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Leading Article

Cystic Fibrosis: A Deadly Disease and the Vast Majority are Unaware of It

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Cystic Fibrosis (CF) is a life-limiting multisystem genetic disease inherited as an autosomal recessive trait, was first described as a clinically distinct entity in 1938 by Anderson. Initially, it was considered a rare and lethal disease of infancy.[1] A major breakthrough in the history of CF occurred in 1989 when its gene was identified on chromosome 7 at position q31.[2] and till now more than 2000 mutations have been identified, grouped into five main classes that affect protein function are associated with CF syndrome. The most prevalent mutation of CFTR is the deletion of a single phenylalanine residue at amino acid 508 (F508del), representing about 70% of Caucasian population.[2] Over the last 8 decades, significant improvement has occurred in the understanding and management of CF. Now, with improved understanding and management of CF, the median life expectancy now is more than 40 years.[3]

The incidence/prevalence of CF is variable in different ethnic background but in the UK is 1 in 2500 live births and in India around 1 in 30000- 40000 live birth. The burden of CF in Bangladesh is not known but if we consider the crude birth rate of 18.8% (2017), the total number of live births in Bangladesh was 3,008,000. The number of children born every year with CF might be about 1203, presuming incidence to be about 1 in 2500 and 100 with a presumed incidence of 1 in 30000.[4]

CF is far more common than previously thought in our context. We have an experience of about 100 cases of CF in children in our country over one and a half decade. The mean age of diagnosis is much delayed at 7.5 years though the mean age of onset is very early (15 month). Consanguinity between parents is significant (24%) in our cases. Many cases are misdiagnosed as pulmonary TB. The clinical features of CF include persistent cough, productive sputum, persistent or recurrent pneumonia, poor weight gain and bronchiectasis on chest radiology and imaging.[5]

Mutations in CF gene lead to defective chloride channel in cells, i.e. CF transmembrane conductance regulator (CFTR). CF is caused by the reduction or dysfunction of the CFTR, a cAMP regulated chloride and bicarbonate channel and a master regulator of other ion channels that exists in the apical membranes of the cells lining the airways, sweat glands, hepatobiliary system, and reproductive tracts. In CF, defective CFTR causes the combination of decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells resulting in dehydration of secretions which is stickier to bacteria promoting infection and inflammation. The earliest lesion is obstruction of the small airways by abnormally viscous airway mucus. A secondary bronchiolitis with plugging of the airways invariably follows and develops into bronchiectasis as the respiratory epithelium become chronically infected first by *Staphylococcus aureus* and *Hemophilus influenzae* and later by *Pseudomonas aeruginosa*. CF is the most common cause of pancreatic insufficiency in childhood. Approximately, two-thirds of children are pancreatic insufficient at birth and 90% will develop by one year of age and may present with growth failure, weight loss, abdominal bloating, foul-smelling oily stools, edema, or diarrhea. So, delayed diagnosis which is more common in our country may lead to severe malnutrition at presentation, is a bad prognostic indicator for survival.[6,7]

CF phenotypes include *classic CF*, *atypical CF-with symptoms* and *atypical CF-without symptoms.* The clinical features of classic CF are recurrent chest

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infections, malabsorption with pancreatic insufficiency in the majority, salt losing syndromes or infant presenting with meconium ileus or rectal prolapse. A positive sweat test and / or two CFTR mutations is diagnostic of CF.

There is a growing group of children and adults who do not present with full spectrum of clinical features associate with classic CF. The term "equivocal CF" or "CFTR related disorders" or "variant CF" have all been used to describe these atypical forms. Frequently, there is a single organ involvement like pancreas-acute or recurrent pancreatitis; lungs-disseminated bronchiectasis, diffuse panbronchiolitis, allergic bronchopulmonary aspergillosis; nose and sinuses-rhinosinusitis; bilary channel-sclerosing cholangitis; vas deferens-isolated obstructive azoospermia. However, the recent consensus recommendation is that clinician should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF, because these terms have no harmonized definition and could be confusing for families or caregivers.[8]

Cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS), also known as CF Screen Positive, Inconclusive Diagnosis (CFSPID) in Europe, describes an inconclusive CF diagnosis following positive newborn screening (NBS). Although the future health of someone designated with CRMS/CFSPID remains unclear, there is a higher risk of experiencing problems in the airways, sinuses, intestines, pancreas, or the reproductive system. In some cases, evolving signs and symptoms, new information about disease-causing CFTR mutations, or changes in sweat chloride concentration levels may ultimately lead to a CF diagnosis.[8,9]

In USA, CF newborn screening program begins with a blood test from the baby to check the levels of immunoreactive trypsinogen (IRT). IRT is normally found in small levels in the body. In people who have CF, IRT levels tend to be high. Some states only test IRT levels on the first blood test. These are called IRT-only states. Other states conduct both an IRT and a DNA test. These are called IRT-DNA states. A positive newborn screening result gives rise to the possibility of CF and that further testing through a sweat test required in order to rule out or diagnose CF. The sweat test should be done at a CF Foundation-accredited care center. The staff will work to schedule the sweat test as soon as possible the newborn reaches 10 days of age. At the latest, babies with a positive NBS or prenatal genetic test should have a sweat test performed by the age of 4 weeks to ensure that any health issues or changes can be found early and treated quickly.

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF. A sweat chloride level ≥60 mmol/L indicates a diagnosis of CF and a sweat chloride level < 30 mmol/L indicates that CF is unlikely. In individuals who fall into the intermediate sweat chloride level 30-59 mmol/L, genetic analysis is required. Several commercial laboratories test for 30-96 of the most common CFTR mutations and this testing identifies ≥90% individuals who carry 2 CF mutations. A second, confirmatory, sweat test following an initial positive result is not necessary; this is a change from previous CF foundation diagnostic guidelines.

CF is a clinical and not a genetic diagnosis, although it acknowledges that genetic testing may have a role in sorting out atypical clinical situations. The diagnostic criteria for CF are as follows: one or more characteristic phenotypic features consistent with CF-chronic sinopulmoary disease/ gastrointestinal and nutritional abnormalities/ salt loss syndromes/ male urogenital abnormalities resulting in obstructive azoospermia or a history of CF in sibling or a positive newborn screening test result and an increased sweat chloride concentration or identification of two CF mutations or demonstration of abnormal nasal potential difference (NPD) / intestinal current measurement (ICM).

Treatment plan should be comprehensive and linked to close monitoring and early, aggressive intervention. Though treatment is mainly supportive and symptomatic, initial efforts after diagnosis should be intensive and should include baseline assessment, initiation of treatment, cleaning of pulmonary airways and education of the patients and parents. Follow-up evaluations are scheduled every 1-3 months, depending on the age at diagnosis. An interval history and physical examination should be obtained at each visit. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and sensitivity studies.

A nurse, physical therapist, respiratory therapist, social worker, and dietitian as member of multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan.[10]

Treatment for CF lung disease is evolving, incorporating the newer therapies developed over the last two decades. Current management of CF incorporates antibiotics, inhaled mucolytics, vigorous airway clearance, nutritional support, anti-inflammatory agents, and increasingly small molecule potentiators and correctors in an attempt to forestall progression. Nutrition has become a major clinical focus in recent years and target weight for length is the 50th percentile during the first two years of life. It is estimated that an infant with CF has caloric needs closer to 150 kcal/kg than the standard of 100-120 kcal/kg. Up to 90% of patients with CF have loss of exocrine pancreatic function as well as inadequate digestion and absorption of fats, proteins and fat-soluble vitamins. So, patients with CF need life-long replacement of pancreatic enzymes and fat-soluble vitamins. The predominant morbidity and mortality from CF continue to result from progressive pulmonary involvement. The CF lung is susceptible to infection; endobronchial infection induces an intense inflammatory response that leads to bronchiectasis and eventually respiratory failure.[11] Though there is no cure for CF, the survival rate has improved dramatically over the past 30-40 years. The data of the US Cystic Fibrosis Foundations suggests that life expectancy has increased from 31 to 37 years over last one decade. Similarly, reports from the UK concluded that with continuing improvement in survival of CF patients in successive cohorts, prediction of median survival of above 50 years of age for individuals born in 2000 centuries continues to look realistic.

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