdelendi. PBS sendromlu hastaların cinsiyetleri, yaş ortalamaları, hastanede yatış süreleri ve biyokimyasal değerleri araştırıldı.

Bulgular: İncelenen toplam 17 KF'li vakadan 7'sinde PBS bulundu (%41.2). PBS'li hastaların 4'ü kız (%57.1) olup, yaş ortalaması 3.1±1.3 ay (1-5 ay)'dı. Beş hastada PBS ilk tanı anında tespit edilirken (%29.4), diğer 2 hastada (%11.7) izlemde gözlendi.

Sonuçlar: KF'li hastaların %6.4-16.8 kadarında, ilk başvuru klinik bulgularının PBS şeklinde olduğu bildirilmektedir. Takip etmekte olduğumuz hastalarımızın %41.2'sinde PBS tablosu saptanmış olup, hastaların %29.4'ünde ilk başvuru bulgusu PBS olmuştur. Sonuç olarak PBS tablosu, KF'li hastalarda nadir rastlanan bir klinik tablo olmayıp ayırıcı tanıda mutlaka düşünülmelidir.

Anahtar Kelimeler: Çocuklar, kistik fibrozis, Psödo-Bartter sendromu, metabolik, alkaloz

INTRODUCTION

Cystic fibrosis (CF) is one of the most common, multisystemic autosomal recessive inherited disease. Although CF involves multiple organs, it mainly affects respiratory and gastrointestinal systems (1, 2).

Pseudo-Bartter's syndrome is a clinical entity characterized by hypokalemia, hypochloremia associated with metabolic alkalosis. CF, pyloric stenosis, continuous gastric drainage, cyclic vomiting, chloride loosing diarhea, and inappropriate laxative use can cause PBS (1).

PBS can be an initial manifestation of CF or develops later during follow up (3-10). It has been suggested that sweat electrolyte loss is increased and intensive reabsorption occurs in the renal tubules in CF (11). Due to chloride depletion, decreased sodium and chloride reabsorption in the loop of Henle results in increased sodium delivery to the distal tubules and increased absorption of sodium in exchange for potassium and hydrogen, causing hypochloremic hypokalemic metabolic alkalosis (11). The incidence of PBS may be increased in CF patients due to chronic sweat electrolyte loss, especially in high environmental temperatures, and in CF patients who have chronic vomiting and low dietary intake of salt and water (3-10).

MATERIAL AND METHODS

Seventeen patients with CF who have been following in our pediatric pulmonology and gastroenterology departments were evaluated with respect to PBS diagnosed either at the beginning or during follow up, retrospectively.

The diagnosis of CF was made by genetic analysis and the elevated sweat chloride test. Sweat chloride test was performed in all patients except one of them. Patients' demographic characteristics, clinical features, biochemical parameters, sweat chloride test values, and genetic mutation analysis were presented from their medical records.

Patients diagnosed as PBS were compared to patients with CF who haven't experienced a PBS attack with respect to age, sweat chloride test results, and genetic mutation analysis. Independent samples t test was used for statistical analysis of data. p value less than 0.05 was considered as statistically significant.

RESULTS

Pseudo-Bartter's syndrome is found in 7 (41.2%) out of 17 patients with CF. Four of them were girls (57.1%) and the mean age of the patients was 3.1±1.3 months (1-5 months). Five (29.4%) out of 7 patients were diagnosed as PBS at the first diagnosis of CF and 2 (11.7%) patients developed PBS during follow up of the disease.

All CF patients other than PBS presented with growth failure, recurrent lung infections, vomiting and diarrhea. Children with episodes of PBS presented with vomiting and diarrhea and clinical signs of dehydration without any previous respiratory symptoms.

The episodes of PBS took place during warmer months in 5 patients (71.4%) and during winter in 2 patients.

Physical examination of the patients with PBS revealed dehydration from mild to moderate degree. Mean sodium, potasium, chloride, urea, and creatinine levels were 125.7±3.7 meq/L, 2.8±0.3 meq/L, 80±7.9 meq/L, 36.7±21.5 mg/dL, and 0.49±0.1 mg/dL; respectively. Mean pH and bicarbonate values were 7.52±0.02 and 38±5.3 mmmol/L on blood gas analysis. Urinary chloride values were lower than 10 mEq/L in all patients. Renin and aldosterone analysis were performed in only 3 cases due to lack of diagnostic facilities. Renin and aldosterone levels were normal in 1 patient and elevated in 2. Demographic characteristics and laboratory values have been shown in Table 1.

Table 1. Demographic and laboratory values of the patients.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Gender	girl	girl	boy	boy	girl	girl	boy
Age (months)	4	5	3	3	4	1	2
Na (meq/L)	128	130	124	120	123	125	130
K (meq/L)	3.0	2.8	2.8	3.0	3.4	2.4	2.8
Cl (meq/L)	78	84	82	63	82	86	85
Urea (mg/dL)	24	46	15	78	41	18	35
Creatinin (mg/dL)	0.28	0.40	0.20	0.70	0.31	0.24	0.30
pH	7.54	7.51	7.50	7.53	7.50	7.51	7.58
HCO3 (mmmol/L)	48.5	39.5	35.2	39.5	31.8	37.0	34.7
Sweat chloride tests (meq/L)	69 109	108 93	138 143	72 106	115 109	113 84	Absent
Cystic fibrosis mutation analysis	ΔF-508 +/-	R347P +/+	G85E +/-	R347P +/+	Not detected	ΔF-508/ I-148 T	ΔF-508 +/+

Sweat chloride test values was not statistically different between patients experienced PBS attack and patients who did not experienced any PBS attack (104.5±23.4 vs.101.8±32 mEq/L; p=0.789).

Consanguineous marriage was present in 6 out of 17 (35.3%) patients with CF. The genotypes were D-F508 in 3 patients (42.9%, 2 of them were heterozygotes), R347P in 2 (28.6%), and G85E in 1 (14.3%) patient. No mutation was detected in 1 (14.3%) patient of PBS group. D-F508 mutation was heterozygote in 1 patient; G542X was homozygote in 1, N1303 was heterozygote in 1, and W1282X was heterozygote in 1. However, no mutation was found in genetic analysis of 6 CF patients without PBS.

DISCUSSION

CF is an autosomal recessive inherited disorder caused by mutations in the CF gene, which codes for a protein named 'CF-transmembrane conductance regulator' (CFTR) (1,11). Although the exact prevalenceof CF in our country is not known, the estimated prevalence varies from 1/2500 to 1/3500 in whites and 1/17000 in African Americans in the Unites States (1). The clinical features, age at diagnosis, severity of symptoms, and disease progression vary according to the type of the mutation (1).

PBS is mostly unrecognised in patients with CF. PBS prevalence in CF varies from 6.6-16.8% between different countries (4,9). In a previous study from our country (3),,PBS has been reported in 12% of the patients with CF; whereas in this study, 7 out of 17 patients had PBS in this study and 5 (29.4%) of them showed PBS attack as the presenting manifestation at the time of diagnosis. Laboratory evidence of PBS was also detected in 5 of 7 patients at the time of diagnosis .

In this study, the median age of diagnosis for PBS was 3.1 months. In previous studies, most children presented as PBS were under 6 months of age (3, 6, 7, 10). These babies are mostly breast fed and more vulnerable to salt depletion due to low salt content of the breast milk. In our study, multiple factors including hot weather, exclusively breast fed infants with a mean age of 3 months, and episodes of vomiting and diarhea were contributory factors for development of PBS episodes.

The episodes took place during the warmer months in 5 patients (71.4%), which are thought to be caused by increased sweating and electrolyte loss through the skin. Gastroenteritis (vomiting, diarrhea) act as the contributory factor in these situations.

In CF, sweat electrolyte loss leads to reabsorption of sodium from the renal tubules in exchange for potassium and hydrogen ions leading to contraction of extracellular space and activation of renin-angiotensin system (1,11). In this study, aldosterone levels were investigated in only 3 patients. Aldosterone levels were found to be elevated in 2 patients and normal in 1. Low potassium levels could lead to suppression of aldosterone, despite elevated levels of aldosterone was expected andurine chloride levels were low in all patients as expected.

The diagnosis of CF has been based on a positive sweat chloride test, presence of typical clinical features (respiratory, gastrointestinal, or genitourinary findings) or a positive family history (1, 12). However, in our patients there was no previous history of respiratory complaints, no history of CF in one of their siblings, and no gastrointestinal symptoms to suggest the possibility of CF.The only symptom was hypokalemic metabolic alkalosis accompanied by vomiting and diarhea in our patients group. Laboratory evidence of PBS attack was detected in 5 patients at the time of diagnosis. Therefore, it should be kept in mind that at diagnosis of CF, presenting as PBS is much more common than expected and CF should be considered in the differential diagnosis of hypokalemic metabolic alkalosis especially in patients less than 6 months of age. In consistent with Fustik's study, sweat chloride test values in CF patients having PBS attack was not statistically different from those in CF patients who haven't experienced any PBS attack (7). We could not find any literature about a specific mutation associated with CF patients having PBS attack. Although, we found that ΔF-508 mutation was more common in CF patients having PBS attack, number of patients are limited to draw any conclusion in this study.

The clinical features suggestive of CF vary with the age at the time of clinical presentation. In our study, the incidence of PBS was higher than expected and the mean age of patients was 3.1 months. In order to make the correct diagnosis, attacks of the patients with hypochloremic metabolic alkalosis should be evaluated for the diagnosis of CF, especially in patients less than 6 months of age. Patients with CF are prone to develop PBS. Then, sodium supplementation and adequate hydration are very important in hot weather especially in patients less than 6 months of age and evaluation of PBS should be performed in the follow up examinations of CF patients.

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