ORJİNAL MAKALE / *ORIGINAL PAPER*

EVALUATION OF CHILDREN WITH CYSTIC FIBROSIS IN TERMS OF DEMOGRAPHIC, CLINICAL AND GENETIC CHARACTERISTICS

Kistik Fibrozis Tanılı Çocuk Hastaların Demografik, Klinik ve Genetik Özelliklerinin Değerlendirilmesi

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ÖZET

Kistik fibrozis, beyaz ırkın kronik, progresif, resesif geçişli ve yaşamı sınırlayan bir genetik hastalıktır. Ülkemizde kistik fibrozis insidansı 1/300-3500 olarak tahmin edilmektedir. Klinisyenlerin farkındalığını artırmayı amacı ile kistik fibrozis tanısı alan çocuk hastaların demografik, klinik ve genetik özellikleri özetlendi. Çalışma, 2002-2019 yılları arasında kistik fibrozis tanısı alan çocukları içeren retrospektif bir çalışmadır. Çalışmada 180 hasta vardı ve tanı anında ortanca yaş 3,5 aydı. Akrabalık hastaların %37,5'inde ve aile öyküsü %21,6'sında tespit edildi.

Akut/kronik/tekrarlayan solunum problemi (%54,7), yenidoğan tarama test pozitifliği (%54,2) ve Psödo-Bartter sendromu (%31,3) başvuruda en sık görülen tanılardı. Ortanca terde klorür konsantrasyonu 103 mmol/l'di (20-145 mmol/l). Solunum fonksiyon testi yapabilen 77 hastanın, öngörülen ortanca 1. saniye zorlu ekspiratuvar volümü %78'di (18-126) ve ağır obstrüktif akciğer hastalığı 48/77 (%62,3) hastada tespit edildi. En sık saptanan mutasyon p.Phe508delPhe [c.1521_1523delCTT; %25 (90/360)] iken, p.Lys684fs [c.2051_2052delAAinsG; %5,3 (19/360)], p.Glu92Lys [c.274G>A; %4,4 (16/360)] ve p.Asn1303Lys [c.3909C>G; 3,9% (14/360)] sırasıyla diğer sık görülen mutasyonlardı.

Sonuç olarak, akut/kronik/tekrarlayan solunum problemi ve Pseudo-Bartter sendromu ile başvuran hastalarda birinci basamak test olan terde klor konsantrasyonu uygulanmalıdır. Ülkemizde yenidoğan tarama programı Ocak-2015'den itibaren uygulanmaya başlanmış olması ile birlikte, yenidoğan tarama testinin yanlış negatif sonuçlarının olabileceği ve 2015 yılından önce doğmuş olan bireylerde klinik şüphe varlığında tanı için altın standart olan ter testi yapılmalıdır.

Anahtar kelimeler:
Kistik fibrozis, *Pseudomonas aeruginosa*, solunum fonksiyon testi, yenidoğan tarama testi

ABSTRACT

Cystic fibrosis is a chronic, progressive, and life-limiting genetic disease in the Caucasian population. The incidence is estimated as 1/3000-3500 in Turkey. We aimed to summarize the demographic, clinical and genetic characteristics of our patients to increase the awareness of clinicians. We conducted a retrospective study in children diagnosed with cystic fibrosis between 2002-2019. There were 180 patients, and the median age at diagnosis was 3,5 months. Consanguinity and family history was present in 37,5% and 21,6% patients, respectively. Acute/chronic/recurrent respiratory abnormalities (54,7%), newborn screening test positivity (54,2%) and Pseudo-Bartter syndrome (31,3%) were the most common manifestations at the admission. The median sweat chloride concentration was 103 mmol/l (20-145 mmol/l). Of the 77 patients who underwent the pulmonary function test, the median predicted forced expiratory volume 1 second was 78% (18-126), and severe obstructive pulmonary disease was determined in 48/77 (62,3%) patients. Mutation p.Phe508delPhe (c.1521_1523delCTT) was the most frequent variant with an allele frequency of 25% (90/360). The other common variants were p.Lys684fs [c.2051_2052delAAinsG; 5,3% (19/360)], p.Glu92Lys [c.274G>A; 4,4% (16/360)] and p.Asn1303Lys [c.3909C>G; 3,9% (14/360)], respectively. In conclusion, patients presented with acute/chronic/recurrent respiratory abnormalities and Pseudo-Bartter syndrome are suggested to the sweat chloride test, which is the first-tier. Although the newborn screening program has been implemented since January 2015 in Turkey, the sweat chloride test that is the gold standard for diagnosing should be performed in the presence of clinical suspicion, as a newborn screening test may have false-negative results, and the patients born before 2015.

Key words:
Cystic fibrosis, newborn screening, pseudomonas aeruginosa, respiratory function test

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INTRODUCTION

Cystic fibrosis (CF, OMIM # 219700) is the most common life-shortening and fatal disease in Caucasians. Cystic fibrosis is caused by mutations in the transmembrane conduction regulation (CFTR; 7q31 chromosome) gene and shows autosomal recessive transmission. To date, over 2000 mutations have been identified that cause disease. The incidence of CF in European countries is around 1/2000-3000, 1/2900 in North American countries, and 1/4000-350,000 in Asia (Bobadilla et al.,, 2002; Mirtajani et al.,, 2017). Although CF incidence is unclear in Turkey, Köse and colleagues reported as 1/3000-3500 (Kose et al., 2008). The newborn screening program (NBS) is being implemented in Turkey since January 2015. The Turkish Ministry of Health has been trying to eliminate NBS deficiencies day by day. It aims to prevent the delay in the diagnosis of patients and to ensure that they receive treatment without delay (Mak et al., 2016; Coffey et al., 2017). Many studies shown that patients diagnosed earlier have better nutritional status in later life, growth parameters are better observed, and lung conditions are better than patients with late diagnosis (Accurso et al., 2005; Farrell et al., 2001). However, the study conducted by Topal et al., has been shown that the Turkish primary care physicians' knowledge of diagnosis and treatment of CF is not sufficient (Topal et al., 2019). In this study, we aimed to summarize the symptoms, complications, pulmonary function test results, genetic characteristics and mortality of our CF patients to increase the awareness of the clinicians.

MATERIAL and METHODS

This was a retrospective observational study that included patients diagnosed with CF between January 2002 and July 2019 at Ege University Faculty of Medicine (EUMF), Department of Pediatric Pulmonology.

Diagnosis of Cystic Fibrosis

Cystic fibrosis, CF-related metabolic syndrome/CF screen positive, inconclusive diagnosis (CFMS/CFSPID) and CFTR-related disorder were defined if patients met the inclusion criteria according to the Cystic Fibrosis Foundation (CFF) consensus guidelines in 2017 (Farrell et al., 2017).

Data collection

The age at diagnosis, gender, consanguinity, family history, nutritional status at the first admission [weight according to height (<2 years of age) and body mass index (BMI) (≥2 years of age) was calculated and data were given as the standard deviation score (SDS)] (Turck et al., 2016), clinical manifestations at diagnosis [prenatal screening (PS), newborn screening positivity (NBS), acute/chronic/recurrent respiratory abnormalities, Pseudo-Bartter syndrome (PBS), failure to thrive/malnutrition, steatorrhea/malabsorption, meconium ileus and other diagnoses (nasal polyp, digital clubbing, acute/chronic pancreatitis, prolonged neonatal jaundice and salty tasting skin)], the sweat chloride concentration (SCC), pancreatic insufficiency (PI) (those were defined fecal elastase value <100 mcg/g and/or positive stool fat analysis), microbiological agents detected in sputum/bronchoalveolar lavage fluid (BALF), forced expiratory volume in 1 second (FEV1), genetic results and mortality were recorded and evaluated from the medical records of patients.

Cystic fibrosis-related complications

CF-related respiratory tract complications; allergic bronchopulmonary aspergillosis (ABPA) (Stevens et al., 2003), pneumothorax needing for chest tube, bronchiectasis, nasal polyp, allergic fungal sinusitis, pulmonary hypertension, and

CF-related gastrointestinal complications; distal intestinal obstruction syndrome (DIOS) (Colombo et al., 2011), rectal prolapse, steatohepatitis, liver parenchymal disease, gall sludge and/or cholelithiasis, and CF-related endocrinological complications; bone mineral density (CMD), CF-related diabetes (CFRD) (Kelly and Moran, 2013; Sermet-Gaudelus et al., 2011) were recorded and evaluated from the medical records of patients.

Mutation nomenclature

Mutation information was reconciled according to the Human Genome Variation Society (HGVM) nomenclature, which is recommended to describe as an international standard of sequence variants. Mutations were described at both DNA and protein levels.

Statistical analysis

Quantitative data are reported as mean ± standard deviation (SD) or as median with range, while qualitative data are reported as observed frequencies and percentages. The ethics committee of EUMF Clinical Research approved the study (ethics committee number: 19.9.1T/38).

RESULTS

Between January 2002 and July 2019, CF, CFRD and CFMS/CFSPID were detected in 150 (83,3%), 22 (12,2%) and 8 (4,4%) patients, respectively. Of the 180 patients, the median age at diagnosis was 3,5 months. The ratio of female/male was 89/91. Family history and consanguinity were founded in 38 (21,6%), 66 (37,5%) patients, respectively (Table 1).

The most common clinical manifestations were acute/chronic/recurrent respiratory abnormalities (54.7%), NBS positivity (54.2%), PBS (31.3%), steatorrhea/malabsorption (26.8%), failure to thrive/malnutrition (24.6%) and meconium ileus (9.5%). The nutritional status at the admission was <0 SDS in 70.9% of patients and 10,5% of them were <-3 SDS (Table 2).

Pancreatic insufficiency was present in 63/73 (84.9%) patients. The sweat chloride test (SCT) was performed in 163 patients, and the median SCC was 101 mmol/L (20-145 mmol/L). The most CF-related complications in our study were determined in the respiratory tract (66.9%), gastrointestinal (46%) and endocrine (19.7%) systems. *Pseudomonas Aerouginosa (PA), Haemophilus influenzae non type B (Hib), methicillin susceptible staphylococcus aureus (MSSA) and Burkholderia cepacia complex (BCC)* were present in 68 (54.8%), 63 (52.1%), 51 (42.1%) and 3 (2.5%), respectively. Of the 68 patients who PA was grown up in the sputum culture/BALF, 39 (32%) were *chronic PA colonization* with a median age of 10 years. The median predicted FEV1 was 78% (18-126) and severe obstructive pulmonary disease was detected in 62.3% (48) of the patients (Table 2).

Table 1. Demographic features of patients

Total patients (n: 180)	**n %**
Age at diagnosis (m onths)*	3.5 (1-384)
Male	91 (50,6)
Consanguinity	66 (37,5)
Family history	38 (21,6)
Nutritional status**	
Normal	50 (29,1)
−1- 0 SDS	33 (19,2)
−2- −1 SDS	46 (26,7)
−3- −2 SDS	25 (14,5)
<−3 SDS	18 (10,5)
Sweat chloride concentration (mmol/l)*	101 (20-145)
Diagnosis	
CF	150 (83,3)
CF-related disease	22 (12,2)
CFMS/CFSPID	8 (4,4)
Follow-up time (year)*	2,1 (0,1-16,8)

*Median (range)
*** Nutritional status (SDS): Weight according to height was calculated for patients under 2 years and body mass index (BMI) was calculated for patients older than 2 years.
CF: Cystic fibrosis; CFMS/CFSPID: Cystic fibrosis metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis.

Mutation p.Phe508delPhe (c.1521_1523delCTT) was the most frequent variant with an allele frequency of 25% (90/360). The other common variants were p.Lys684fs [c.2051_2052delAAinsG; 5,3% (19/360)] and p.Glu92Lys [c.274G>A; 4,4% (16/360)] (Table 3). Pediatric death was present in 12 (6,6%) patients.

DISCUSSION

Cystic fibrosis is a hereditary disease of secretory cells, sinuses, lungs, pancreas, liver and reproductive tract that leads to pathological changes in these systems that express CFTR (Ratjen and Doring, 2003). The diagnosis of CF as early as possible has a significant effect on the survival of the patients (Dijk et al., 2011).

Table 2. Clinical feature of patients

	n (%)
Symptoms reported at diagnosis	
Acute/chronic/recurrent respiratory abnormalities	91 (54,7)
Newborn screening positivity	32 (54,2)
Pseudo-Bartter syndrome	56 (31,3)
Steatorrhea/malabsorption	48 (26,8)
Failure to thrive/malnutrition	44 (24,6)
Family history	17 (9,5)
Meconium ileus	17 (9,5)
Prenatal screening**	3 (1,7)
Other diagnosis***	16 (7)
Respiratory complications	117 (66,9)
GIS complications	81 (46)
Endocrinologic complications	34 (19,7)
Sputum/BALF bacteriologic culture	
Pseudomonas aerouginosa	68 (54,8)
Haemophilius influenzae non-type b	63 (52,1)
Meticilline sensitive Staphylococcus Aureus	51 (42,1)
Meticilline resistant Staphylococcus Aureus	15 (12,4)
Burcholderia Cepacia Complex	3 (2,5)
Chronic *Pseudomonas aerouginosa* colonisation	39 (32)
Predicted FEV_1*	78 (18-126)
The classification of pulmonary severity	
Normal/mild disease	12 (15,6)
Moderate disease	17 (22,1)
Severe disease	48 (62,3)
Death	12 (6,6)
Age at death (year)*	20,5 (5-39)

*Median (range)
**Prenatal diagnosis: Amniocentesis and perinatal carrion villus biopsy.
***Other diagnosis: Nasal polyp, digital clubbing, acute or chronic pancreatitis, prolonged neonatal jaundice and salty tasting skin.
GIS: Gastrointestinal; BALF: Bronchoalveolar lavage; FEV1: Forced expiratory volume 1 second.

In our study, the median age at diagnosis was 3.5 months. Acute/chronic/recurrent pulmonary abnormalities, NBS positivity and PBS were the most common clinical manifestations, and about one-third of the parents had consanguinity and one-quarter of the family history. Besides these findings, 70.9% of the patients had lower nutritional parameters at diagnosis than healthy children of the same age.

Many studies have shown that early diagnosis and treatment of CF have been associated with better nutritional status, respiratory functions and less PA colonization and hospitalization (Coffey et al., 2017). European CF and CFF Patient Registry Annual Data Report in 2017 showed that the median age at diagnosis was 4 months ("Cystic Fibrosis Foundation Patient Registry 2017 Annual Data Report" ; Zolin A 2019).

Cystic fibrosis affects multiple systems, but more frequent the lungs, liver, intestine, pancreas, and sweat glands (Ratjen et al., 2015). However, symptoms vary in patients diagnosed with CF-related disorder and CFMS/CFSPID. If these patients are not carefully investigated by clinicians, false diagnoses such as tuberculosis, bronchiectasis, pneumonia, asthma and malabsorption disorders can be made. This low diagnostic awareness may lead to delay in the

diagnosis of CF patients. Van Dommelen et al., showed that diagnostic SCT may be an indication in patients with recurrent lung infections (Van Dommelen et al., 2009).

Table 3. Distrubition of all allels

Legacy Name	*cDNA Name*	*Protein Name*	*n*	*%*
1248+1G>A	c.1116+1G>A	No protein name	2	0.6
1342-11TTT>G	c.1210-11T>G	No protein name	1	0.3
1525-1G>A	c.1393-1G>A	No protein name	4	1.1
1677delTA	c.1545_1546delTA	p.Tyr515*	5	1.4
2183AA>G	c.2051_2052delAAinsG	p.Lys684fs	19	5.3
2184delA	c.2052delA	p.Lys684Asnfs	6	1.7
2184dupA	c.2052dupA	p.Gln685Thrfs	1	0.3
2789+5G>A	c.2657+5G>A	No protein name	11	3.1
3041-15T->G	c.2909-15T>G	No protein name	1	0.3
306delTAGA	c.174_177delTAGA	p.Asp58fs	1	0.3
3120+1G>A	c.2988+1G>A	No protein name	2	0.6
3154delG	c.3022delG	p.Val1008fs	1	0.3
3199del6/I1023delG	c.3067_3072delATAGTG	p. Ile1023_Val1024del	2	0.6
3849+10kbC>T	c.3718-2477C>T	No protein name	1	0.3
4382delA	c.4251delA	p.Glu1418fs	2	0.6
621+1G>T	c.489+1G>T	No protein name	7	1.9
621+3A>G	c.489+3A>G	No protein name	1	0.6
A46D	c.137C>A	p.Ala46Asp	2	0.6
F508del	c.1521_1523delCTT	p. Phe508delPhe	90	25
	c.2339delG	p.Gly780Valfs	1	0.3
	c.2361delA	p.Val788Leufs	1	0.3
	c.2997delA	p.Ile1000Leufs	2	0.6
C524*	c.1572C>A	p. Cys524Ter	1	0.3
D110H	c.328G>C	p. Asp110His	5	1.4
D1152H	c.3454G>C	p.Asp1152His	7	1.9
D1154Y	c.3460G>T	p.Asp1154Tyr	1	0.3
E1044G	c.3131A>G	p.Glu1044Gly	2	0.6
E1228G	c.3683A>G	p.Glu1228Gly	1	0.3
E379*	c.1135G>T	p.Glu379Ter	1	0.3
E831*	c.2491G>T	p.Glu831Ter	1	0.3
E92K	c.274G>A	p.Glu92Lys	16	4.4
E92X	c.274G>T	p.Glu92Ter	1	0.3
F992L	c.2976T>A	p.Phe992Leu	1	0.3
G1244E	c.3731G>A	p.Gly1244Glu	1	0.3
G1249W	c.3745G>T	No protein name	1	0.3
G178R	c.532G>A	p.Gly178Arg	2	0.6
G542*	c.1624G>T	p.Gly542Ter	13	3.6
G576A	c.1727G>C	p.Gly576Ala	1	0.3
G85E	c.254G>A	p.Gly85Glu	2	0.6
H1054D	c.3160C>G	p.His1054Asp	1	0.3
I1234V	c.3700A>G	p.Ile1234Val	2	0.6
I148T	c.443T>C	p.Ile148Thr	2	0.6
I506V	c.1516A>G	p.Ile506Val	1	0.3
4096-3C->G	c.3964-3C>G	No protein name	2	0.6
K174*	c.520A>T	No protein name	2	0.6
K68E	c.202A>G	p.Lys68Glu	1	0.3
L467F	c.1399C>T	p.Leu467Phe	2	0.6
L732*	c.2195T>G	p.Leu732Ter	2	0.6
L997F	c.2991G>C	p.Leu997Phe	2	0.6
M1137V	c.3409A>G	p.Met1137Val	2	0.6
N1303K	c.3909C>G	p.Asn1303Lys	14	3.9
Q1411*	c.4231C>T	p.Gln1411Ter	2	0.6
R1066C	c.3196C>T	p.Arg1066Cys	5	1.4
R1158*	c.3472C>T	p.Arg1158Ter	2	0.6
R117C	c.349C>T	p.Arg117Cys	2	0.6
R117H	c.350G>T	p.Arg117Leu	2	0.6
R170C	c.508C>T	p.Arg170Cys	1	0.3
R334W	c.1000C>T	p.Arg334Trp	2	0.6
R347H	c.1040G>A	p.Arg347His	1	0.3
R347P	c.1040G>C	p.Arg347Pro	4	1.1
R668C	c.2002C>T	p.Arg668Cys	1	0.3
R75*	c.223C>T	p.Arg75Ter	1	0.3
S1196*	c.3587C>G	p.Ser1196Ter	1	0.3
S1455*	c.4364C>G	p.Ser1455Ter	1	0.3
S466*	c.1397C>A	p.Ser466Ter	2	0.6
S737F	c.2210C>T	p.Ser737Phe	1	0.3
S945L	c.2834C>T	p.Ser945Leu	4	1.1
T1036N	c.3107C>A	p.Thr1036Asn	2	0.6
T1220I	c.3659C>T	p.Thr1220Ile	1	0.3
W1098L	c.3293G>T	p.Trp1098Leu	2	0.6
W1282*	c.3846G>A	p.Trp1282Ter	1	0.3

According to Turkey's Statistical Agency, the consanguineous marriage rate in 2016 was determined to be 23,2% (Agency 2016). Fallahi et al., found that the rate of consanguinity in Iranian CF patients was 68%, while another study in Pakistan conducted by Abdul Aziz et al., reported that the consanguinity and family history rate was found 55.8% and 9.3%, respectively (Aziz et al., 2017; Fallahi et al., 2010). Since CF is an inherited autosomal recessive, the marriage of individuals at risk of carrying the same mutation increases CF incidence. Education programs for community are needed in the Middle East and developing countries, where consanguineous marriages are a high rate.

Respiratory tract involvement is the most affected system in CF. Chronic recurrent infections, inflammation, and impaired mucociliary clearance cause structural changes in the lung. Thus, progressive lung disease is the most common cause of death. The number of pulmonary infections, sputum bacteriology and pulmonary exacerbation with BCC shortens the survival of patients (Corey and Farewell 1996; Milla and Warwick 1998; Kulich et al., 2003). Prompt initiation of medical therapy, regular use and physiotherapy play a key role in the expected life duration. Hypokalemic alkalosis is rare in infants and the most common causes are Bartter and PBS. In cases of hypokalemic alkalosis detected in infants, SCT may be proper. The incidence varies according to seasonal temperatures. It is important to increase salt support and fluid support for patients when diarrhea, vomiting and extra hot air is present. We found growth retardation in 70.9% of our patients. ECFS patient registry report showed that half of CF patients had malnutrition. While more people continue to achieve an adequate nutritional status in the CF population, malnutrition remains a major problem in patients. In infants and children (<1 year of age) with CF, poor nutritional status results in stunted growth and development. Weight and length for age percentiles should be calculated at each visit. It should be kept in mind that regression and/or pause in the growth percentiles of these patients may be an important warning sign. The patients have significant energy intake deficits relative to their energy needs. Nutritional deficiencies of the patients affect pulmonary muscles and pulmonary functions and exercise tolerance. However, poor nutritional status reduces quality of life and shortens life expectancy (Turck et al., 2016). The PI occurs in 87% of patients (Naehrig et al., 2017). Growth retardation, fatty and stinking stools, and abundant defecation are the most common symptoms. We found PI in 84.9% (62/73) of our patients. Similarly, Karakoç et al., reported that PI was present in 83% of the patients (Karakoç et al., 1998). In our study, 9.5% of patients were operated due to meconium ileus in the neonatal period and were subsequently diagnosed. Meconium ileus occurs 20% of the patients and presents in the neonatal period because of obstruction caused by dark and sticky meconium (Naehrig et al., 2017). If the meconium is absent in the first 48 hours after birth, the clinician should consider meconium ileus with abdominal distention and/or biliary vomiting.

Newborn screening program has both short-term and long-term positive clinical outcomes and a

cost-effective health strategy for community screening (Castellani et al., 2016). Different NBS programs are used in the countries (e.g. Immunoreactive trypsinogen (IRT)/DNA/IRT or IRT/IRT or IRT/mutation analysis/DNA sequence). The national NBS program in Turkey has been included as IRT/IRT in January 2015. Hence, the patients diagnosed with NBS are found a high rate of 54.2% (32) in our study. We performed SCT in 90.5% of patients. Of the 32 patients who were positive NBS, 14 were diagnosed with CF by their first SCT but of the remaining 18 patients, SCT was determined as a negative value in 3 patients and, as intermediate values in 15 patients. However, CF was confirmed in 10 patients by repeated SCT and DNA sequence analyzing. The remaining 8 patients were diagnosed with CRMS/CFSPID and are followed up by our clinic because of the risk of CF development over the years. Edmondson and colleagues reported that 17% of patients with NBS positivity, whose sweat test resulted in negative, were diagnosed with CF and CFMS/CFSPID in the follow-up period (Edmondson et al., 2018). Because the clinical spectrum of CF is highly variable, the follow-up of NBS-positive patients and/or patients with SCT resulting in negative and intermediate values on clinical suspicion should be continued. Intermittent SCT may help to diagnose in these patients. It is known that the main disorder in patients with CF increases the tendency to chronic infection in the airways by various mechanisms. This is very important in the pathogenesis of permanent damage, which plays an important role in the morbidity and mortality of the patients. Microorganisms that cause infections often in CF have been reported as PA (63%), MSSA (70%) and Hib (50%) (Naehrig, Chao, and Naehrlich 2017). Significant improvement has been found in the survival of patients with CF following the widespread use of broad-spectrum, especially antipseudomonal antibiotics. If there have been any decreasing in pulmonary function test, and/or exercise capacity, and/or bodyweight and, increased cough or sputum content, pulmonary exacerbation and intravenous (Iv) antibiotic treatment should be considered. Here, an aminoglycoside is used together with a beta-lactam such as ceftazidime or carbapenem and treatments are continued for at least 2-3 weeks. If symptoms such as cough and sputum are not accompanied by a significant decrease in pulmonary function test (PFT), then a mild exacerbation of the disease is considered, and oral antibiotics may be used for treatment (Noone and Knowles 1999). Oral quinolines, such as ciprofloxacin, norfloxacin or ofloxacin are used for antipseudomonal activity. There are studies showing that inhaled antibiotics for prophylactic use in patients with PA colonization improves pulmonary function tests and reduces the frequency of exacerbations requiring hospitalization. In our study, PA was detected in 54.8% of patients, while MSSA was found in 42.1% of the patients. Chronic PA colonization was seen in 32% of patients and inhaled antibiotic prophylaxis was given to these patients.

In our study, we found that the median of predicted FEV1 was 78% (18-126). Of the 122 patients who underwent PFT, 48 (62.3%) had a severe obstructive pulmonary disease (FEV1 <40%). The nutritional status of the patients is parallel to the PFT. Therefore, it is recommended to check the patient's growth parameters, and increase the calories and protein in the dietary supplement, and give fat-soluble vitamin supplementation, and adjust the dosage of pancreatic enzyme replacement therapy, and use of proton pump inhibitors. Despite these interventions, nasojejunal tube or percutaneous endoscopic gastrostomy should be performed if growth arrest or regression is observed. Clinically, PA is associated with more parenchymal damage, a more rapid decline in lung function, and earlier mortality. Emerson and et al., found that PA was associated with a 2.6-fold increase in the 8-year mortality in children (Emerson et al., 2002). Therefore, IV or inhaled antibiotics should be administered when first pseudomonas growth is detected. If eradication is not achieved, these cures should be repeated. The most common mutation in our patients is p.Phe508delPhe (c.1521_1523delCTT) (deltaF508del), which is positive in 25% of the patients. Other mutations most common were p.Lys684fs [c.2051_2052delAAinsG; 5.3% (19/360)], p.Glu92Lys [c.274G>A; 4.4% (16/360)] and p.Asn1303Lys [c.3909C>G; 3.9% (14/360)], respectively. Because of the high molecular heterogeneity of the Turkish population, deltaF508del mutation, which constitutes 70% of the mutations in Northern Europe and America, has been detected only in a few patients, so DNA sequence analyzing is suggested determining the rare mutations. In a study by Onay et al.,, the frequency of deltaF508del mutation was 18.6% (Onay et al., 1998). Pediatric mortality was present in 12 (6.6%) patients and the median age at death was 20.5 (5-39) years. According to the CFF annual report, the median age at death increased from 26.8 in 2002 to 30.6 in 2017 ("Cystic Fibrosis Foundation Patient Registry 2017 Annual Data Report"). The survival of patients has been prolonged with the development of new medical treatments. Gene therapies for CF involve more mutations day by day. To benefit from effective gene therapies for these patients, early diagnosis, close follow-up

and prompt implementation of the treatments are indispensable.

In conclusion, the number of children with CF being followed in various centers in Turkey is much less than the number thought to exist. It should be remembered that early diagnosis and treatment directly increase the patient's life expectancy and quality. Therefore, increasing the knowledge and experience of CF in clinicians will enable the diagnosis and treatment of these patients in the early period.

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