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The clinical importance of sweat chloride levels in children with repeated pulmonary infection or growth retardation

Tekrarlayan akciğer enfeksiyonlu veya gelişme geriliği olan çocuklarda ter klor düzeylerinin klinik önemi

Abdülaziz Gültürk, Köksal Deveci*, Ali Kaya, Ahmet Sami Güven, Enver Sancakdar, Ömer Cevit

Pediatrics Clinic (A. Gültürk, MD), Özel Sivas Anadolu Hospital, TR-58070 Sivas, Department of Clinical Biochemistry (Assist. Prof. K. Deveci, MD, Assist. Prof. E. Sancakdar, MD), Department of Pediatrics (Assist. Prof. A. Kaya, MD, Assist. Prof. A. S. Güven, MD, Prof. Ö. Cevit, MD), Cumhuriyet University School of Medicine, TR-58140 Sivas

Abstract

Aim. Cystic fibrosis occurs as a consequence of mutations in the gene regulation of transmembrane message and shows autosomal recessive inheritance. The disease is more frequent among white people; Clinical findings and symptoms in cystic fibrosis can be very different due to the age of patients, type of mutation and complications. In our country, the most common complaints of cystic fibrosis patients in application to hospital are problems in respiratory tract and growth retardation. In this study, we aimed to findhe frequency of cystic fibrosis in children who applied to our clinic with growth retardation and/or recurrent pulmonary infections. **Method.** This prospective study was conducted between September 2009 and September 2010 in 218 children who applied to our clinic with symptoms of malnutrition and/or recurrent pulmonary infections and had not been diagnosed as cystic fibrosis before. These patients underwent sweat test and their clinical chracteristics were noted. The diagnosis of cystic fibrosis was made by using positive sweat test , appropriate clinical findings and by exclusion of other diseases that also cause recurrent pulmonary infections or malnutrition. **Results.** The mean age of children was 54.40 ± 48.70 months. Of all children, 100 (45.9%) were male and 118 (54.1%) were female. Positive sweat test was found in 9 (4.2%) children. The frequency of cystic fibrosis was found to be 7.8 % in children with recurrent pulmonary infections and 10.5% in children with weight percentile values <3 p. and 9.3% in children with height percentile values <3 p. **Conclusion.** Sweat test is clinically important for the early diagnosis of cystic fibrosis and in prevention of complications related to this disease in children with growth retardation or recurrent pulmonary infections.

Keywords: Cystic fibrosis, sweat test, pulmonary infection, growth retardation

Özet

Amaç. Kistik fibrozis, transmembran ileti regülasyonu genindeki mutasyon sonucu oluşur ve otozomal resesif kalıtım gösteren bir hastalıktır. Beyaz ırkta daha sık görülür. Hastalığın klinik bulguları hastanın yaşı, mutasyonun tipi ve komplikasyonlarına bağlı olarak çok büyük değişiklikler göstermektedir. Ülkemizde de en sık başvuru nedeni solunum yolu problemleri ve büyüme gelişme geriliğidir. Bu çalışma ile rekürren akciğer enfeksiyonu veya gelişme geriliği şikâyetleri ile kliniğimize başvuran hastalarda kistik fibrozis sıklığının arastırılması amaçlanmıştır. **Yöntem.** Bu prospektif çalışmada; Eylül 2009 ve Eylül 2010 tarihleri arasında tekrarlayan akciğer enfeksiyonu ve gelisme geriliği sikâyetleri ile kliniğimize basvuran ve daha önce tanı almamış 218 hastada ter testi yapılarak, kistik fibrozis sıklığı araştırılmış ve hastaların klinik özellikleri incelenmiştir. Vakalarda kistik fibrozis tanısı; kistik fibrozis kliniği ile uyumlu bulgulara sahip olma, diğer hastalıkların dışlanması ve ter testi pozitifliği esaslarına göre kondu. **Bulgular.** Vakaların yaşları ortalama 54,40±48,70 ay idi. Vakaların 100 (%45,9)'ü kız, 118 (%54,1)'i erkek idi. Ter testi sonucu çocukların 9 (%4,2)'unda pozitif bulundu. Tekrarlayan akciğer enfeksiyonu olan çocuklarda kistik fibrozis sıklığı %7,8 , ağırlık ve boy persantilleri < 3 persantil olan çocuklarda ise kistik fibrozis sıklığı sırasıyla %10,5 ve %9,3'dü. **Sonuç.** Gelişme geriliği ve tekrarlayan akciğer enfeksiyonu olan çocuklarda kistik fibrozis tanısının erken konulması ve geç komplikasyonlarının önlenmesi için ter testi klinik olarak önemlidir.

Anahtar sözcükler: Kistik fibrozis, ter testi, akciğer enfeksiyonu, gelişme geriliği

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***Corresponding author:**
Dr. Köksal Deveci, Tıbbi Biyokimya Anabilim Dalı, Cumhuriyet Üniversitesi Tıp Fakültesi, TR-58140 Sivas. E-mail: drkdeveci@gmail.com

Introduction

Cystic fibrosis (CF) occurs as a result of a mutation in the gene of trans membrane conduction regulation and is the most fatal disorder with autosomal recessive heredity in the white race [1]. CF is seen frequently in white race, one per 2500-3000, while in our country trials with limited patients have been performed and it was concluded that it was one per 3000. However, no any trial with large population until today, and taking into consideration that consanguineous marriage is very frequent and diarrhea and pulmonary tract infections are in the leading causes of death during the first five years, we can postulate that this ratio is higher.

Sweat test is considered as the golden standard for the diagnosis of CF since the year 1959, which was described for the first time [2]. Sweat is collected in this test by Gibson Cooke method or by Macroduct/Nanoduct sweat collection method. Macroduct/ Nanoduct method performed recently is suggested to be a considerably reliable and effective sweat collection system [3-5]. Chloride level in the sweat <60 mmol/L is considered to be normal (sweat test may be found within normal limits in some cases - atypical CF), while results higher than 80 mmol/L support CF diagnosis. Level of 60-80 mmol/L should be considered as suspicious, should be repeated and evaluated together with the clinical picture of the patient.

Repeated pulmonary infections and sinopulmonary diseases in children, malabsorption due to pancreatic dysfunction, pseudomonas aeruginosa and staphylococcus aureus growth in the phlegm together with development of finger clubbing and chronic liver disease are indications for sweat test for CF [6, 7].

In addition to CF , sweat test may be found high in many disorders and situations such as adrenal insufficiency, anorexia nervosa, atopic dermatitis, autonomic dysfunction, coeliac disease, ectodermal dysplasia, exercise, familial cholestasis, fucosidosis, glycogen depot disease Type I, hypogammaglobulinaemia, hypothyroidism, hypoparathyroidism, malnutrition, nephrogenic diabetes insipidus, protein calorie malnutrition, pseudohypoaldosteronism [8].

In this study, it was aimed to evaluate the clinical importance of sweat test in children admitted for complaints of repeated pulmonary infections and growth retardation.

Material and method

Ninety-four patients admitted to the pediatrics clinic in the Medical School of Cumhuriyet University complaining from repeated pulmonary infection and growth retardation between the dates of September 2009 and September 2010 were included to this study. Patient group of repeated pulmonary infection was formed from patients having one of more diagnostic criteria of repeated pneumonia, chronic cough, wheezing, plenty and continuous phlegm, bronchiectasis, atelectasis, asthma findings resistant to treatment, repeated bronchitis and bronchiolitis, and patient group of growth retardation from patients having one of more diagnostic criteria of weight gaining difficulty, chronic diarrhea, meconium ileus, oily, fatty and abundant defecation, rectal prolapse, vomiting, abdominal distention. Recurrent pneumonia was defined as more than 1 episode of pneumonia in 1 year or more than 3 episodes in a lifetime. BMI was calculated as weight/height, and all patients were separated to three groups according to BMI: group 1; <3.p, group 2; <3-10.p, group 3; >10.p. One hundred and twenty four subjects who were not diagnosed as CF served as the control group.

Detailed medical history was taken from the patients included in the study population. Physical examination was made after the detailed medical history. Weight (kg), cranial circumference (cm), height (cm) were examined. Growth-development curves of Neyzi et al. [9] were utilized in the evaluation of height, weight and development of the patients.

Sweat test of the patients were performed with an instrument trademark of NANODUCT® in two phases based on iontophoresis technique. In the first phase, sweat was stimulated in cleaned and dried forearm by pilocarpine gel, and in the second phase conductivity measurement was performed by special measurement heads in the same area. In the evaluation, 59 mmol/L was considered as negative measurement, 60-79 mmol/L as measurement within the limits, and higher than 80 mmol/L as positive. All positive and suspicious patients underwent sweat test minimum twice.

SPSS vs 15.0 (SPSS Inc., IL) software was used for statistical evaluation. Descriptive tests and chi-square test was performed in the statistical analysis. A p-value of 0.05 was considered statistically significant.

Results

94 patients who were admitted for repeated pulmonary infection and growth retardation were evaluated in the study. 12 patients (5.5%) were diagnosed as CF and 4 patients (1.8%) were diagnosed as atypical CF. 78 patients (35.68%) were diagnosed as non-CFclinical disease. Of 218 patients included to the study, 100 (45.9%) were female and 118 (54.1%) were male. Average age (year or month) of the children and neonates who were included in the study and diagnosed and their standard deviation is shown in the Table 1. While there was no statistically significant difference between the CF status and age groups ($p>0.05$); most of the patients diagnosed as CF were under a year of age The incidence of inability to gain weight was 17.69 % among patients applying to our clinic for both growth retardation and inability to gain weight and 15.38% in patients diagnosed as CF.

Table 1. Demographic characteristics of groups.

Characteristics	CF group (n=12)	Atypical CF group (n=4)	Non-CF disease grup (n=78)	Healthy group (n=124)
Age groups (no.) [a]				
<1	1 (8.3 %)	0 (0 %)	3 (3.8 %)	4 (3.2 %)
1< age ≤ 12	5 (50.0 %)	0 (0 %)	15 (19.2 %)	22 (17.7%)
> 12	6 (41.7 %)	4 (100 %)	60 (76.9 %)	98 (79.0 %)
Gender [b]				
Female (no.)	6 (50.0 %)	3 (75.0 %)	26 (66.7 %)	65 (52.4 %)
Male (no.)	6 (50.0 %)	1 (25.0 %)	52 (33.3 %)	59 (47.6 %)

[a] χ^2 =9.49 p=0.131
[b] χ^2 =8.53 p=0.04
CF: Cystic fibrosis

The result of sweat test was lower than 60 mmol/L in 191 of the children (89.7%), between 60-80 mmol/L in 13 (6.1%) and higher than 80 mmol/L in 9 (4.2%) patients. In 5 patients (2.5%) the test failed because of the unability to collect sweat.
A statistically significant correlation was found in the relation between the sweat test results and height percentiles ($p<0.05$). Among patients who had sweat test results of 60-80 mmol/L; 38.5% of patients had 3-10 height percentiles. In patients having sweat chloride levels of >80 mmol/L; 66.7% of patients had height percentiles under three. It was 38.5%. in patients whohad height percentiles of 3-10 and among patients whose sweat test results were higher than 80 mmol/L; 66.7% of them had height percentiles e under the 3rd percentiles (Table 2).

A statistically significant correlation was found in the relation between the sweat test results and weight percentiles in the study group ($p<0.05$). Among patients who had

sweat test results of 60-80 mmol/L; 53.8% of patients had weight percentiles under three and in patients having sweat chloride levels higher than 80 mmol/L 66.7% s were under the 3rd weight percentiles (Table 3).

In the evaluation of the patients included in the study, 26.1% of the patients did not have any lung infection, while 13.3% had lung infection once and 29.4% had three times or more. A statistically significant correlation was found between CF diagnosis and the numbers of having lung infection (P<0.05). The more exacerbations of lung infection, the higher rates of patients diagnosed as CF (Table 4).

In the evaluation the sweat test results of the patients according to the clinical diagnosis, 9 patients diagnosed as CF (75.8%) had their sweat test results higher than 80 mmol/L, while 3 patients (31.2%) had their sweat test between 60-80 mmol/L. In the clinically healthy group only one patient (0.08%) had a sweat test result between 60-80 mmol/L, while in the clinically non-CF diagnosed group 5 patients (6.6%) had their sweat test results between 60-80 mmol/L (p<0.05) (Table 5).

Table 2. The relation between the sweet test results and height percentiles.

Sweat chloride level		Height percentiles			Total
		< 3.p	3–10. p	> 10	
<60	n	45	39	107	191
	%	23.6%	20.4%	56.0%	100.0%
60-80	n	6	5	2	13
	%	46.2%	38.5%	15.4%	100.0%
>80	n	6	0	3	9
	%	66.7%	.0%	33.3%	100.0%
Total	n	57	44	112	213
	%	26.8%	20.7%	52.6%	100.0%

χ^2 =16.26 p=0.0003

Tablo 3. The relation between the sweet test results and weight percentiles.

Sweat chloride level		Weight percentiles			Toplam
		< 3.p	3-10. p	>10	
<60	n	51	35	105	191
	%	26.7%	18.3%	55,0%	100.0%
60-80	n	7	2	4	13
	%	53.8%	15.4%	30,8%	100.0%
>80	n	6	0	3	9
	%	66.7%	.0%	33.3%	100.0%
Total	n	64	37	112	213
	%	30.0%	17.4%	52.6%	100.0%

χ^2 =10.90 p=0.03

Table 4. The relation between clinical diagnosis and the number of lung infections.

Clinical diagnosis groups		The numbers of lung infections				Total
		0	1	2	>2	
Healthy group	n	37	20	44	23	124
	%	29.8%	16.1%	35.5%	18.5%	100.0%
CF group	n	1	2	4	5	12
	%	8.3%	16.7%	33.3%	41.7%	100.0%
Non- CF group	n	18	6	19	35	78
	%	23.1%	7.7%	24.4%	44.9%	100.0%
Atypical CF group	n	1	1	1	1	4
	%	25.0%	25.0%	25.0%	25.0%	100.0%
Total	n	57	29	68	64	218
	%	26.1%	13.3%	31.2%	29.4%	100.0%

χ^2 =19.43 p=0.02
CF:Cystic fibrosis

Table 5. The sweat chloride levels of the patients according to the clinical diagnosis.

Clinical diagnosis groups		Sweat chloride levels			Total
		<60	60-80	>80	
Healthy group	n	120	1	0	121
	%	99.2%	.8%	.0%	100.0%
CF group	n	0	3	9	12
	%	.0%	25.0%	75.0%	100.0%
Non- CF group	n	71	5	0	76
	%	93.4%	6.6%	.0%	100.0%
Atypical CF group	n	0	4	0	4
	%	.0%	100.0%	.0%	100.0%
Total	n	191	13	9	213
	%	89.7%	6.1%	4.2%	100.0%

χ^2 =236.79 p=0.0001
CF:Cystic fibrosis

Discussion

Patients with CF can be diagnosed mostly during the infanthood or childhood period, however some diagnoses may be overlooked until the adult period. More than 98% of the males with CF are infertile and fertility decreases in the sick women. Patients usually are admitted with repeated or not healed pulmonary infection, chronic cough, repeated exacerbations of bronchitis and malnutrition picture [10]. In our study, we evaluated the results of the routine sweat test application in children admitted with repeated pulmonary infection, growth retardation and unability to gain weight.

Growth retardation in CF patients may occur due to several factors. The most important factors between them are increased food needs, malabsorption, insufficient energy take, liver disease and diabetes mellitus. Pancreas insufficiency seen in 85-90% of the patients may cause to malabsorption of fat, protein and other nutritional elements [11]. It was found in studies that energy consumption in CF patients in rest is increased 4-33% in comparison to that in normal controls. Depleted pulmonary functions increase the work load on the respiratory muscles and cause an increase in the resting energy expenditure. Anorexia, vomiting, decrease in food intake may be seen due to the pulmonary infections. Some cytokines increased due to acute and chronic infections may also have an appetite decreasing effect. Nausea, abdominal pain, coughing, gastroesophageal reflux, depression, decrease in the palate sense and metabolic disorders due to liver disease may also be factors to cause anorexia. Behavioural nutritional difficulties may also cause insufficient food intake [12, 13]. Liver involvement seen in approximately 10% of the patients increases the tendency to malabsorption and may cause losses specific nutritional elements such as fat-soluble vitamins and coagulation factors. Diabetes developed due to CF is associated with both nutritional status and depleted pulmonary functions and causes an increase in the general mortality rate. In a study performed in a third step paediatric hospital in Germany, in which 475 patients were retrospectively involved, malnutrition was found in 24.1%. 17.7% of the patients were found to have light malnutrition, 4.4% moderate and 1.7% severe. It is indicated that one third (33.3%), i.e. a big percentage of these patients who were found to have malnutrition were diagnosed as CF [14]. The incidence of inability to gain weight was 17.69 % among patients applying to our clinic for both growth retardation and inability to gain weight and 15.38% in patients diagnosed as CF. The ratio of inability to gain weight in our CF patients was not as high as the ratio of a study performed by Daniels et al from Germany [15].

Of 66 patients admittted for growth retardation, 46.8% were found to have body weight under 10 percentiles, and 47.6% to have height under 10 percentiles. We found CF in 15.38% of patients admitted for growth retardation. In patients diagnosed as CF, 66.7% had body weight under 3 percentiles, and 58.3% had height under 3 percentiles. In a study

in which 104 CF cases were evaluated, 69.9% of the patients were measured to have their weight under 10 percentiles, and 58.3% to have height under 3 percentiles at the time of diagnosis [16]. The results of our study are consistent with this literature data and shows that CF should be definitely considered in the differential diagnosis of the growth retardation.

The leading symptoms in CF are signs of chronic obstructive pulmonary disease (seen almost in all cases in several grades) and pancreatic insufficiency (present in 80-90% of the patients) [17]. Obstruction of ducti of the submucosal glands and covering the airways by thick and viscous mucopurulent secretions, rich from neutrophils, are typical pathological findings for CF. Pulmonary infection, bronchiectasis, atelectasis, asthma resistant to treatment and cough are the most frequently seen clinical pictures at the admission. In our study, 13.3% of the patients enrolled to study had pulmonary infection once, 31.2% had twice and 29.4% had three times or more. 47.1% of the patients having positive sweat test had repeated pulmonary infections. The more pulmonary infection exacerbations, the higher rate of patients diagnosed to have CF [18]. Similarly, in the studies of Göçmen et al. [19] and Kaya et al. [20], 87% and 57% of the patients, respectively, were admitted with respiratory system symptoms, including repeated pulmonary infections. In the studies of Cesur et al. [10], in accordance with our study, 68.3% percent of the patients included in the study were admitted with respiratory symptoms, such as cough, stridor, wheezing, 57% of the cases with sweat test positivity were found to have repeated pulmonary infections [18].

In conclusion, we wanted to emphasize in this study that sweat test application is important in children admitted to the clinic for growth retardation or repeated pulmonary infections in order to diagnose CF early and to avoid late complications.

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