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Diagnosing and managing cystic fibrosis in the developing world

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Summary Cystic fibrosis (CF), earlier believed to be non existent in non Caucasians, is now a pan ethnic disease, having being reported from various regions of the world over last one decade. Apart from limited resources, the major problems in diagnosis and management of CF in developing countries include: lack of awareness among pediatricians, absence of facilities for diagnosis (sweat chloride estimation and genetic studies), lack of trained manpower for care of specific problems, and non availability of appropriate drugs. Care of children with CF may not be a priority for governments in countries where childhood mortality rates are high, predominantly due to acute infections.

An indigenously developed and relatively inexpensive method of sweat collection and chloride estimation using pilocarpine iontophoresis and titration, respectively, may be an alternative to the commercially available costly equipment.

Having a team of trained nurse, physiotherapist, and dietician for optimal care of CF patients may not be feasible due to inadequate resources. Training a single person (e.g. nurse) to deliver comprehensive CF care may be a feasible alternative. To overcome problems of non availability of appropriate drugs (enzymes, inhaled antibiotics, DNAse, etc), locally available drugs may be used. Examples include use of hypertonic saline in place of DNAse, enteric coated enzyme tablets in place of enteric coated spherules, etc.

Factors that are associated with decreased survival in CF patients from developing countries are age of onset of symptoms <2 months, severe malnutrition at the time of diagnosis, colonization with Pseudomonas at the time of diagnosis and frequency of pneumonia >4 episodes/year. All these factors can be modified except onset of symptoms before 2 months of age, by early diagnosis and appropriate treatment.

Many of the above mentioned hurdles have been successfully overcome by us to establish CF services in a resource-limited setting. We conclude that education of pediatricians about the disease, early diagnosis using indigenous technology and aggressive physiotherapy with nutritional management and judicious use of antibiotics can improve the quality of life and survival in CF patients in resource-limited settings.

Cystic fibrosis (CF) is the commonest inherited life limiting disease in Caucasian population. Reports of CF from other parts of world over last one decade[1–7] have made it a pan ethnic disease from a disease believed to be non existent in other races. Strong belief propagated by scientific community that CF is an exclusive disease of Caucasian population led to under diagnosis of CF in other parts of world. The diagnostic facilities were not developed.

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Now more recently with interaction of Pediatricians from different parts of world, more and more cases of CF are being diagnosed in developing countries. In developing countries the resources are limited and infections are still the leading cause of mortality and morbidity, the priority for government is to control infections. CF is not on the priority of governmental and research agencies. We developed CF services at our institute with help from International Cystic Fibrosis (Mucoviscidosis) Association and Cystic Fibrosis Worldwide over last 8 years. We will discuss the problems faced by us and how we overcome them.

PROBLEMS IN DIAGNOSIS

Non availability of sweat testing facility

With a population of over one billion in India, diagnostic facilities for CF are available in less than 10 centers throughout country. Even if a clinician suspects CF in a child he/she is not able to confirm the diagnosis as the patients may have to travel hundreds of kilometers on personal cost to get sweat test. Clinicians feel that even if a diagnosis is made, how it is going to help the patients as majority of the patients may not afford treatment and are going to die sooner or later. Therefore diagnosis of CF is not confirmed in majority of the teaching institutions and pediatric residents may not see even a single case of CF during their training. The equipments available commercially for sweat tests are costly and not available easily. The ongoing costs for each test further limits its commercial viability.

To overcome these problems, we developed an indigenous method for sweat chloride estimation based on pilocarpine iontophoresis and manual titration. The method has been validated.[8] 50 samples of known strength of saline were analysed by two persons independently. The mean difference between estimated chloride value between two observers was -2.5 ± 4.2 mEq/L (95% CI: -3.67 to 1.33). 50 sweat samples of patients were analysed by two persons independently and inter-observer variability was -1.12 ± 4.34 mEq/L (95% CI: -2.23 to 0.8). With sweat chloride value of >60 mEq/L, two (4%)of the patients samples were misclassified and with sweat chloride values of less than 40 mEq/L again 2 (4%) of samples were misclassified. All the four misclassified values were in the borderline range.[8] The cost of equipment is <US$ 10 and cost per test is <US$ 1.

Mutations and their heterogeneity

The other method for diagnosis is to demonstrate two mutations in CF patients. There are limited number of reports on mutation studies in Indian children with CF. The available reports suggest that the mutations in Asia and specifically Indian subcontinent may be different. Small studies from India suggest that frequency of deltaF508 mutation may vary between 19-34% in Indian children.[2,3,7,9–11] At our center mutational spectrum of 124 CF children was studied using single strand conformational polymorphism (SSCP). On screening 19 exons, at least one mutation could be identified in 59 (47.5%). 26 (21%) patients were homozygous and 12 (10%) were heterozygous for deltaF508 mutation. The other mutations were very heterogeneous. The mutations present in more than one family were 3849 + 10kb C > T, 3601 − 20T > C, 1161delC and S549N. Six novel mutations were also identified**.** There was regional variation in the mutations. At present it is difficult to suggest definite strategy for mutation analysis that can be used for diagnosis of CF in Indian patients.[9,12]

Suggestions for diagnosis

In view of problems of using molecular diagnosis and non availability of Nasal potential difference measurement in developing countries, sweat chloride remains the diagnostic test for CF. Providing sweat chloride test for diagnosis of CF remains a low priority for agencies providing health care. It is unlikely that laboratories in hospital will start sweat testing by using commercially available macroduct sweat collecting system. Therefore, we suggest use of alternative cheaper methods for doing sweat test. There is need to train persons for doing sweat testing and initially supporting salary, and chemicals may enhance development of CF services in developing countries.

In the absence of sweat testing it is also advised to pediatricians to look for supportive evidence for CF such as hypochloremic metabolic alkalosis, hyponatremia, hypokalemia or isolation of pseudomonas on culture from respiratory secretions in a clinical setting of CF. If any of these are present, the patient may be asked to travel to a center where sweat testing is available.

PROBLEMS IN MANAGEMENT

Problems in management include lack of trained manpower, resources for sustaining CF care, non availability of medications and no state support.

Lack of trained manpower

Since majority of Pediatricians may not have seen a single case of CF during their training, they may not be aware about the clinical features of CF. Due to delayed diagnosis and inadequate treatment of CF and different climatic changes there may be some difference in the clinical features of CF in developing countries.

Difference in clinical features

The reports describing clinical features of CF from developing countries are few and include small number of cases. A review of 20 Asian children diagnosed as CF till 1994 in USA suggest that the mean age of diagnosis was delayed to 12