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Review Article

CYSTIC FIBROSIS SCENARIO IN INDIA

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ABSTRACT
Abnormal transport of chloride ion in the epithelial cells is caused by a autosomal recessive monogenic condition known as cystic fibrosis (CF). It belongs to the rare genetic disease in India. Persistent coughing with phlegm, pneumonia, bronchitis, bulky stool and hard bowl movement are most symptoms of the disease. Mutation in CFTR (cystic fibrosis transmembrane conductance regulator) gene present on chromosome 7 having 230 kb nucleotides with 23 exons leads to development of disease. Determination of sweat electrolyte is considered as optimal diagnostic method. Results of previous studies have shown that cystic fibrosis increase the sodium and chloride concentrations. Mutations like ΔF508, G542X, R553X, N130K and 621+1 (G →T) are most common in CF patients in India. Among them ΔF508 is most severe and predominant mutation. Reports have shown as high as 56% frequency of ΔF508 in Indian patients. CF can be treated with anti-inflammatory drugs, CFTR modulators and combination therapies. Early screening can be an effective strategy for early diagnosis and treatment of cystic fibrosis.

Keywords: Cystic fibrosis, CFTR gene, Mutations, ARMS- PCR.

1. INTRODUCTION
Among all the genetic disorders, cystic fibrosis is considered as one of the most vital autosomal recessive monogenic disorder [1-4]. This causes abnormal transport of chloride ions through the apical membranes of epithelial cells. Since the sweat glands become impermeable for chloride ion, it leads to elevated concentration of chloride in sweat. Not only this, re-absorption of sodium is reduced for maintaining electro-neutrality. Hence person will have higher concentration of chloride and sodium in the sweat [3, 5-8]. Determination of these ions in the sweat is one of the easy and fastest methods for diagnosis of cystic fibrosis. In 1989, it was found that mutation in cystic fibrosis transmembrane regulator (CFTR) gene is responsible for this condition. The gene is located in the q arm of chromosome 7 [9-14]. CF is known to affect multiple organs and systems. Lungs, pancreas, respiratory tract, and exocrine glands are key organs whereas it can affect hepatobilliary, reproductive and endocrine systems. [2, 5-7, 12, 15].

2. EPIDEMIOLOGY OF CYSTIC FIBROSIS
Cystic fibrosis is one of the extremely rare genetic disorders in India. It was seen in the rate of 1 in 40,000 newborn [3, 8, 12, 15, 16]. In north European descent the frequency of around 1 in 3,000 is seen. Ireland has the highest incidence of 1 in 1,400 [1, 4, 12, 16]. Studies have shown that the incidence varies depending on race and ethnicity [3]. It was seen that only 1 in 10,000 and 1 in 20,000 cases were observed in Latin Americans and African Americans [1, 4, 7, 10, 11, 16]. The incidence may be lower than this in people of Asian origin [3, 8, 11]. As per recent study in USA, the rate of survival with CF has improved in last two decades by more than 1.8% per year [11, 13, 16]. Recent development in newborn screening has improved the survival rate by allowing early treatment. Alone in US, the diagnosis more than 58% newborns were screened for the disease in 2010 as compared to 8% in 2000 [1, 5, 17]. Many other countries have reported the screening of more than 50% of cystic fibrosis population before the age of 18 years [1, 3, 11, 13].

3. PATHOPHYSIOLOGY

Mutation CFTR gene leads to complete absence or malfunction of CFTR protein resulted into abnormal chloride conductance especially on the apical membrane of epithelial cells. This leads to airway surface liquid depletion in lungs creating critical condition [2, 5, 11]. The airway surface liquid is known to play vital role to support ciliary stability and functioning, ciliary collapse and decreased mucociliary transport. This consequence leads to vicious circle of phlegm retention, infection, and inflammation [6, 7, 11]. Gradual development of bronchiectasis leads to irreversible changes in lungs which lead to accelerate infection and pathogenesis leading to critical conditions [2-5, 9, 13].

3.1. Symptoms

Persistent coughing along with phlegm, lung infection, pneumonia, bronchitis, frequent greasy and bulky stool, difficulty with bowel movement are the most common symptoms of CF. In male infertility is also seen associated with CF [1, 5, 12, 15, 18].

3.2. Laboratory Diagnosis

CF is a genetic disease hence family history plays an important role in suspecting the disease. Since it is a recessive disease, only one or two of the family members can show the symptoms of disease [1, 2, 4, 11]. In a small family, with lesser members, the chances of prediction also decrease. Determination of chloride and sodium in sweat and blood is also significant test. However, it can be affected by many other factors. Hence, it should not be used alone [1, 2, 6, 9, 11]. For accurate diagnosis, it is highly recommended to determine presence of mutations in ΔF508, R553X, N130K, G542X and 621+1 (G →T) locations of gene [11, 12, 16, 17]. ARMS-PCR is one the most efficient technique for molecular diagnosis of CF [3, 5, 13, 15, 16]. Since it is a recessive disorder, the expression of the disease needs the presence of mutations on both the alleles. Newborns are screening after two or three days of born with a blood test. Here immuno reactive trypsinogen produced by pancreas is detected. Elevated level of IRT is an indication of possible CF [3, 6, 15].

4. CF MUTATIONS IN INDIA

As mentioned earlier, ΔF508 mutation is the most prominent mutation causing development of CF. It accounts for more than 50% cases among all the CF [7, 8, 16, 17]. In a recent screening study, Indians were identified with 2 novel mutations (3622Inst, 3601-20T→C/U) and another 2 very rare mutations (3849+10Kb C→T/U, R560H), in addition to ΔF508 mutation, indicating a different spectrum of CF mutations among Indians [19]. Screening of exon 10 and exon 11, the hot-spot regions of the gene have lead to the identification of a rare splice-site mutation at 1525-1(G→A) and a very common polymorphism (M470V), along with ΔF508 mutation [6-8, 11, 12, 20].

5. PRENATAL DIAGNOSIS

Initially, prenatal diagnosis was only possible with the family history of CF. During pregnancy, systematic ultrasound examinations for diagnosis of bowel echogenicity with abnormality can be a suggestive of CF [2]. Development in the field of biotechnology and molecular diagnostic has enable to diagnose the CF at prenatal level. Data base prepared for CFTR gene and identification of more than 1000 different mutations according to geographical and ethnic variations has enable easy and fast prenatal screening of CF. Direct detection of presence of mutations provides fast and accurate diagnosis [11, 12, 15-17].

6. GENOTYPE-PHENOTYPE CORRELATION

Till now a good correlation between genotype-phenotype was observed only with pancreas. In case of lung, the involvement is found very less as compared to pancreas. Similar to lungs, liver also cannot directly correlate as it may be affected by many other environmental factors. However, significant correlation was seen with congenital bilateral - absence of the vas deferens in earlier studies [1, 4, 7, 10-12].

7. TREATMENT

Till now, cystic fibrosis has no definite cure or treatment. However, one cannot decline the scope of medicines as it helps controlling the side effects, prevent or reduce intricacies, and make the conditions mild for better living. The types of medicine and dosages vary from patients to patients. In case of lung malfunction medicine can be swallowed, inhaled or injected. Antibiotics are also used for prevention of chest infections. Dornase alfa, hypertonic saline and mannitol are given for thinning the mucus in the lungs and smoothen the cough [4, 9]. Ivacaftor along with lumacaftor is highly recommended to widen the airways and make breathing easier. Steroids are also used to treat small growths inside the nose like nasal polyps [3, 4, 15]. Active cycle of breathing techniques (ACBT) consisting of deep breathing, huffing, coughing and relaxed breathing significantly helps to

move mucus away. Alternatively, airway clearance devices can also be used to remove mucus from the airways [1, 2, 4, 9-11, 19]. In cases of severe cystic fibrosis, a lung transplant can be recommended which is a serious surgery with moderate to high risk carries risk. Successful transplantation may greatly improve the quality and duration of life CF patients [6, 9, 11, 19, 20]. Based on the overall studies carried out till date, it was concluded that cystic fibrosis is not curable at present but its early screening and detection can help in better treatment from the early phase of life. Genetic screening is the most potential tool for diagnosis the disease in newborns.

8. FUTURE SCOPE

Understandings of CF pathophysiology are not yet clear and needs more attention which comes out with much other important information. Gene therapy for replacement of mutated gene is currently one of the most active investigation areas in CF therapy.

Conflict of interest

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