

Clinical presentation of cystic fibrosis at the time of diagnosis: a multicenter study in a region without newborn screening

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Background/aims: Cystic fibrosis is the most common inherited lethal disease, which could be frequently identified late in regions without newborn screening. There are dramatically better outcomes in the early diagnosis of cystic fibrosis patients. This study aimed to evaluate the spectrum of manifestations of cystic fibrosis at first admission leading to diagnosis. **Materials and Methods:** This study was performed in a multi-referral pediatrics center in Iran. Data of patients with cystic fibrosis at the time of diagnosis were recorded based on a checklist denoting demographic characteristics, clinical and laboratory features. All of the patients had two documented sweat chloride tests. **Results:** One hundred and ninety seven patients with cystic fibrosis were enrolled in this study. Among them, 119 patients (74%) were less than six months and 34 patients (21%) were between 6 and 12 months of age. The most common clinical findings were failure to thrive, recurrent pulmonary infections, and steatorrhea in 178 (90%), 139 (71%), and 135 (69%) patients, respectively. The most common radiologic abnormality was hyperaeration. In patients with salty tasting skin, steatorrhea, metabolic alkalosis, radiologic findings, and liver function abnormalities, the mean age at the time of diagnosis was significantly low than in the subjects without these findings. **Conclusion:** This study suggests that some conditions such as failure to thrive, recurrent respiratory infections, steatorrhea, metabolic alkalosis, and salty tasting skin should be considered as clinical screening tools for cystic fibrosis, especially in regions with high rate of cystic fibrosis. In these regions, awareness and clinical suspicion of medical professionals are crucial for early diagnosis of cystic fibrosis patients in the pre-diagnostic period.

Key words: Cystic fibrosis, diagnosis, clinical manifestations, screening

Kistik fibrozisin tanı anındaki klinik prezentasyonu: Yeni doğan taraması olmayan bir bölgede çok merkezli çalışma

Giriş ve Amaç: Kistik fibrozis en sık karşılaşılan kalıtsal ölümcül hastalıktır ve yenidoğan taramasının yapılmadığı bölgelerde hastalar geç tespit edilebilir. Erken tanı konulan kistik fibrozis hastalarının sonuçları dramatik olarak daha iyidir. Bu çalışmada kistik fibrozis hastalarında ilk başvuruda tespit edilen tanıya götüren bulgularının incelenmesi amaçlanmıştır. **Gereç ve Yöntem:** Bu çalışma İran'da birden çok pediatrik referans merkezinde gerçekleştirildi, hastaların tanı anındaki demografik, klinik ve laboratuvar verileri kontrol listesi ile kayıt altına alındı. Tüm hastaların 2 adet ter klor testi mevcuttu. **Bulgular:** Kistik fibrozis tanısı olan 197 hasta çalışmaya dahil edildi. Bu hastalardan, 119'unun (%74) yaşı 6 aydan küçüktü ve 34 hastanın (%21) yaşı 6-12 ay arasındaydı. En sık karşılaşılan klinik bulgular büyüme geriliği (n=178; %90), tekrarlayan akciğer enfeksiyonları (n=139; %71) ve steatore (n=135; %69) olarak tespit edildi. En sık karşılaşılan radyolojik anormallik akciğerlerde aşırı havalanmaydı. Terde tuz tadı, steatore, metabolik alkaloz, radyolojik anormallikler ve karaciğer testlerinde anormallik olan hastaların ortalama tanı yaşı diğerlerine göre düşük bulundu. **Sonuç:** Bu çalışma sonuçlarına göre büyüme geriliği, tekrarlayan solunum sistemi enfeksiyonu, steatore, metabolik alkaloz ve tuzlu cilt tadı kistik fibrozis ile sık karşılaşılan bölgelerde klinikte uyarıcı olmalıdır. Bu bölgelerde, dikkat ve klinik şüphe ile hastaların erken tespit edilmesi mümkün olabilir.

Anahtar kelimeler: Kistik fibrozis, tanı, klinik bulgular, tarama

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Manuscript received: 07.10.2013 **Accepted:** 22.10.2013

Turk J Gastroenterol 2013; 24 (6): 541-545
doi: 10.4318/tjg.2013.0653

INTRODUCTION

Cystic fibrosis (CF) is the most common fatal disease among autosomal recessive disorders, which still carries a serious prognosis, despite advances in treatment (1). Its clinical consequences include pancreatic dysfunction, progressive pulmonary damage leading to respiratory failure, gastrointestinal problems, liver disorder, electrolyte and acid base imbalance, and eventually wherever cystic fibrosis transmembrane conductance regulator (CFTR) gene carries out its function (2).

There are dramatically better outcomes in the early diagnosis of CF patient (3). Early diagnosis and treatment intervention lead to better nutritional status and less severe lung disease (4, 5). Sims et al (6) showed that clinical diagnosis after two months of age is associated with worse outcomes, a greater treatment burden, and a lower quality of life. Newborn screening program made a revolution in early diagnosis and care management in CF patients. However, in several countries, there is still no such a program (7, 8).

In the regions without newborn screening, most CF patients have various symptoms in the prediagnostic period ranging from several months to years. Parents may repeatedly attend different medical professions for treating these manifestations (9). Therefore, physician awareness from diversity of early clinical manifestations of CF, particularly atypical type, would be determinant for suspecting CF in the prediagnostic period and early diagnosis of CF patients in these regions (10). Although most articles focus on the spectrum of the late manifestations of CF (11-13), there is not any multicenter study on the early manifestations of the disease in these regions. The aim of this study was to evaluate the spectrum of manifestations of CF at first admission leading to diagnosis.

MATERIALS and METHODS

Patients

In this retrospective study, we evaluated the medical records of CF patients, who were diagnosed to have CF at first admission and were referred to Children's Medical Center, the pediatric center of excellence in Iran, and other pediatric treatment centers throughout the country during the period of 2000-2010. Children's Medical Center Hospital serves as a referral center for patients with a known or suspected CF in Iran, and many centers referred their patients for definite diagnosis. Diag-

nosis of all patients had been confirmed by clinical history and at least two documented sweat chloride tests (SCT) with values greater than or equal to 60 mEq/L. The sweat chloride concentration was measured by a quantitative pilocarpine iontophoresis sweat test as Gibson-Cooke procedure (14). Patients diagnosed based on clinical judgment or without two documented SCTs were excluded from this study. The study was approved by the medical ethics committee of Tehran University of Medical Sciences and was done with supervision of the Iranian Society for Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN).

Methods

A medical checklist was completed for all patients. This checklist containing demographic, history, clinical examination and laboratory data was designed based upon literature (1, 12). In this checklist, the failure to thrive (FTT) was defined as weight less than the third to fifth percentile for age on more than one occasion. Recurrent respiratory infection was defined as three or more respiratory infections (e.g., sinusitis, otitis, bronchitis) in one year. Salty tasting skin was defined as complaint of parents from a salty taste of kissing. Hyperaeration was defined using indices described by Gibson et al (15). The checklist was sent via email, regular mail, or fax to all pediatric treatment centers throughout Iran. The checklists were collected by the same way and reviewed for accuracy and completeness by all the authors. Liver function abnormality was defined as either elevated liver enzymes or cholestasis markers according to the literature (16).

Statistical Analysis

Statistical analysis was done with SPSS version 15.0. Descriptive statistics were used for all parameters. Pearson χ^2 testing or Fisher's exact test was used to compare quantitative data and independent student's t-test was applied to analyze continuous data. A *p-value* of less than 0.05 was considered as statistically significant.

RESULTS

Enrolled Patients

Four hundred and forty five checklists were gathered, of which 197 patients fulfilled our study criteria, including established diagnosis based upon clinical history and at least two documented SCTs. The records of the first admission at the time of diagnosis were evaluated. Children's Medical Cen-

ter Hospital was the place of diagnosis for 128 (65%) patients.

Patients' Characteristics

The patients' age ranged between one month and seven years at the time of diagnosis. One hundred

and nineteen patients (74%) were less than six months of age, 34 patients (21%) were between 6 and 12 months, and the remaining 5% were more than one year of age. Among the study population, 116 patients (59%) were male.

Family History

Among patient's parents, 134 (68%) parents were first-degree relatives. Moreover, in 27 families (13.7%), there was history of CF disease. Seventeen deaths because of CF were reported among their families.

Clinical Characteristics

The most common clinical and laboratory manifestations at first admission were gastrointestinal problems (Table 1). Notwithstanding the presence of family history of CF, all of patients were symptomatic before diagnosis.

Imaging

There were only 78 plain chest X-ray (CXR) reports available. The most common abnormality in the CXR reports was hyperaeration, which was seen in 56 (72%) reports (Figure 1).

Association Study

In patients with salty tasting skin, steatorrhea, metabolic alkalosis, triad of edema, anemia and hypoalbuminemia, radiologic findings, and liver

Table 1. Frequency of clinical finding and relative past medical history of CF patients at first admission, N: 197

Findings	Number of patients	Percent
Failure to thrive	178	90
Recurrent respiratory infection	139	71
Greasy stool	135	69
Metabolic alkalosis	104	53
Salty tasting skin	81	41
Hyperaeration*	51	26
Liver function abnormality	31	16
Skin rash#	25	13
Clubbing	18	9
Cholestasis	11	6
Meconium ileus	11	6
Nasal polyp	6	3
Intussusception	6	3

Other findings like cirrhosis, gall stone, rectal prolapse were recorded in 2 or 3 patients.

No one presented with pancreatitis at diagnosis time.

*: Data were available only for 143 patients. #: Skin rash was diffuse maculopapular rash mostly on the trunk and head

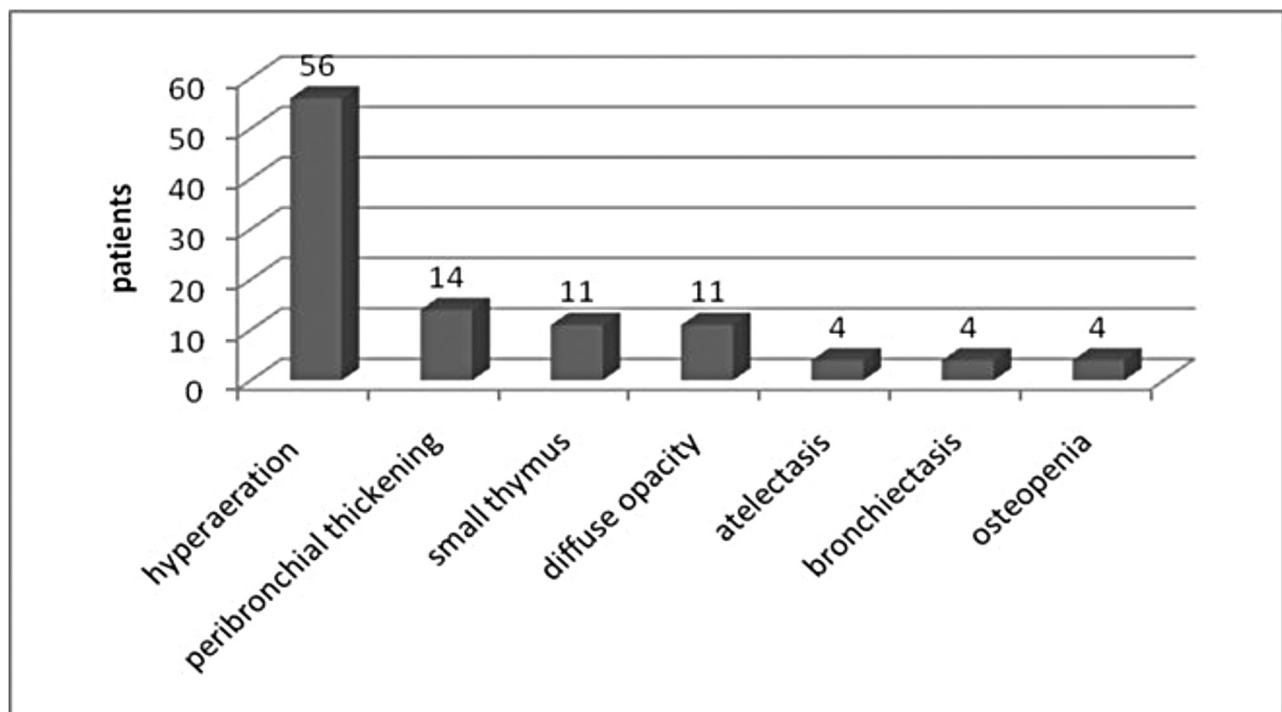


Figure 1. The results of chest X-ray in CF patients, N: 78.

Table 2. Variables associated with the age of the patients at the time of diagnosis

	Present	Absent	<i>p-value</i>
Salty tasting skin	4.34±2.60	5.48±4.34	0.041
Steatorrhea	4.52±2.91	6.02±4.97	0.019
Metabolic alkalosis	4.34±2.85	5.74±4.46	0.020
FTT	5.14±3.88	3.73±1.84	0.020
Radiologic abnormality	4.18±2.73	5.94±4.49	0.003
Liver function abnormality	3.52±1.96	5.25±3.92	0.045

A *p*-value of less than 0.05 is statistically significant. Data are presented as Mean±SD of age (in month).

function abnormalities, the mean age at the time of diagnosis was significantly low than in subjects without these findings ($p < 0.05$), whereas patients with FTT were significantly older than the others at the time of diagnosis (Table 2). Mean age was significantly low in patients diagnosed in the Children's Medical Center than in the other centers (4.11 ± 3.11 vs. 6.35 ± 4.23 months, $p < 0.001$).

Some manifestations correlated with FTT, as the most common manifestation in our patients (Table 2). Fifty-five percent of patients were affected by cholestasis and FTT, while 93% of patients were without cholestasis but had FTT ($p < 0.001$, OR: 1.3, 95%CI: 1-1.7).

DISCUSSION

Early diagnosis of CF, as the most common life-threatening inherited disease, results in a very significant survival advantage for patients with CF (3). In regions without newborn screening, clinical screening tools for identification of potential patients to consider for SCT would be very useful (17).

The results from this study showed that the most common manifestation at first admission was FTT, which is also considered as the earliest feature of CF in infants diagnosed by neonatal screening (17). This would suggest that in countries without a newborn screening program, FTT could be used as a clinical screening tool (17).

More than 70% of CF patients at first admission had history of recurrent respiratory infections. A study has suggested that recurrent respiratory infections may be considered as an indication for a sweat test (18). Hyperaeration and hyperinflation were the most common findings in the chest radiographs in our study, similar to other studies (19).

Steatorrhea was found in more than half of the patients. In CF patients, the pancreas develops a progressive atrophy causing steatorrhea and nutritive deficiencies. CF is the most frequent cause of exocrine pancreatic insufficiency in childhood (20). Patients with this manifestation were diagnosed significantly sooner, pursuant to be more obvious to be reported by the parents.

There was metabolic alkalosis in nearly half of our patients. In other studies, prevalence of metabolic alkalosis in CF patients was reported between 16.5 and 46% (21, 22). This difference may be due to delayed CF diagnosis, hot climate (maybe due to the dehydration), or due to presence of variable CF mutations (22).

Salty tasting skin was seen in almost half of the patients at first admission. Because this finding depends on good history taking and high clinical suspicion, its frequency may be more than the reported. In many cases, a parent makes the diagnosis because the infant tastes salty. In this study, the patients with salty tasting skin were diagnosed sooner (23). Skin rash was an uncommon finding in other studies (24, 25), but in the present study, there were skin rashes as diffuse maculopapular rash mostly on the trunk and head in nearly 15% of patients.

Although meconium ileus has no influence on CF outcome, it may attract the attention of medical professions to the CF, as one of the most important cause of meconium ileus (26) and so may lead to early diagnosis and treatment intervention (26). In our study, only one out of 11 neonates with meconium ileus was followed for CF investigation which shows the lack of clinical suspicion.

It was suggested that screening for CFTR mutations should be routine for all azoospermic males prior to proposing intracytoplasmic sperm injection.

tion treatment (27). Our study also showed the importance of this recommendation. There were two fathers with history of infertility among the parents of our study population. Pregnancy in these families was induced by assisted reproductive technology without any attention to the cause of paternal infertility.

The results from our study showed conditions such as FTT, recurrent respiratory infections, steatorrhea, metabolic alkalosis, and salty tasting skin in

areas with high rate of consanguineous marriages, thus should be noted as indicators for SCT. No newborn screening program, unequal diagnostic facilities within patient's management centers, and limited diagnostic centers in large areas of the world suggest emphasizing physicians' awareness and use of clinical screening tools. At present, high index of clinical suspicion is mandatory for early detection and prompt treatment intervention until upgrading of diagnostic facilities.

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