LATE DIAGNOSIS OF CYSTIC FIBROSIS

Mohammad Asim[1], Muhammad Ali Khan Malik[2], Sawera Tahir[2], Shaila Wazir Khan[3], Martin Ledson[3]

ABSTRACT

Introduction: Cystic fibrosis (CF) is a chronic, multisystem progressive disease that involves the respiratory tract, pancreas, intestine, sweat glands and reproductive tract. Worldwide incidence is 1:2500 live births with mutations carried by 1:26–27 individuals. In people with CF, the defective gene causes a thick, sticky buildup of mucus in the lungs, pancreas, and other organs. CF is no longer a disease of childhood, late diagnosis (LD-CF) may occur and is being made more frequently. When CF is diagnosed in adults, it appears to be clinically different to pediatric presentation. Prognosis and life expectancy seems to be better when the disease is diagnosed in adulthood although the disease course is seriously affected by frequent respiratory infections and early bacterial colonization.

Materials & Methods: This is a retrospective review study conducted at Liverpool Heart and Lung Hospital, Liverpool, United Kingdom from 1984 to 2007. The following variables were taken into account, age, gender, type of test used for diagnosis, Body mass index (BMI), gene testing and presence of any disease before diagnosis.

Results: A total of 30 patients were diagnosed with Cystic Fibrosis out of 250 cases. The mean age of late diagnosis was 29 years with a mean BMI of 24. In the LD patients, the frequency of Gene Delta 508 mutation was 23 (77%) while 7 (23%) patients were positive for Gene R117H mutations. Out of a total of 30 patients, 14 (46%) were confirmed via Cystic Fibrosis Gene Testing, 14 (47%) via Cystic Fibrosis Gene Testing and Sweat Testing while 2 (7%) were confirmed via Cystic Fibrosis Gene Testing, Sweat Testing and Nasal Potential Difference. Patients were previously diagnosed with Asthma 20%, Bronchiectasis 30%, ABPA 3%, Sinusitis 7%, Recurrent LRTI 7%, Unexplained Cough 7%, Bronchiectasis and Celiac Disease 3%, Asthma and Bronchiectasis 23%.

Conclusion: Cystic Fibrosis is not only a disease of childhood anymore. Though rare, it can be diagnosed later in life. Therefore, prolonged and unexplained Pulmonary and GIT symptoms must be dealt with caution when concerning adults and the possibility of CF must be considered. To confirm the late diagnosis of Cystic Fibrosis, the most common test used was the Cystic Fibrosis Gene Testing. Sweat testing and Gene Delta 508 mutation played a major role in confirming the late diagnosis of Cystic Fibrosis.

Key-words: Adult, Cystic Fibrosis, Delayed Diagnosis, Genetic Testing.

INTRODUCTION

Cystic fibrosis (CF) is a chronic, multisystem progressive disease that involves the respiratory tract, pancreas, intestine, sweat glands and reproductive tract. Worldwide incidence is 1:2500 live births with mutations carried by 1:26–27 individuals. CF is a common autosomal recessive disorder caused by mutations of the cystic fibrosis trans-membrane regulator gene (CFTR) classified in six subgroups on the basis of bimolecular mechanisms[1].

In people with CF, the defective gene causes a thick, sticky buildup of mucus in the lungs, pancreas, and other organs. Most people with cystic fibrosis also have digestive problems[2]. In the lungs, the mucus clogs the airways and traps bacteria leading to infections, extensive lung damage, and eventually respiratory failure[3].In people with cystic fibrosis, mucus blocks the ducts of the pancreas reducing the production of insulin and preventing digestive enzymes from reaching the intestines to aid digestion. Problems with digestion can lead to diarrhea, malnutrition, poor growth, and weight loss. In adolescence or adulthood, a shortage of insulin can cause a form of diabetes known as cystic fibrosis-related diabetes mellitus (CFRDM)[2].

CFTR gene has now been found and most of them are rare. Cystic fibrosis is usually diagnosed in childhood, with up to 50% of patients presenting in the first year of life[4]. Typical modes of presentation are meconium ileus, failure to thrive, recurrent pulmonary infections, diarrhea, and steatorrhea. It may however be diagnosed in adult patients. Patients diagnosed late usually present with respiratory symptoms, or with male infertility due to congenital bilateral absence of the vas deferens (CBAVD)[5].

Late diagnosis (LD-CF) may occur and is being made more frequently. When CF is diagnosed in adults, it appears to be clinically different to pediatric presentation. Prognosis and life expectancy seems to be better

[1] Pulmonologist, Consultant, Rehman Medical Institute, Peshawar.
[2] Student Final Year MBBS, Rehman Medical College, Peshawar, Khyber Pakhtunkwa, Pakistan
[3] Pulmonologist, Consultant, Liverpool Heart and Lung Hospital, Liverpool, United Kingdom

Address for correspondence:
Dr Mohammad Asim
Consultant Pulmonologist and Assistant Professor Hayatabad Medical College, Peshawar
Email: drasimwazir@yahoo.co.uk

when the disease is diagnosed in adulthood although the disease course is seriously affected by frequent respiratory infections and early bacterial colonization.

The main cause of morbidity and mortality of CF adult patients is due to bronchial and lung involvement causing chronic bronchiectasis, which is responsible for more than 90% of fatal events. Chronic pulmonary bacterial colonization and recurrent infectious exacerbations dominate the clinical picture in CF[1].

We have found that patients presenting with CF in adult age appear to be different compared to patients presenting in childhood. They tend to have subtler findings such as mild expression of disease, absent symptoms and unusual presentations in addition to a better lung function, high rates of pancreatic sufficiency, fewer complications and a better prognosis[6]. The traditional sweat test results may also not be positive.

MATERIALS & METHODS

This is a retrospective review study conducted at Liverpool Heart and Lung Hospital, Liverpool, United Kingdom from 1984 to 2007. The following variables were taken into account, age, gender, type of test used for diagnosis, Body mass index (BMI), gene testing and presence of any disease before diagnosis.

RESULTS

Table 1 summaries the basic characteristics/data of patients with late diagnosis (LD) of cystic fibrosis. Out of 250 cases, 30 patients were diagnosed late with cystic fibrosis. In the LD patients, male to female ratio was 1.35:1. The mean age of LD patients was 16-51. Body mass index (BMI) for the LD group of patients fell in the normal range; 24 (14-35).

DNA of all LD patients was analyzed for CFTR mutations. In the LD patients, the frequency of Gene Delta 508 mutation was 23 (77%) while 7 (23%) patients were positive for Gene R117H mutations as shown in Figure 1.

Figure 2 shows various tests used to confirm the diagnosis of Cystic Fibrosis. Out of a total of 30 patients, 14 (46%) were confirmed via Cystic Fibrosis Gene Testing, 14 (47%) via Cystic Fibrosis Gene Testing and Sweat Testing while 2 (7%) were confirmed via Cystic Fibrosis Gene Testing, Sweat Testing and Nasal Potential Difference.

Figure 3 shows the previous diagnosis of Cystic Fibrosis patients. 20% were previously diagnosed with Asthma, Bronchiectasis 30%, Adult Bronchopulmonary Aspergillosis(ABPA) 3%, Sinusitis 7%, Recurrent Lower Respiratory Tract Infection (LRTI) 7%, Unexplained Cough 7%, Bronchiectasis and Celiac Disease 3% while Asthma and Bronchiectasis 23%.

DISCUSSION

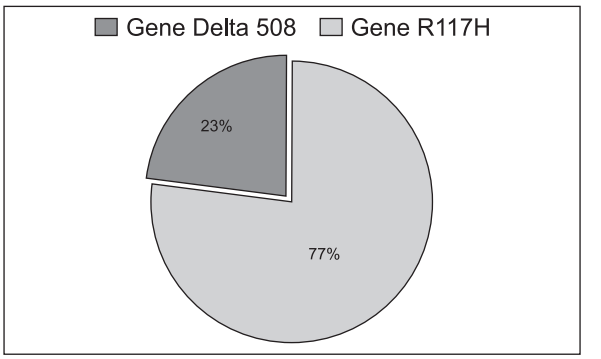

Fig 1: Gene Mutations in CF Patients

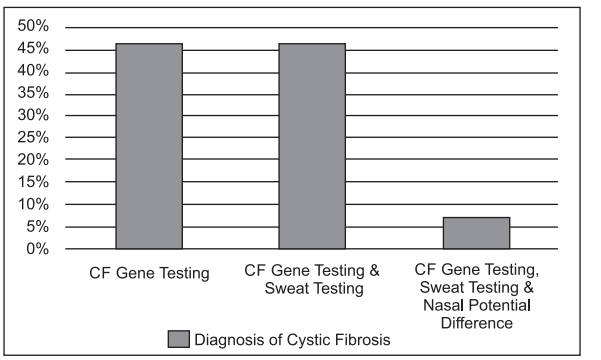

Fig 2: Diagnosis of Cystic Fibrosis by Testing

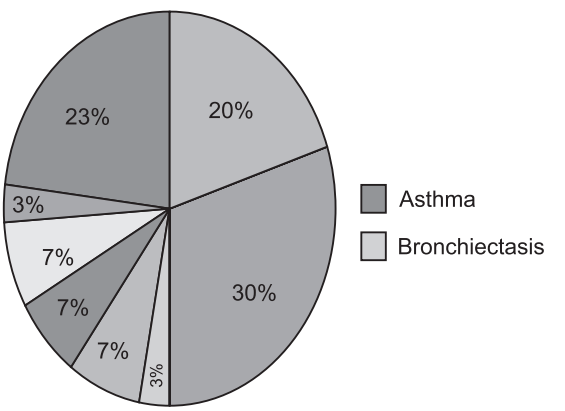

Fig 3: CF Patients with Previous Diagnosis

Table 1: Basic Characteristics of late diagnosis group.

Mean Age (years) (range)	29 (16-51)
Mean BMI* (range)	24 (14-35)

*BMI=body mass index

This study describes the clinical and genetic features of patients in which cystic fibrosis was diagnosed late. Patients with Cystic Fibrosis diagnosed later in life rather than in childhood have variable and atypical presentations, and often have milder disease, better

lung function, high pancreatic sufficiency, fewer complications and a better long-term prognosis[6]. Correct diagnosis allows institutions of correct therapy, more informed discussion of prognosis and appropriate genetic counseling. The following discussion addresses issues of diagnosis, genetic basis and varied clinical picture of CF in the patients.

All of our late diagnosed patients satisfied the current criteria of diagnosis, namely a compatible phenotype plus Genetic testing, Sweat testing and nasal potential difference. Recent advances in genetic testing have identified a large number of CFTR mutations[12]. Our study has found out that most patients were positive for Gene Delta 508 mutations (77%) which correlated with another study stating that the most common mutation is that of Gene Delta 508[7].

Our study employed different diagnostic methods for Cystic Fibrosis namely Gene Testing, Sweat Testing and Nasal Potential Difference. In addition to Sweat testing being the hallmark diagnosis similar to another study making use of Sweat testing to identify 65% of their Late CF patients[10], Genetic Testing proved beneficial (47% Patients tested positive) as Gene Delta 508 and Gene R117H mutations were found positive. In addition to this, Nasal Potential difference was also found to be beneficial in diagnosing Cystic Fibrosis in adults which is consistent with another study employing the use of Nasal Potential Difference alone in diagnosing 33% of patients[10].

Combination of Sweat testing and Genetic testing confirmed diagnosis in this study (47%) was lower in comparison to a study conducted in Pulmonary Department, Cochin Hospital, Paris (91%)[11].

Our study has documented considerable morbidity and delay in diagnosis of CF when identification of the disease was based on clinical suspicion. By time of diagnosis, some patients were already seriously ill. Despite the common perception that CF is primarily a respiratory disease, we found that some patients had GI or malnutrition symptoms before diagnosis. Respiratory symptoms however predominated in this group of patients with only a minority (4) having bowel symptoms which is consistent with another study also stating that GIT symptoms rarely lead to a diagnosis[8].

Our study showed that a majority of patients (63%) had no previous hospital admissions and a minority of patients (33%) had received I/V antibiotics prior to the diagnosis whereas the mean age of diagnosis in our study was found to be 29 correlating with other studies in which the mean age of diagnosis was found to be 27[9].

Our study found out that patients with Late Diagnosis of Cystic Fibrosis were previously diagnosed with other respiratory syndromes such as Asthma and Bronchiectasis (23%) which is consistent with another publication stating the presence of respiratory syndromes in CF patients such as disseminated Bronchiectasis, Asthma and COPD[12] as well as only Asthma (20%) which is consistent with another study identifying 15% of 144 Adult CF patients with asthma[13].

CONCLUSION

Cystic Fibrosis is not only a disease of childhood anymore. Though rare, it can be diagnosed later in life. Therefore, prolonged and unexplained Pulmonary and GIT symptoms must be dealt with caution when concerning adults and the possibility of CF must be considered. To confirm the late diagnosis of Cystic Fibrosis, the most common test used was the Cystic Fibrosis Gene Testing. Sweat testing and Gene Delta 508 mutation played a major role in confirming the late diagnosis of Cystic Fibrosis.

RECOMMENDATIONS

It is recommended through this study that Cystic Fibrosis must be thought of even in adults as opposed to the trends concerning CF being a pediatric disease and diagnosis. Physicians should be more vigilant and consider late diagnosis of Cystic Fibrosis as the differentials in adult cases. With effective treatment, survival can be increased.

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